# Empagliflozin for type 2 diabetes: ERG commentary on second submission by Boehringer Ingelheim.

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# 2 List of abbreviations

| | |
|---|---|
| **ACD** | Appraisal consultation document |
| **BMI** | Body mass index |
| **BNF** | British National Formulary |
| **CEAC** | Cost-effectiveness acceptability curve |
| **CEAF** | Cost-effectiveness acceptability frontier |
| **CHF** | Congestive heart failure |
| **CORE** | Center for Outcomes Research |
| **DPP-4** | Dipeptidyl peptidase-4 |
| **EQ-5D** | Euroqol 5 dimensions |
| **ERG** | Evidence review group |
| **FDA** | Food and Drug Administration |
| **GP** | General practitioner |
| **GTI** | Genital tract infection |
| **GLP-1** | Glucagon-like peptide-1 |
| **HbA1c** | Glycosylated haemoglobin |
| **HDL** | High density lipoprotein |
| **ICER** | Incremental cost effectiveness ratio |
| **IHD** | Ischaemic heart disease |
| **INS** | Insulin |
| **LCI** | Lower confidence interval |
| **LDL** | Low density lipoprotein |
| **LY** | Life year |
| **MD** | Mean difference |
| **MI** | Myocardial infarction |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Care Excellence |
| **NMA** | Network meta-analysis |
| **PSA** | Probabilistic sensitivity analysis |
| **PSS** | Personal social services |
| **PSSRU** | Personal Social Services Research Unit |
| **QALY** | Quality adjusted life year |
| **QOF** | Quality and Outcomes Framework |
| **QoL** | Quality of life |
| **RCT** | Randomised controlled trial |
| **SBP** | Systolic blood pressure |
| **SGLT2i** | Sodium glucose co-transporter 2 inhibitor |
| **STA** | Single technology appraisal |
| **TTO** | Time trade off |
| **TZD** | Thiazolidinedione |
| **UCI** | Upper confidence interval |
| **UKPDS** | UK prospective diabetes study |
| **UTI** | Urinary tract infection |
| **WTP** | Willingness to pay |

# 3 Summary

The manufacturer of empagliflozin, Boehringer Ingelheim, was asked in the ACD to address concerns with the network meta-analysis (NMA) and with the modelling provided in the first report.

## 3.1 Summary of clinical effectiveness evidence provided.

New NMAs have been provided. The ERG considers them to be of good quality, and they successfully address the shortcomings of the previous NMAs with the minor caveat that it does not incorporate a quality assessment of the included randomised controlled trials (RCTs). In the ERGs opinion the new NMAs are robust, clearly presented and appropriate. The conclusions are supported by the documented analyses and are reasonably summarised at the end of the submission with the exception that no mention is made that the NMAs show a greater incidence of urinary infections during treatment with sodium glucose cotransporter-2 inhibitors (SGLT-2is).

The conclusions drawn by the manufacturer may be summarised as follows:
Across the analyses it appears that the SGLT-2is are of broadly similar efficacy and safety. With regard to HbA1c reduction at 52 weeks, across all three regimens (dual and triple therapy, and add-on to insulin regimens), empagliflozin is at least as effective as its active comparators and clearly superior to placebo. For HbA1c in insulin add on therapy 25 mg empagliflozin appears statistically superior to 10 mg (this trend is evident at 24 weeks but not significant) making the comparison of 25 mg empagliflozin versus alternative active interventions more favourable for empagliflozin than in the 10 mg empagliflozin comparisons (note that the 10 and 25mg packs are equally priced). With regard to weight loss at 52 weeks, across all three regimens, empagliflozin is at least as effective as other SGLT-2is, is superior to sulphonylurea in dual therapy and to sitagliptin in both dual and triple therapy. Similarly across all three regimens with regard to effects on SBP at 52 weeks empagliflozin appears at least as effective as other SGLT-2is, and is superior to sulphonylurea in dual therapy and to sitagliptin in both dual and triple therapy. Overall the SGLT-2is offer significant weight loss and blood pressure reductions compared to placebo and sulphonylureas. In addition, there is a numerical but not statistically significant advantage compared to the DPP-4is in terms of weight loss and blood pressure.

## 3.2 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer presents four sets of analyses.
For add-on to metformin, empagliflozin 10mg and 25mg are compared with:

- dapagliflozin 10 mg

- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to metformin plus sulfonylurea, empagliflozin 10mg and 25mg are compared with:

- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to metformin plus thiazolidinedione, empagliflozin 10mg and 25mg are compared with:

- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to insulin, empagliflozin 10mg and 25mg are compared with:

- dapagliflozin 10 mg
- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

The cost effectiveness estimates use the CORE model. A lifetime horizon is modelled, with the perspective for costs being the NHS and PSS and the perspective for benefits being that of the patient. Costs and benefits are discounted at 3.5%.

Clinical effectiveness estimates are applied for each treatment for:

- HbA1c
- SBP
- BMI
- Non-severe hypoglycaemic events
- Severe hypoglycaemic events
- Urinary tract infections (UTIs)
- Genital tract infections (GTIs)

The estimates for these are largely drawn from the revised manufacturer network meta-analyses.

Most of the other model inputs are based upon the CORE default values, though the manufacturer revises the costs of complications and the utility decrements associated with the complications of diabetes during their incident year. Utility decrements for UTIs and GTIs are taken from the STA of dapagliflozin.

After the initial HbA1c effect, HbA1c is modelled as increasing though time. Once HbA1c hits a 7.5% threshold the patient is assumed to switch to insulin therapy. This therapy switch only affects BMI, adverse event rates and therapy costs.

*As add-on to metformin*

The manufacturer analyses suggest that empagliflozin 25mg is both the cheapest and the most effective. Most of the comparators were around 0.035 quality adjusted life years (QALYs) worse in terms of effectiveness, though canagliflozin 300mg was close to equivalence with a loss of only around 0.007 QALYs. But despite a slightly lower cost from complications, canagliflozin 300mg remained more expensive than empagliflozin 25mg by around £300 due to its higher treatment costs.

*As add-on to metformin plus sulfonylurea*

Empagliflozin 25 mg is estimated to remain the cheapest, but empagliflozin 10mg costs only £67 more and yields an additional 0.007 QALYs so has a cost effectiveness estimate of £9,751 per QALY. Canagliflozin 100 mg costs £16 more than empagliflozin 10 mg and is estimated to be very slightly inferior by 0.002 QALYs so is formally dominated by empagliflozin 10mg, though the differences are not meaningful within the context of the modelling. Canagliflozin 300 mg costs £222 more than empagliflozin 10 mg and yields an additional 0.045 QALYs, suggesting a cost effectiveness estimate of £4,933 per QALY. But given this, it appears that canagliflozin 300 mg also extendedly dominates empagliflozin 10 mg. As a consequence, canagliflozin 300 mg is estimated to yield an additional 0.052 QALYs over empagliflozin 25 mg at an additional cost of £289, resulting in a cost effectiveness estimate of £5,558 per QALY.

A probabilistic comparison of empagliflozin 25 mg with canagliflozin 300 mg results in estimates of the probability of empagliflozin being cost effective at thresholds of £20,000 per QALY and £30,000 per QALY of 17% and 11% respectively.

*As add-on to metformin plus thiazolidinedione*

Sitagliptin 100 mg is estimated to be the cheapest, with canagliflozin 100 mg being £107 more expensive but yielding an additional 0.026 QALYs so having a cost effectiveness estimate of £4,115 per QALY. Empagliflozin 25 mg costs £103 more but yields 0.018 QALYs less than canagliflozin 100 mg so is dominated by it. Compared to canagliflozin 100 mg, canagliflozin 300 mg yields an

additional 0.035 QALYs at an additional cost of £355, giving a cost effectiveness estimate of £10,143 per QALY. Empagliflozin 10 mg is estimated to be the most expensive, but to yield 0.072 fewer QALYs than canagliflozin 300 mg.

In the pairwise comparison with empagliflozin 25 mg, canagliflozin 300 mg results in an additional 0.053 QALYs at a cost of £252, suggesting a cost effectiveness estimate of £4,755 per QALY.

A probabilistic comparison of empagliflozin 25 mg with canagliflozin 300m g results in estimates of the probability of empagliflozin being cost effective at thresholds of £20,000 per QALY and £30,000 per QALY of 14% and 7% respectively.

*As add-on to insulin*

Depending upon the analyses examined, results differ slightly. But broadly, canagliflozin 100 mg is estimated to result in around an additional 0.010 to 0.020 QALYs and save between £200 and £300 compared to the empagliflozins. Canagliflozin 300 mg is estimated to be the most effective with a gain over canagliflozin 100 mg of between 0.033 and 0.038 QALYs at an additional cost of between £143 and £364. This results in cost effectiveness estimates of between £4,333 per QALY and £9,579 per QALY for canagliflozin 300 mg compared to canagliflozin 100 mg.

In the pairwise comparison with empagliflozin 25 mg, canagliflozin 300 mg results in an additional 0.049 QALYs at a cost of £171, suggesting a cost effectiveness estimate of £3,490 per QALY.

## 3.3 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG asked at clarification for more information about the CORE modelling equations but received very little in reply. The underlying assumptions, structure and implementation of CORE is a black box to the ERG.

The ERG has cloned and rerun all the manufacturer base case analyses. The results of these while qualitatively the same as those reported by the manufacturer are not exactly the same. Total QALYs remain similar but costs in both arms rise, though roughly in proportion meaning that cost effectiveness estimates are not much affected. The reasons for this do not appear to be due to random sampling and are unclear.

The ERG is unclear about how the rates of non-severe hypoglycaemia inputted to CORE have been calculated, though the relativities between comparators are as per those implied by the manufacturer network meta-analysis.

It is not clear why severe hypoglycaemia has not been considered for the comparison as add-on to insulin, given that there are estimates for these within the network meta-analysis.

The sources of the rates of GTIs inputted to CORE do not appear to have been documented, and the rates also appear to differ from those of the original submission.

The revisions to the CORE default costs and utilities are not obviously justified. The costs of the complications of diabetes appear to be somewhat too high. That said, in the opinion of the ERG the CORE default quality of life decrement per BMI point increase of -0.0038 is incorrect and should be -0.0061.

For the add-on to metformin analyses, sulfonylureas have not been included as comparators within the economics despite them being within the scope and within the manufacturer network meta-analysis. The sulfonylureas are cheap. Not including them risks seriously biasing the analyses. However it could be argued that they should tried first, and regarded as precursors not comparators.

The manufacturer tabulation of results presents pairwise comparisons. This is difficult to read and absorb, and is non-standard. The ERG has tabulated all comparators for a given set of analyses within a single table. This permits an easier comparison, highlights dominance and where dominance does not occur what the net QALY gains are, and perhaps more reliably what the net costs might be anticipated to be.

The "deterministic" analyses of the manufacturer appear to have selected the 2$^{nd}$ order sampling option within CORE. This may have been an inadvertent mistake, meaning that both the manufacturer "deterministic" analyses and the probabilistic analyses 2$^{nd}$ order sampling. The former was run over 1,000 patients and 1,000 bootstraps, the latter over 50,000 patients and 500 bootstraps. The approach of the probabilistic modelling underlines the importance of achieving convergence for a given bootstrap, something which may not have occurred over the 1,000 patients of the "deterministic" modelling.

The ERG modelling did not select selected the 2$^{nd}$ order sampling option within CORE. If the manufacturer approach was correct, the ERG approach is incorrect. The differences in approach also mean that there is no ready read across between any of the results of the manufacturer with those of the ERG.

The ACD recommended probabilistic analyses. It appears that probabilistic modelling has only been presented for a subset of analyses. This may have been due to time constraints as these take a long time to run within CORE, but given the concerns outlined above this is something of a weakness. The ERG analyses have only been run for the deterministic analyses, due to time constraints.

## 3.4 ERG commentary on the robustness of evidence submitted by the manufacturer

**Strengths**

As recommended in the ACD the analyses have been run within a model that has been validated and used in other NICE appraisals: the IMS CORE model. The additional validation data now available from the 5th Mount Hood challenge, while from a paper authored by one of the CORE modellers, presents further evidence of CORE being among the better performing models of the complications and mortality associated with type 2 diabetes.

Aside from a couple of minor inconsistencies, the modelling within CORE has used the results of the revised network meta-analysis.

**Weaknesses and areas of uncertainty**

Across all the analyses, it should be borne in mind that all modelling within type 2 diabetes tries to model the impact of the changes in interim outputs such as HbA1c to the patient relevant outcomes of the complications of diabetes and overall survival. This is in itself complicated and subject to considerable uncertainty. There may be a hierarchy of model outputs in terms of increasing uncertainty: the direct drug costs, the direction of the quality of life impacts from weight changes, the QALY impact of BMI changes for a given set of assumptions, the costs of complications, the quality of life impacts of complications and overall survival. These uncertainties may argue for a degree of caution when examining the results particularly if the incremental amounts are small, though what constitutes small is a moot question.

## 3.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG analyses revise the costs of complications and the utilities used, and also do not select 2nd order sampling as an option within CORE. The ERG has not been able to perform any probabilistic analyses due to the time they take to run in CORE.

The ERG has revised the CORE economics module to apply the UKPDS 65 costs as calculated by the ERG and the UKPDS 62 quality of life decrements in favour of those drawn from Sullivan et al (2011) by the manufacturer.

For the comparisons as add-on to insulin the ERG has also revised the rates of UTIs for canagliflozin 300mg to be equal to 10.73 for the comparison with empagliflozin 10mg and to 9.30 for the comparison with empagliflozin 25mg.

The ERG has undertaken analyses for quality of life decrements per BMI point of zero, 0.0038 and 0.0061. The 0.0061 value is preferred by the ERG. Note that these analyses assume that the initial net effect upon BMI is maintained for the patient lifetime. Convergence of a patient's BMIs between the arms over time would tend to cause the cost effectiveness estimates to fall somewhere between those that assume no BMI impact upon quality of life and those that assume the 0.0061 per BMI point.

*As add-on to metformin*

Empagliflozin is no longer estimated to be the least costly, with sitagliptin 100mg now being so. Canagliflozin 100mg and empagliflozin 25mg are estimated to have broadly the same total costs, but empagliflozin 25mg is more effective. This leads to empagliflozin 25mg either dominating or extendedly dominating canagliflozin 100mg. As the BMI quality of life decrement is increased from zero to 0.0061 the cost effectiveness of empagliflozin 25mg compared to sitagliptin 100mg improves from around £1,373 per QALY to £686 per QALY. The other comparators are dominated by empagliflozin 25mg if there is no quality of life decrement associated with BMI, though canagliflozin is of broadly the same effectiveness but more costly. As the BMI quality of life decrement is increased, canagliflozin 300mg ceases to be formally dominated by empagliflozin 25mg but does not approach conventional cost effectiveness thresholds.

*As add-on to metformin plus sulfonylurea*

Empagliflozin 25mg is estimated to be the least costly, but canagliflozin 100mg is only £40 more costly and yields an additional 0.030 QALYs if there is no quality of life impact from BMI, suggesting a cost effectiveness estimate of £1,333 per QALY. If the quality of life decrement of BMI is 0.0061 this estimate worsens to £3,226 per QALY. Empagliflozin 10mg is associated with a higher cost and a QALY loss compared to canagliflozin 100mg. Canagliflozin 300mg is associated with an additional cost of £157 compared to canagliflozin 100mg. But there is a gain of 0.030 QALYs and a cost effectiveness of £5,233 per QALY if there is no BMI quality of life impact, this improving to £2,996 per QALY for a BMI decrement of 0.0061.

For the pairwise comparison of empagliflozin 25mg with canagliflozin 300mg, if there is no BMI quality of life impact the cost effectiveness of canagliflozin 300mg is estimated to be £3,283 per QALY with this improving to £3,040 per QALY for a BMI decrement of 0.0061.

*As add-on to metformin plus thiazolidinedione*

Sitagliptin 100mg is estimated to be the least costly, with canagliflozin 100mg being £130 more costly and slightly inferior if there is no quality of life impact from BMI. But a BMI decrement of 0.0061 causes a gain of 0.052 QALYs resulting in a cost effectiveness estimate of £2,321 per QALY.

Empagliflozin 10mg and empagliflozin 25mg are estimated to be £130 and £241 more costly than sitagliptin 100mg, so are respectively cost neutral and £111 more costly than canagliflozin 100mg. If there is no quality of life impact from BMI they are associated with losses of 0.044 QALYs and 0.022 QALYs compared to sitagliptin 100mg. With a BMI decrement of 0.0061 canagliflozin 100mg becomes the appropriate comparator, and they are associated with losses of 0.046 QALYs and 0.028 QALYs. Canagliflozin 300mg is estimated to cost an additional £480 compared to sitagliptin and yield an additional 0.007 QALYs if there is no BMI quality of life impact, resulting in a cost effectiveness estimate of £68,571 per QALY. The BMI quality of life decrement of 0.0061 causes canagliflozin 100mg to become the appropriate comparator, with the cost effectiveness of canagliflozin 300mg relative to it being £9,358 per QALY.

*As add-on to insulin*

Empagliflozin is estimated to be the least costly, with canagliflozin 100mg being between £200 and £371 more costly. A gain of between 0.010 QALYs and 0.018 QALYs from canagliflozin 100mg is anticipated if there are no BMI quality of life impacts, resulting in cost effectiveness estimates of around £20,000 per QALY. The gains increase to between 0.029 QALYs and 0.037 QALYs for a BMI coefficient of 0.0061, resulting in cost effectiveness estimates of between £6,849 per QALY and £9,973 per QALY.

Canagliflozin 300mg is estimated to be the most effective, with an additional cost of between £341 and £448 compared to canagliflozin 100mg. Given gains of between 0.026 QALYs and 0.040 QALYs if there is no BMI quality of life impact these translate into cost effectiveness estimates of between £11,200 per QALY and £13,115 per QALY. For a BMI quality of life decrement of 0.0061 these cost effectiveness estimates improve to between £9,655 per QALY and £10,525 per QALY.

Comparing canagliflozin with empagliflozin 10mg sees an additional cost of £712. With BMI quality of life impacts of zero and 0.0061 the gains are estimated to be 0.044 QALYs and 0.070 QALYs, resulting in cost effectiveness estimates of £16,182 per QALY and £10,230 per QALY.

Comparing canagliflozin with empagliflozin 25mg sees an additional cost of £269. With BMI quality of life impacts of zero and 0.0061 the gains are estimated to be 0.054 QALYs and 0.068 QALYs, resulting in cost effectiveness estimates of £4,981 per QALY and £3,933 per QALY.

## 3.6 Conclusion

The clinical effectiveness of empagliflozin is not in doubt, and the key question is how it compares with other drugs such as other flozins, including the previous approved dapagliflozin and canagliflozin, and the gliptins.

The conclusion in the first ERG report said;

"The evidence from the trials of empagliflozin show that it is clinically effective in improving glycaemic control, though not dramatically so, with mean reductions in HbA1c ranging from 0.38 to 0.64%, when 0.5% is usually regarded as clinically meaningful. Empagliflozin also provides modest reductions in blood pressure and weight. Its clinical effectiveness is similar to other drugs already approved, canagliflozin, dapagliflozin, and sitagliptin.

Costs are similar, except for the higher dose of canagliflozin. Given that and the similar clinical effects, and despite concerns with model and modelling, the ERG expects empagliflozin to be as cost-effective as the comparators."

The concerns with the NMA have been resolved by provision of a new one. Boehringer argues that "the SGLT-2is are of similar efficacy and safety" and the ERG considers this to be a reasonable verdict.

New modelling has been provided in the tried and tested CORE model. The ICERs vary a lot but appear to be acceptable estimates given the clinical effectiveness, cost and utility estimates and the assumptions that feed into them. The inputs and the model structure are reasonable. Uncertainties around the ICERs arise because of very small differences in costs and QALYs.

# 4 Background

In the ACD,[1] NICE drew attention to a number of concerns with the first submission from Boehringer, including;

> The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include:
>
> - revised estimation of the incremental cost-effectiveness ratios of empagliflozin using a validated economic model, informed by the corrected results of network meta-analyses and compared with relevant comparators (sodium-glucose cotransporter-2inhibitors and dipeptidyl peptidase-4 inhibitors)
> - sensitivity analyses which should also include probabilistic exploration of parameter uncertainty.

For convenience, the summary from the first ERG report [2] is attached as Appendix I. Key points included;

*"The main weakness in the evidence base was that all but one of the trials compared empagliflozin with placebo rather than active comparators such as a gliptin. One trial compared empagliflozin with glimepiride, a sulphonylurea, in dual therapy with metformin, but the ERG considered that this was less relevant because sulphonylureas should be a precursor to flozins, given the very low cost of the former. In the trial against glimepiride there was little difference in HbA1c (0.1%) but those on the sulphonylurea gained weight where those on the flozin lost weight, giving a difference of 4.5 kg at 2 years".*

*"The ERG had some concerns with the network meta-analysis (NMA) in which some errors were detected, but correcting these made little difference – no difference in HbA1c results and only slight differences in hypoglycaemic episodes."*

The Boehringer submission stated that;

"*The overall differences in QALYs and costs were marginal in all analyses and no treatment was clearly the optimum choice."*

The ERG agreed with this summary.

The ERG had more serious concerns with the Boehringer model;

*"Serious problems with the model raise doubts about the estimates of cost-effectiveness and the uncertainty surrounding them. This does not necessarily mean that the conclusion of equivalence*

*(based on clinical trial data and the NMA, and similar pricing) is incorrect, but the model is incapable of showing this in a robust way."*
The ERG did not regard the model as fit for purpose.

The second submission provides a new NMA and new modelling using the CORE model.

#### 4.1.1 Brief description and critique of manufacturer's new NMA

The core of the manufacturer's synthesis and assessment of evidence rests heavily on NMAs of 24 or 52 week trials, with data from these NMA analyses being used in the economic modelling. The ERG found several potentially important shortcomings in the originally submitted NMAs. These are summarised in Appendix II. However it was considered unlikely these flaws would materially alter the results from the analyses. The major conclusions from the NMAs were that the three licenced SGLT-2is (canagliflozin, dapagliflozin and empagliflozin) were equivalent to each other in clinical effectiveness, and were equivalently effective to DPP-4is (e.g. sitagliptin) for most outcomes and superior to them for weight loss.

The currently submitted document of 69 pages describes newly undertaken NMAs. The major difference between these NMAs and the previous ones is that the networks focus only on the three SGLT-2is and sitagliptin. The ERG agrees that this is a reasonable approach.

The new submission successfully addresses the shortcomings of the previous NMAs with the minor caveat that it does not incorporate a quality assessment of the included RCTs. In the ERGs opinion the new NMAs are robust, clearly presented and appropriate. The conclusions are supported by the documented analyses and are reasonably summarised at the end of the submission with the exception that no mention is made that the NMAs show a greater incidence of urinary infections during treatment with SGLT-2is.

The conclusions drawn by the manufacturer may be summarised as follows:
Across all the analyses it appears that the SGLT-2is are of broadly similar efficacy and safety. With regard to HbA1c reduction at 52 weeks, across all three regimens, empagliflozin is at least as effective as its active comparators and clearly superior to placebo. For HbA1c in insulin add on therapy 25 mg empagliflozin appears statistically superior to 10mg (this trend is evident at 24 weeks but not significant) making the comparison of 25 mg empagliflozin versus alternative active interventions more favourable for empagliflozin than in the 10 mg empagliflozin comparisons (note that10 and 25mg packs are equally priced). With regard to weight loss at 52 weeks, across all three regimens,

empagliflozin is at least as effective as other SGLT-2is, is superior to sulphonylurea in dual therapy and to sitagliptin in both dual and triple therapy, Similarly across all three regimens with regard to effects on SBP at 52 weeks empagliflozin appears at least as effective as other SGLT-2is, while in addition is superior to sulphonylurea in dual therapy and to sitagliptin in both dual and triple therapy. Overall the SGLT-2is offer significant weight loss and blood pressure reductions compared to placebo and sulphonylurea. In addition, there is a numerical but not statistically significant advantage compared to the DPP-4is in terms of weight loss and blood pressure.

### 4.1.2 Results of network meta-analysis reported by the manufacturer

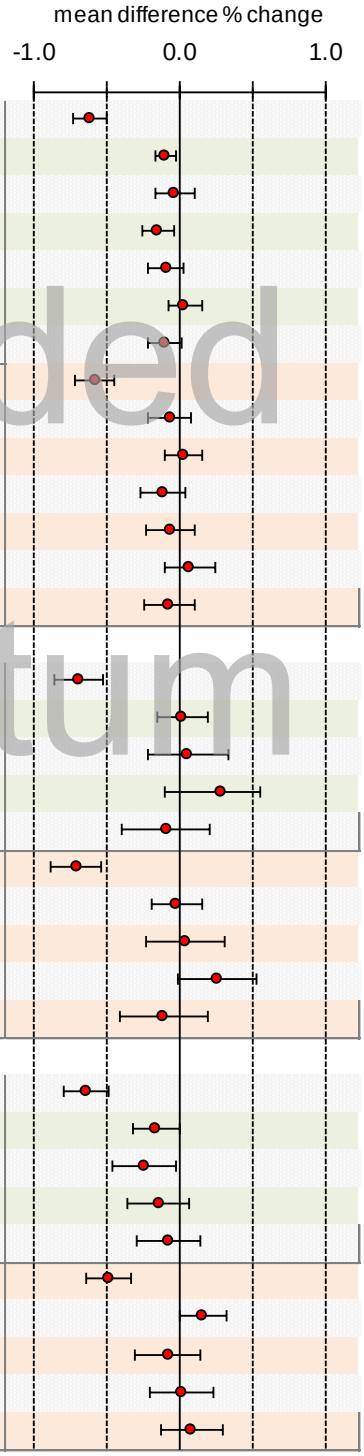
The manufacturer presented NMA results for multiple outcomes in many comparisons for four treatment regimens of which the three summarised here are dual, triple, and add on to insulin regimens.

The outcome statistic for outcomes was either mean difference or relative risk. These are summarised in tables in Appendix 3 but mean differences (or the lack of them) are shown graphically below.

The manufacturer presented the NMA results as effect sizes with upper and lower confidence intervals rounded to two decimal places only. This rounding means that on occasions the lower and upper confidence intervals (LCI and UCI) do not balance evenly each side of the point estimate, this is seen occasionally in the graphical summaries of results. In a few instances the imbalance was greater than might be expected from the rounding process only; the reason for this is unclear.

**Figure 1. Mean difference (MD) in change in HbA1c at 52 weeks in dual, triple and insulin add on therapies.**

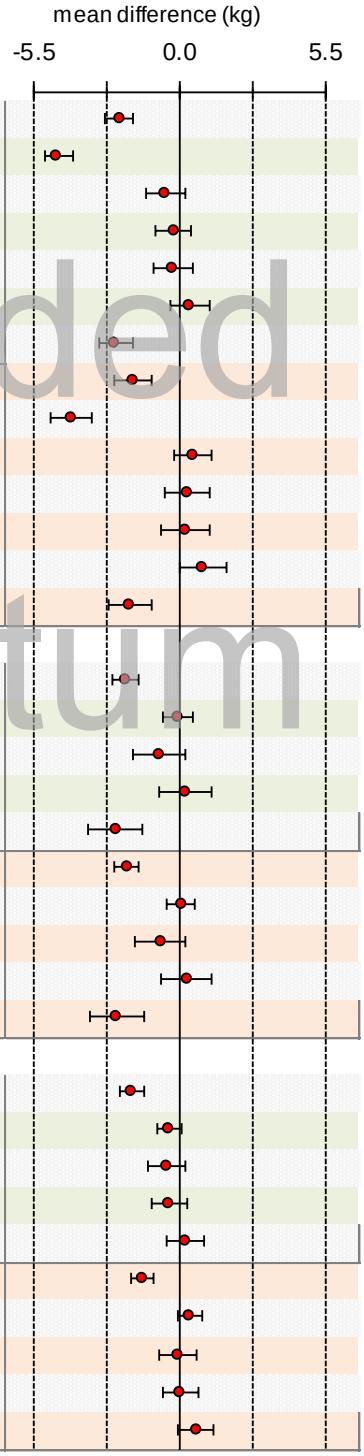
| Therapy | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | -0.62 | -0.73 | -0.5 |
| Dual | empag 25 | Sulphonylurea | -0.1 | -0.17 | -0.02 |
| Dual | empag 25 | Empagliflozin 10mg | -0.03 | -0.16 | 0.1 |
| Dual | empag 25 | Dapagliflozin 10 mg | -0.15 | -0.26 | -0.03 |
| Dual | empag 25 | Canagliflozin 100 mg | -0.09 | -0.21 | 0.03 |
| Dual | empag 25 | Canagliflozin 300 mg | 0.03 | -0.08 | 0.15 |
| Dual | empag 25 | Sitagliptin 100 mg | -0.1 | -0.22 | 0.02 |
| *Dual* | *empag 10* | *placebo* | *-0.58* | *-0.72* | *-0.45* |
| *Dual* | *empag 10* | *Sulphonylurea* | *-0.06* | *-0.21* | *0.08* |
| *Dual* | *empag 10* | *Empagliflozin 25mg* | *0.03* | *0.16* | *-0.1* |
| *Dual* | *empag 10* | *Dapagliflozin 10 mg* | *-0.11* | *-0.27* | *0.04* |
| *Dual* | *empag 10* | *Canagliflozin 100 mg* | *-0.06* | *-0.23* | *0.11* |
| *Dual* | *empag 10* | *Canagliflozin 300 mg* | *0.07* | *-0.1* | *0.24* |
| *Dual* | *empag 10* | *Sitagliptin 100 mg* | *-0.07* | *-0.24* | *0.1* |
| Triple | empag 25 | placebo | -0.69 | -0.86 | -0.52 |
| Triple | empag 25 | Empagliflozin 10mg | 0.02 | 0.19 | -0.15 |
| Triple | empag 25 | Canagliflozin 100mg | 0.06 | 0.33 | -0.21 |
| Triple | empag 25 | Canagliflozin 300mg | 0.28 | 0.55 | -0.1 |
| Triple | empag 25 | Sitagliptin 100mg | -0.09 | 0.21 | -0.39 |
| *Triple* | *empag 10* | *placebo* | *-0.71* | *-0.88* | *-0.54* |
| *Triple* | *empag 10* | *Empagliflozin 25mg* | *-0.02* | *-0.19* | *0.15* |
| *Triple* | *empag 10* | *Canagliflozin 100mg* | *0.04* | *-0.23* | *0.31* |
| *Triple* | *empag 10* | *Canagliflozin 300mg* | *0.26* | *-0.01* | *0.53* |
| *Triple* | *empag 10* | *Sitagliptin 100mg* | *-0.11* | *-0.41* | *0.19* |
| insulin + on | empag 25 | placebo | -0.64 | -0.8 | -0.49 |
| insulin + on | empag 25 | Empagliflozin 10mg | -0.16 | -0.32 | 0 |
| insulin + on | empag 25 | Dapagliflozin2.5mg | -0.24 | -0.46 | -0.02 |
| insulin + on | empag 25 | Dapagliflozin 5mg | -0.14 | -0.36 | 0.07 |
| insulin + on | empag 25 | Dapagliflozin 10mg | -0.07 | -0.29 | 0.14 |
| *insulin + on* | *empag 10* | *placebo* | *-0.48* | *-0.64* | *-0.33* |
| *insulin + on* | *empag 10* | *Empagliflozin 25mg* | *0.16* | *0* | *0.32* |
| *insulin + on* | *empag 10* | *Dapagliflozin2.5mg* | *-0.08* | *-0.3* | *0.14* |
| *insulin + on* | *empag 10* | *Dapagliflozin 5mg* | *0.01* | *-0.2* | *0.23* |
| *insulin + on* | *empag 10* | *Dapagliflozin 10mg* | *0.08* | *-0.13* | *0.3* |




Superseded
See erratum

**Figure 2. Mean difference (MD) in body weight (kg) at 52 weeks in dual, triple and insulin add on therapies.**

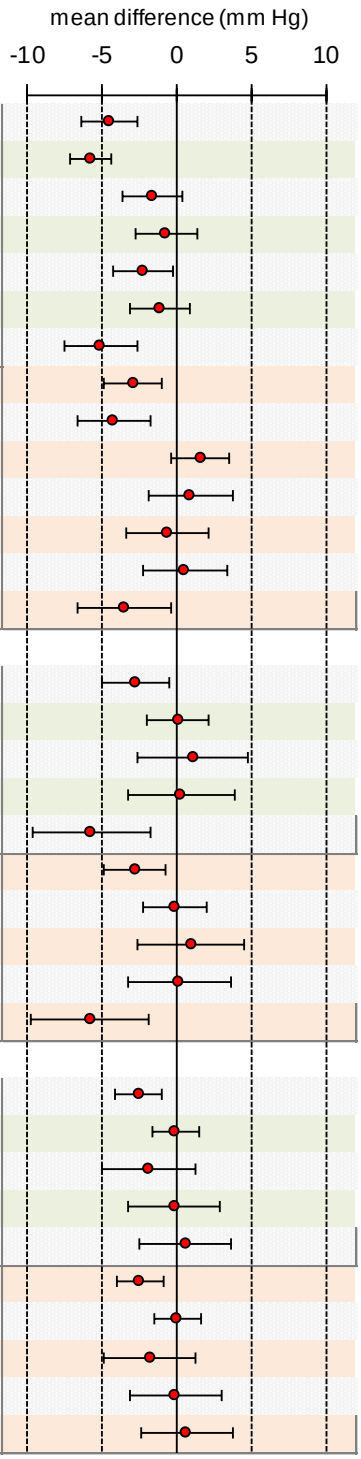
| Therapy | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | -2.28 | -2.83 | -1.72 |
| Dual | empag 25 | Sulphonylurea | -4.62 | -5.11 | -4.03 |
| Dual | empag 25 | Empagliflozin 10mg | -0.52 | -1.24 | 0.22 |
| Dual | empag 25 | Dapagliflozin 10 mg | -0.23 | -0.89 | 0.43 |
| Dual | empag 25 | Canagliflozin 100 mg | -0.29 | -1.01 | 0.49 |
| Dual | empag 25 | Canagliflozin 300 mg | 0.36 | -0.37 | 1.14 |
| Dual | empag 25 | Sitagliptin 100 mg | -2.44 | -3.01 | -1.76 |
| *Dual* | *empag 10* | *placebo* | *-1.76* | *-2.49* | *-1.02* |
| *Dual* | *empag 10* | *Sulphonylurea* | *-4.10* | *-4.84* | *-3.30* |
| *Dual* | *empag 10* | *Empagliflozin 25mg* | *0.52* | *-0.22* | *1.24* |
| *Dual* | *empag 10* | *Dapagliflozin 10 mg* | *0.28* | *-0.54* | *1.12* |
| *Dual* | *empag 10* | *Canagliflozin 100 mg* | *0.22* | *-0.66* | *1.17* |
| *Dual* | *empag 10* | *Canagliflozin 300 mg* | *0.87* | *-0.01* | *1.81* |
| *Dual* | *empag 10* | *Sitagliptin 100 mg* | *-1.92* | *-2.68* | *-1.07* |
| Triple | empag 25 | placebo | -2.05 | -2.56 | -1.55 |
| Triple | empag 25 | Empagliflozin 10mg | -0.05 | -0.59 | 0.49 |
| Triple | empag 25 | Canagliflozin 100mg | -0.77 | -1.75 | 0.19 |
| Triple | empag 25 | Canagliflozin 300mg | 0.22 | -0.74 | 1.20 |
| Triple | empag 25 | Sitagliptin 100mg | -2.42 | -3.45 | -1.38 |
| *Triple* | *empag 10* | *placebo* | *-2.00* | *-2.49* | *-1.51* |
| *Triple* | *empag 10* | *Empagliflozin 25mg* | *0.05* | *-0.49* | *0.59* |
| *Triple* | *empag 10* | *Canagliflozin 100mg* | *-0.72* | *-1.68* | *0.23* |
| *Triple* | *empag 10* | *Canagliflozin 300mg* | *0.28* | *-0.68* | *1.24* |
| *Triple* | *empag 10* | *Sitagliptin 100mg* | *-2.37* | *-3.40* | *-1.35* |
| insulin + on | empag 25 | placebo | -1.81 | -2.26 | -1.36 |
| insulin + on | empag 25 | Empagliflozin 10mg | -0.40 | -0.86 | 0.06 |
| insulin + on | empag 25 | Dapagliflozin2.5mg | -0.46 | -1.17 | 0.25 |
| insulin + on | empag 25 | Dapagliflozin 5mg | -0.38 | -1.08 | 0.33 |
| insulin + on | empag 25 | Dapagliflozin 10mg | 0.23 | -0.48 | 0.93 |
| *insulin + on* | *empag 10* | *placebo* | *-1.41* | *-1.82* | *-1.00* |
| *insulin + on* | *empag 10* | *Empagliflozin 25mg* | *0.40* | *-0.06* | *0.86* |
| *insulin + on* | *empag 10* | *Dapagliflozin2.5mg* | *-0.06* | *-0.74* | *0.62* |
| *insulin + on* | *empag 10* | *Dapagliflozin 5mg* | *0.02* | *-0.65* | *0.70* |
| *insulin + on* | *empag 10* | *Dapagliflozin 10mg* | *0.63* | *-0.05* | *1.31* |




Superseded
See erratum

**Figure 3. Mean difference (MD) in change systolic blood pressure at 52 weeks in dual, triple and insulin add on therapies.**

| Therapy | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | -4.49 | -6.44 | -2.57 |
| Dual | empag 25 | Sulphonylurea | -5.80 | -7.19 | -4.41 |
| Dual | empag 25 | Empagliflozin 10mg | -1.60 | -3.56 | 0.34 |
| Dual | empag 25 | Dapagliflozin 10 mg | -0.70 | -2.78 | 1.41 |
| Dual | empag 25 | Canagliflozin 100 mg | -2.23 | -4.24 | -0.23 |
| Dual | empag 25 | Canagliflozin 300 mg | -1.07 | -3.07 | 0.94 |
| Dual | empag 25 | Sitagliptin 100 mg | -5.09 | -7.56 | -2.63 |
| *Dual* | *empag 10* | *placebo* | *-2.89* | *-4.84* | *-0.94* |
| *Dual* | *empag 10* | *Sulphonylurea* | *-4.20* | *-6.58* | *-1.79* |
| *Dual* | *empag 10* | *Empagliflozin 25mg* | *1.60* | *-0.34* | *3.56* |
| *Dual* | *empag 10* | *Dapagliflozin 10 mg* | *0.90* | *-1.91* | *3.78* |
| *Dual* | *empag 10* | *Canagliflozin 100 mg* | *-0.63* | *-3.42* | *2.15* |
| *Dual* | *empag 10* | *Canagliflozin 300 mg* | *0.54* | *-2.26* | *3.35* |
| *Dual* | *empag 10* | *Sitagliptin 100 mg* | *-3.49* | *-6.62* | *-0.34* |
| Triple | empag 25 | placebo | -2.72 | -4.94 | -0.48 |
| Triple | empag 25 | Empagliflozin 10mg | 0.09 | -1.98 | 2.19 |
| Triple | empag 25 | Canagliflozin 100mg | 1.10 | -2.60 | 4.77 |
| Triple | empag 25 | Canagliflozin 300mg | 0.28 | -3.27 | 3.88 |
| Triple | empag 25 | Sitagliptin 100mg | -5.70 | -9.69 | -1.68 |
| *Triple* | *empag 10* | *placebo* | *-2.80* | *-4.89* | *-0.72* |
| *Triple* | *empag 10* | *Empagliflozin 25mg* | *-0.09* | *-2.19* | *1.98* |
| *Triple* | *empag 10* | *Canagliflozin 100mg* | *1.00* | *-2.59* | *4.59* |
| *Triple* | *empag 10* | *Canagliflozin 300mg* | *0.20* | *-3.28* | *3.69* |
| *Triple* | *empag 10* | *Sitagliptin 100mg* | *-5.79* | *-9.74* | *-1.86* |
| insulin + on | empag 25 | placebo | -2.51 | -4.07 | -0.93 |
| insulin + on | empag 25 | Empagliflozin 10mg | -0.05 | -1.61 | 1.52 |
| insulin + on | empag 25 | Dapagliflozin2.5mg | -1.84 | -4.97 | 1.22 |
| insulin + on | empag 25 | Dapagliflozin 5mg | -0.12 | -3.21 | 2.95 |
| insulin + on | empag 25 | Dapagliflozin 10mg | 0.60 | -2.47 | 3.70 |
| *insulin + on* | *empag 10* | *placebo* | *-2.45* | *-4.03* | *-0.88* |
| *insulin + on* | *empag 10* | *Empagliflozin 25mg* | *0.05* | *-1.52* | *1.61* |
| *insulin + on* | *empag 10* | *Dapagliflozin2.5mg* | *-1.79* | *-4.91* | *1.28* |
| *insulin + on* | *empag 10* | *Dapagliflozin 5mg* | *-0.07* | *-3.16* | *3.01* |
| *insulin + on* | *empag 10* | *Dapagliflozin 10mg* | *0.65* | *-2.42* | *3.74* |



# 5 Cost effectiveness

## *5.1 ERG comment on manufacturer's review of cost-effectiveness evidence*

Not applicable.

## *5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG*

### 5.2.1 NICE reference case checklist

| Attribute | Reference case and TA Methods guidance | 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.<br><br>The scope specifies as add-on to metformin:<br>• sulfonylurea<br>• pioglitazone<br>• DPP-IV<br>• GLP-1<br>• dapagliflozin<br><br>The scope also suggests consideration of therapy as an add-on to sulfonylurea.<br><br>The scope specifies as add-on to metformin plus SU:<br>• pioglitazone<br>• DPP-IV<br>• GLP-1<br>• Insulin<br><br>The scope specifies as add-on to metformin plus TZD: | <br><br><br>The submission examines add-on to metformin:<br>• sulfonylurea is not considered<br>• pioglitazone is not considered<br>• sitagliptin 100mg<br>• GLP-1 is not considered<br>• dapagliflozin 10mg<br>• canagliflozin 100mg<br>• canagliflozin 300mg<br><br><br>The submission examines add-on to metformin:<br>• pioglitazone is not considered<br>• sitagliptin 100mg<br>• GLP-1 is not considered<br>• canagliflozin 100mg<br>• canagliflozin 300mg<br>• Insulin is not considered at this line<br><br>The submission examines add-on to metformin: |

| | | |
|---|---|---|
| | • DPP-IV<br>• GLP-1<br>• Insulin<br><br>Note that the scope also suggests that there could be add-ons to metformin plus a DPP-IV and metformin plus a GLP-1.<br><br>The scope specifies as add-on to insulin. | • sitagliptin 100mg<br>• GLP-1 is not considered<br>• canagliflozin 100mg<br>• canagliflozin 300mg<br>• Insulin is not considered at this line<br><br>The submission examines add-on to insulin. |
| **Patient group** | As per NICE scope. | Yes. |
| **Perspective costs** | NHS & Personal Social Services | Yes. |
| **Perspective benefits** | All health effects on individuals | Yes. |
| **Form of economic evaluation** | Cost-effectiveness analysis | Yes. |
| **Time horizon** | Sufficient to capture differences in costs and outcomes | Yes. Lifetime. |
| **Synthesis of evidence on outcomes** | Systematic review | Yes. Systematic review coupled with network meta-analysis. |
| **Outcome measure** | Quality adjusted life years | Yes. |
| **Health states for QALY** | Described using a standardised and validated instrument | Yes. Both the UKPDS 65 and Sullivan et al (2012) use the EQ-5D. These cover the quality of life values for being complication free and the main diabetes related complications.<br><br>But there are additional quality of life estimates for some other elements of the CORE model, such as retinopathy and ulcer, which have not been checked by the ERG. |
| **Benefit valuation** | Time trade off or standard gamble | Both the UKPDS 65 and Sullivan et al (2012) use the standard UK social tariff which is based upon time trade off. |
| **Source of preference data for valuation of changes in** | Representative sample of the public | Yes. The standard UK social tariff is based upon a representative sample |

| | | |
|---|---|---|
| **HRQL** | | of the UK general public. |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes. |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes. |
| **Probabilistic modelling** | Probabilistic modelling | Partial. This appears to have only been presented for a subset of comparisons. |
| **Sensitivity analysis** | | One way sensitivity analyses around convergence of BMI over time and there being no SBP effect are presented. |

The ACD recommended revised estimation of the incremental cost-effectiveness ratios of empagliflozin using a validated economic model, informed by the corrected results of network meta-analyses and compared with relevant comparators.

### 5.2.2 Model structure

The CORE model is an individual patient level microsimulation model with an annual cycle which simulates the incidence of the complications of diabetes based upon patient baseline characteristics and the treatment's initial impact upon the various risk factors:

- HbA1c
- Systolic blood pressure (SBP)
- total cholesterol
- low density lipoprotein (LDL) cholesterol
- triglycerides
- body mass index (BMI)
- renal functioning

For the current modelling, treatment effects upon these are limited to HBA1c, SBP and BMI, as drawn from the network meta-analysis. Treatments are also associated with adverse events, these encompassing non-severe hypos, severe hypos, urinary tract infections (UTIs) and genital tract infections (GTIs).

A treatment can also be associated with a switch in therapy based upon the HbA1c being simulated as exceeding in this case 7.5%. For the current modelling, change of therapy causes the patient to switch

to insulin which is associated with a change in costs and an increase in the patient's BMI and adverse events falling to zero, but no other clinical effects.

The evolution of the risk factors within CORE coupled with the contemporaneous patient characteristics results in annual probabilities of the complications of diabetes being calculated: fatal and non-fatal myocardial infraction, fatal and non-fatal stroke, angina, congestive heart failure, peripheral vascular disease, microalbuminuria, gross proteinuria, haemodialysis, diabetic retinopathy, cataract, macular oedema, severe vision loss, neuropathy, ulcer and amputation. It is then randomly assessed whether one or more events happen to the patient during that model cycle. Diabetes related deaths and general mortality is also modelled.

### 5.2.3 Population

Patients with type 2 diabetes that is uncontrolled on their current therapy.

### 5.2.4 Interventions and comparators

For add-on to metformin, empagliflozin 10 mg and 25 mg are compared with:

- dapagliflozin 10 mg
- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to metformin plus sulfonylurea, empagliflozin 10 mg and 25 mg are compared with:

- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to metformin plus thiazolidinedione, empagliflozin 10 mg and 25 mg are compared with:

- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

For add-on to insulin, empagliflozin 10 mg and 25 mg are compared with:

- dapagliflozin 10 mg
- sitagliptin 100 mg
- canagliflozin 100 mg
- canagliflozin 300 mg

### 5.2.5 Perspective, time horizon and discounting

The model adopts the NHS and PSS perspective for costs and the patient perspective for health impacts.

A lifetime horizon is adopted and costs and benefits are discounted at 3.5%.

### 5.2.6 Treatment effectiveness and extrapolation

The treatment effectiveness estimates are largely based upon the network meta-analysis of the clinical effectiveness section. The ERG is unclear about the derivation of the rates of GTIs.

Extrapolation is based upon the CORE model. This is a black box to the ERG.

### 5.2.7 Health related quality of life

Health related quality of life values for survival without complications and the main complications of diabetes are mainly drawn from the UKPDS 62[3] with some additional values being drawn from Sullivan et al (2011)[4] as highlighted in the table below. The coefficients of the first column are drawn from the UKPDS 62, while the quality of life values of the second column are the impact they would have upon a baseline quality of life in the absence of complications of 0.814.

**Table 1. Quality of life values: UKPDS 62 and the current submission**

| | UKPDS 62 EQ-5D | | Submission |
|---|---|---|---|
| | Coef. | QoL | Current |
| Constant | 0.814 | 0.814 | 0.814 |
| MI | | | |
| Previous year | -0.129 | 0.685 | **-0.055** |
| Prior to previous year | -0.078 | 0.736 | 0.736 |
| IHD | | | |
| Previous year | -0.205 | 0.609 | 0.682 |
| Prior to previous year | -0.132 | 0.682 | 0.682 |
| Stroke | | | |
| Previous year | -0.181 | 0.633 | **-0.164** |
| Prior to previous year | -0.269 | 0.545 | 0.545 |
| HF | | | |
| Previous year | -0.121 | 0.693 | 0.633 |
| Prior to previous year | -0.181 | 0.633 | 0.633 |
| Amp | | | |
| Previous year | -0.538 | 0.276 | **-0.280** |

| | | | |
|---|---|---|---|
| Prior to previous year | -0.412 | 0.402 | 0.402 |
| Blind one eye/SVL | | | |
| Previous year | -0.094 | 0.720 | 0.670 |
| Prior to previous year | -0.112 | 0.702 | 0.670 |

Note that in the above the values for blind in one eye relate to the UKPDS 62 while CORE applies the 0.670 value to severe visual loss.

For adverse events the submission applies the following quality of life decrements.

**Table 2. Quality of life associated with adverse events**

| | QoL |
|---|---|
| Severe hypo | -0.0118 |
| Non-severe hypo | -0.0035 |
| GTI event | -0.0028 |
| UTI event | -0.0028 |
| Post UTI event | 0.8168 |

The quality of life decrements for the adverse events are the same as those used in the original submission.

The ERG is unclear about the precise meaning of the quality of life value for the post UTI event. The ERG assumes that it means in years subsequent to a UTI the patient will experience a quality of life of 0.8168. But this has to be read in conjunction with the implementation of quality of life within CORE. Apparently, if there are a number of competing quality of life values due to a patient having multiple complications the quality of life value for the complication with the largest quality of life impact is applied and the others are discarded. So if the patient is post UTI but has other complications, it seems that the quality of life value of one of the complications will be applied rather than the post UTI quality of life. But it remains unclear what applies to a patient with no complications who is post UTI. The ERG has no means of assessing whether they have the baseline 0.814 quality of life value applied or the post UTI 0.8168 quality of life value applied, which would be an improvement on the 0.814 baseline value.

The CORE model also associates a quality of life change of 0.0038125 with each BMI point change above a BMI of 25 $kgm^{-2}$. It appears that this is symmetrically applied in that weight decreases result in a utility gain and weight increases result in a utility loss, always assuming that the patient is above 25$kgm^{-2}$.

### 5.2.8 Resources and costs

*Direct drug costs*

The direct drug costs are as below:

**Table 3. Direct drug costs**

| | Annual cost |
|---|---|
| Empagliflozin 10 | £477.30 |
| Empagliflozin 25 | £477.30 |
| Canagliflozin 100 mg | £477.26 |
| Canagliflozin 300 mg | £608.63 |
| Dapagliflozin 10mg | £477.30 |
| Sitagliptin 100 mg | £433.86 |

*The costs of diabetes and its complications*

The costs of diabetes and its complications are mainly drawn from the UKPDS 65,[5] as outlined below.

**Table 4. Costs of the main complications of diabetes**

| | Incidence year | Subsequent year |
|---|---|---|
| No complication | £0 | £0 |
| Incident year | | |
| Fatal MI | £2,511 | .. |
| Non-fatal MI | £8,179 | £5,733 |
| Fatal stroke | £6,774 | .. |
| Non-fatal stroke | £10,932 | £4,760 |
| IHD | £7,628 | £1,204 |
| CHF | £6,773 | £6,566 |
| Blind in one eye | £7,003 | £4,720 |
| Amputation | £13,556 | .. |

As far as the ERG can ascertain, there is no annual management costs for diabetes in the absence of complications. For these patients it appears that only the direct drug costs apply.

Within CORE it appears that amputation is only associated with a cost in the year of incidence.

Severe hypoglycaemia is associated with a £90 cost. UTIs and GTI are associated with a £36 cost, this being in line with a single GP consultation.

### 5.2.9 Cost effectiveness results

The pairwise comparisons often assume a different clinical effectiveness for the comparator when compared with empagliflozin 10 mg and when compared with empagliflozin 25 mg. Due to data deficiencies, the comparator is often assumed to have the same clinical effectiveness for a parameter as empagliflozin 10 mg or as empagliflozin 25 mg depending upon which pairwise comparison is being made. This complicates the presentation of results. The approach adopted by the ERG is to first present the results assuming that the comparators have the clinical effectiveness estimates of the comparisons with empagliflozin 10 mg, and then to present the results assuming that the comparators have the clinical effectiveness estimates of the comparisons with empagliflozin 25 mg. Note that across all these comparisons the clinical effectiveness estimates for empagliflozin 10 mg and 25 mg remain unchanged.

Given the above approach, for the deterministic modelling it is possible to present all comparators alongside one another and derive the relevant incremental cost-effectiveness ratios (ICERs) and when dominance and extended dominance applies.

The ACD recommended that further analyses should include probabilistic exploration of parameter uncertainty. CORE has the facility to apply 2$^{nd}$ order sampling and the manufacturer has submitted the results of a number of probabilistic modelling exercises for the various pairwise comparisons undertaken. For reasons that are unclear, the set of these appears to be incomplete as outlined in the following table.

**Table 5. Probabilistic modelling presented for empagliflozin 10mg and 25mg**

| | +MET | +MET+SU | +MET+TZD | +INS |
|---|---|---|---|---|
| vs dapagliflozin 10mg | ✓ | n.applicable | n.applicable | ✓ |
| vs sitagliptin 100mg | ✓ | ✓ | ✓ | ✓ |
| vs canagliflozin 100mg | × | ✓ | ✓ | × |
| vs canagliflozin 300mg | × | ✓ | ✓ | × |

Due to CORE only permitting pairwise comparisons, the results of the probabilistic modelling are similarly based upon pairwise comparisons. The ERG had hoped that it would be possible to link the individual iterations of simulations by a common comparator. For instance, one iteration of a simulation of empagliflozin 10 mg compared with canagliflozin 100 mg could be linked with confidence to the corresponding iteration of a simulation of empagliflozin 10 mg compared with canagliflozin 300 mg due to the common absolute values for costs and quality adjusted life years (QALYs) in the empagliflozin 10 mg arm. But unfortunately the probabilistic sensitivity analysis

(PSA) output of CORE is limited to incremental QALYs and incremental costs and as a consequence there is no way to link iterations between pairwise comparisons.

As a consequence, for the probabilistic modelling it is not possible to present all comparators alongside one another and derive the Cost Effectiveness Acceptability Frontier (CEAF) - Box 1. This is something of a limitation. In the opinion of the ERG, due to what are at times quite limited absolute differences between some comparators in the deterministic modelling, a consideration of the likelihood of one treatment being the most cost effective based upon the probabilistic modelling may be quite important to this assessment.

**Box 1. CEAFs**

**Cost effectiveness acceptability frontiers**

For a given willingness to pay of pay $\lambda$, for a treatment with $Q_A$ QALYs and $C_A$ costs the monetised health benefits net of costs are calculated as $\lambda Q_A - C_A$. In deterministic analyses the treatment with the highest health benefits is the most cost effective.

Probabilistic analyses over N iterations generate a scatterplot of points on the cost effectiveness plane. For a given willingness to pay, for each iteration each treatment has a health benefit associated with it.

The cost effectiveness acceptability curve (CEAC) shows which treatment has the highest probability of being cost effective. In other words, for a given willingness to pay the CEAC portrays the treatment that has the highest number of iterations where it is estimated to be the most cost effective, with the height of the CEAC being this proportion.

The cost effectiveness acceptability frontier (CEAF) shows the probability of the treatment with the highest expected health benefit being the most cost effective. In other words, for a given willingness to pay, for each iteration the health benefit of each treatment is calculated. These health benefits are averaged across the iterations to find the treatment which has the highest expected health benefit. For a given willingness to pay, the CEAF portrays the treatment that has the highest expected health benefit with the height of the CEAF being the number of iterations where this treatment is estimated to be the most cost effective expressed as a proportion of the total number of iterations.

Given continuous distributions, the CEAC and the CEAF are usually quite similar. One reason for them differing is due to unlikely events having a large impact. For instance, the treatment A might uniquely among the comparators have a probability of curing patients. The probability of a cure with treatment A may be very small, but if patients are cured it results in a very large QALY gain. The small probability of this occurring will not unduly affect the CEAC as this just reflects the proportions within the iterations. At a certain willingness to pay another treatment B may be judged to have a greater probability of being the most cost effective and so at this point the CEAC would relate to treatment B. But at the same willingness to pay the unlikely outcome of a cure and resulting very large QALY gain with treatment A may be sufficient for it to have the highest expected health benefit, despite it not being the treatment that has the highest probability of being cost effective. So at this point the CEAF would relate to treatment A and would lie below the CEAC.

It can be argued that decision making should seek to maximise net health benefits by choosing the treatment with the highest expected health benefits. So decisions should be based upon the CEAF

rather than the CEAC. But if the CEAF lies considerably below the CEAC at the relevant willingness to pay threshold, this may not be so clear cut. Decision makers may prefer the greater certainty of another treatment if it appears that this does not sacrifice too much net health benefits.

In the light of the deterministic modelling results, the ERG has also presented the cost-effectiveness acceptability curve (CEAC) derived from the pairwise comparisons of empagliflozin 25 mg with canagliflozin 300 mg. This comparison is the most challenging for empagliflozin within the manufacturer modelling results, and as a consequence could be argued to be of the most interest to committee. But it should be recognised that this is partial and that CEAFs would form a more reasonable basis for decision making. Viewed in isolation, these CEACs may paint an unduly polarised picture in the context of a decision-making process with a number of other comparators that have been approved by NICE. The manufacturer cost effectiveness estimates for empagliflozin against these comparators are somewhat better than that against canagliflozin 300 mg. Section 7 of the economics of the submission presents the available pairwise CEACs.

*Base case results: Add-on to metformin*

The following presents the base case deterministic results for the patient population having therapy added to metformin. Note that some of the differences in both costs and QALYs are very small, creating considerable uncertainties around the ICERs.

**Table 6. Results: add-on to MET: empag. 10mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,903 | £5,920 | £5,889 | £5,713 | £5,889 | £6,411 |
| Management | £1,030 | £1,033 | £1,029 | £1,025 | £1,029 | £1,032 |
| Complications | £54,828 | £54,582 | £54,691 | £55,040 | £54,801 | £54,469 |
| Total | £61,761 | £61,535 | £61,609 | £61,778 | £61,719 | £61,912 |
| LYs (undiscounted) | 19.915 | 19.983 | 19.897 | 19.769 | 19.879 | 19.969 |
| QALYs | 7.963 | 7.995 | 7.964 | 7.899 | 7.955 | 7.990 |

**Table 7. Cost effectiveness: add-on to MET: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,535 | | 7.995 | | |
| Dapagliflozin 10mg | £61,609 | £74 | 7.964 | -0.031 | Dominated |
| Canagliflozin 100mg | £61,719 | £184 | 7.955 | -0.040 | Dominated |

| | | | | | |
|---|---|---|---|---|---|
| Empagliflozin 10mg | £61,761 | £226 | 7.963 | -0.032 | Dominated |
| Sitagliptin 100mg | £61,778 | £243 | 7.899 | -0.096 | Dominated |
| Canagliflozin 300mg | £61,912 | £377 | 7.990 | -0.005 | Dominated |

**Table 8. Results: add-on to MET: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,903 | £5,920 | £5,889 | £5,713 | £5,886 | £6,409 |
| Management | £1,030 | £1,033 | £1,029 | £1,025 | £1,028 | £1,032 |
| Complications | £54,828 | £54,582 | £54,691 | £55,040 | £54,729 | £54,388 |
| Total | £61,761 | £61,535 | £61,609 | £61,778 | £61,643 | £61,829 |
| LYs (undiscounted) | 19.915 | 19.983 | 19.897 | 19.769 | 19.859 | 19.954 |
| QALYs | 7.963 | 7.995 | 7.964 | 7.899 | 7.949 | 7.986 |

**Table 9. Cost effectiveness: add-on to MET: empagliflozin 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,535 | | 7.995 | | |
| Dapagliflozin 10mg | £61,609 | £74 | 7.964 | -0.031 | Dominated |
| Canagliflozin 100mg | £61,643 | £108 | 7.949 | -0.046 | Dominated |
| Empagliflozin 10mg | £61,761 | £226 | 7.963 | -0.032 | Dominated |
| Sitagliptin 100mg | £61,778 | £243 | 7.899 | -0.096 | Dominated |
| Canagliflozin 300mg | £61,829 | £294 | 7.986 | -0.009 | Dominated |

For reasons that are not clear, no probabilistic modelling for the comparison of empagliflozin 25 mg with canagliflozin 300 mg appears to have been presented for this patient population.

*Base case results: Add-on to metformin plus sulphonylurea*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus sulphonylurea.

**Table 10. Results: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,778 | £5,770 | £5,572 | £5,788 | £6,363 |
| Management | £990 | £988 | £983 | £991 | £994 |

| | | | | | |
|---|---|---|---|---|---|
| Complications | £52,010 | £51,953 | £52,835 | £52,015 | £51,643 |
| Total | £58,778 | £58,711 | £59,390 | £58,794 | £59,000 |
| LYs (undiscounted) | 18.813 | 18.78 | 18.624 | 18.837 | 18.921 |
| QALYs | 7.571 | 7.564 | 7.466 | 7.569 | 7.616 |

**Table 11. Cost effectiveness: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £58,711 | | 7.564 | | |
| Empagliflozin 10mg | £58,778 | £67 | 7.571 | 0.007 | £9,571 |
| Canagliflozin 100mg | £58,794 | £16 | 7.569 | -0.002 | Dominated |
| Canagliflozin 300mg | £59,000 | £222 | 7.616 | 0.045 | £4,933 |
| Sitagliptin 100mg | £59,390 | £390 | 7.466 | -0.150 | Dominated |

The above does not consider extended dominance. It appears that empagliflozin 10 mg is extended dominated by canagliflozin 300 mg. For the pairwise comparison of canagliflozin 300 mg with empagliflozin 25 mg, canagliflozin 300 mg results in an additional cost of £289 but also results in an additional 0.052 QALYs, yielding a cost effectiveness estimate of £5,558 per QALY.

**Table 12. Results: add-on to MET+SU: empag. 25mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,778 | £5,770 | £5,572 | £5,788 | £6,363 |
| Management | £990 | £988 | £983 | £991 | £994 |
| Complications | £52,010 | £51,953 | £52,835 | £52,015 | £51,643 |
| Total | £58,778 | £58,711 | £59,390 | £58,794 | £59,000 |
| LYs (undiscounted) | 18.813 | 18.78 | 18.624 | 18.837 | 18.921 |
| QALYs | 7.571 | 7.564 | 7.467 | 7.569 | 7.616 |

**Table 13. Cost effectiveness: add-on to MET+SU: empag. 25mg comparator effectiveness**

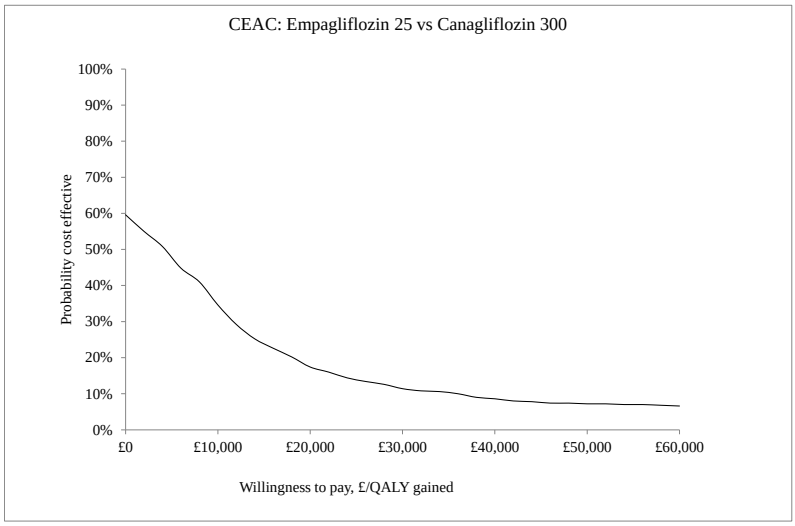
| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £58,711 | | 7.564 | | |
| Empagliflozin 10mg | £58,778 | £67 | 7.571 | 0.007 | £9,571 |
| Canagliflozin 100mg | £58,794 | £16 | 7.569 | -0.002 | Dominated |
| Canagliflozin 300mg | £59,000 | £222 | 7.616 | 0.045 | £4,933 |
| Sitagliptin 100mg | £59,390 | £390 | 7.467 | -0.149 | Dominated |

It appears that empagliflozin 10 mg is extended dominated by canagliflozin 300 mg. For the pairwise comparison of canagliflozin 300 mg with empagliflozin 25 mg, canagliflozin 300 mg results in an

additional cost of £289 but also results in an additional 0.052 QALYs, yielding a cost effectiveness estimate of £5,558 per QALY. This is lower than the £9,571 per QALY of empagliflozin 10 mg compared to empagliflozin 25 mg, so canagliflozin 300 mg is more preferred over empagliflozin 25 mg than empagliflozin 10 mg.

For the probabilistic modelling over 500 iterations the central estimates of the pairwise comparison are a net cost of £124 and a net gain of 0.048 QALYs from canagliflozin 300 mg over empagliflozin 25 mg, resulting in a central cost effectiveness estimate of £2,572 per QALY. This compares with the deterministic estimate of £5,558 per QALY. The CEAC for this comparison is presented below with the probabilities being the probabilities of empagliflozin being the most cost effective.

**Figure 4. CEAC: add-on to MET+SU: empag. 25mg vs canag. 300mg**




| WTP | Prob c/e |
|---|---|
| £0 | 60% |
| £10,000 | 35% |
| £20,000 | 17% |
| £30,000 | 11% |
| £40,000 | 9% |
| £50,000 | 7% |

*Base case results: Add-on to metformin plus thiazolidinedione*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus thiazolidinedione.

**Table 14. Results: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,792 | £5,820 | £5,679 | £5,830 | £6,360 |
| Management | £986 | £988 | £989 | £989 | £991 |
| Complications | £52,388 | £52,046 | £51,976 | £51,932 | £51,755 |
| Total | £59,166 | £58,854 | £58,644 | £58,751 | £59,106 |
| LYs (undiscounted) | 18.723 | 18.767 | 18.822 | 18.791 | 18.849 |
| QALYs | 7.542 | 7.561 | 7.553 | 7.579 | 7.614 |

**Table 15. Cost effectiveness: add-on to MET+TZD: empag. 10mg comparator effectiveness**

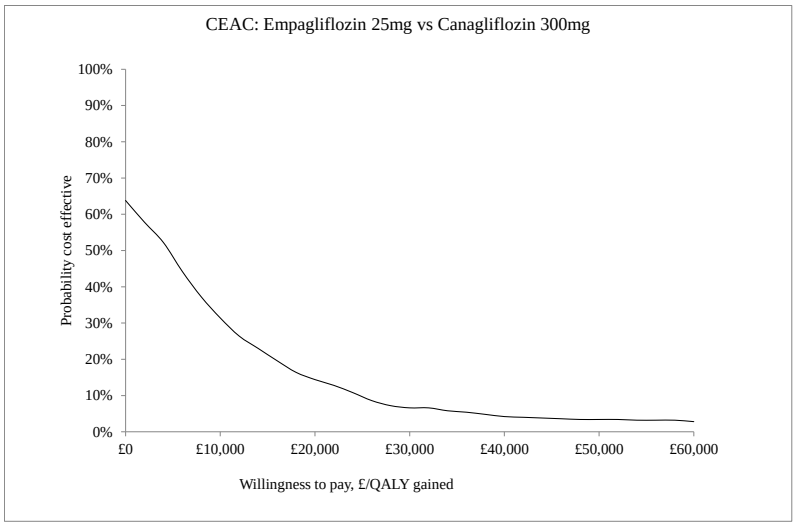
| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Sitagliptin 100mg | £58,644 | | 7.553 | | |
| Canagliflozin 100mg | £58,751 | £107 | 7.579 | 0.026 | £4,115 |
| Empagliflozin 25mg | £58,854 | £103 | 7.561 | -0.018 | Dominated |
| Canagliflozin 300mg | £59,106 | £355 | 7.614 | 0.035 | £10,143 |
| Empagliflozin 10mg | £59,166 | £60 | 7.542 | -0.072 | Dominated |

Comparing canagliflozin 300 mg with empagliflozin 25 mg, there is a net additional cost of £252 and a net gain of 0.053 QALYs. This results in a cost effectiveness estimate for canagliflozin 300 mg versus empagliflozin 25mg of £4,755 per QALY.

The cost effectiveness results that use the clinical effectiveness estimates for the comparators based upon the empagliflozin 25 mg comparison appear to be identical to the above. It would be anticipated that there should be some minor differences for sitagliptin due to the slight differences in non-severe hypoglycaemia. But these differences are slight and may be sufficiently slight not to be reflected in the above.

For the probabilistic modelling over 500 iterations the central estimates of the pairwise comparison are net cost of £190 and a net gain of 0.050 QALYs from canagliflozin 300 mg over empagliflozin 25mg, resulting in a central cost effectiveness estimate of £3,785 per QALY. This compares with the deterministic estimate of £4,755 per QALY. The CEAC for this comparison is presented below with the probabilities being the probabilities of empagliflozin being the most cost effective.

**Figure 5. CEAC: add-on to MET+TZD: empag. 25mg vs canag. 300mg**




| WTP | Prob c/e |
|---|---|
| £0 | 64% |
| £10,000 | 31% |
| £20,000 | 14% |
| £30,000 | 7% |
| £40,000 | 4% |
| £50,000 | 3% |

*Base case results: Add-on to insulin*

The following presents the base case deterministic results for the patient population having therapy added to insulin.

**Table 16. Results: add-on to INS: empag. 10mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £7,046 | £7,095 | £7,095 | £6,952 | £7,133 | £7,679 |
| Management | £986 | £987 | £987 | £987 | £988 | £991 |
| Complications | £52,507 | £52,346 | £52,278 | £52,625 | £52,114 | £51,929 |
| Total | £60,539 | £60,428 | £60,360 | £60,564 | £60,235 | £60,599 |
| LYs (undiscounted) | 18.718 | 18.744 | 18.753 | 18.758 | 18.77 | 18.852 |
| QALYs | 7.523 | 7.534 | 7.545 | 7.511 | 7.545 | 7.583 |

**Table 17. Cost effectiveness: add-on to INS: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,235 | | 7.545 | | |
| Dapagliflozin 10mg | £60,360 | £125 | 7.545 | 0.000 | Dominated |
| Empagliflozin 25mg | £60,428 | £193 | 7.534 | -0.011 | Dominated |
| Empagliflozin 10mg | £60,539 | £304 | 7.523 | -0.022 | Dominated |
| Sitagliptin 100mg | £60,564 | £329 | 7.511 | -0.034 | Dominated |
| Canagliflozin 300mg | £60,599 | £364 | 7.583 | 0.038 | £9,579 |

**Table 18. Results: add-on to INS: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £7,046 | £7,095 | £7,095 | £6,945 | £7,137 | £7,681 |
| Management | £986 | £987 | £987 | £986 | £988 | £991 |
| Complications | £52,507 | £52,346 | £52,278 | £52,599 | £52,208 | £51,804 |
| Total | £60,539 | £60,428 | £60,360 | £60,530 | £60,333 | £60,476 |
| LYs (undiscounted) | 18.718 | 18.744 | 18.753 | 18.713 | 18.785 | 18.852 |
| QALYs | 7.523 | 7.534 | 7.545 | 7.499 | 7.551 | 7.584 |

**Table 19. Cost effectiveness: add-on to INS: empag. 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,333 | | 7.551 | | |
| Dapagliflozin 10mg | £60,360 | £27 | 7.545 | -0.006 | Dominated |
| Empagliflozin 25mg | £60,428 | £95 | 7.534 | -0.017 | Dominated |
| Canagliflozin 300mg | £60,476 | £143 | 7.584 | 0.033 | £4,333 |
| Sitagliptin 100mg | £60,530 | £54 | 7.499 | -0.085 | Dominated |
| Empagliflozin 10mg | £60,539 | £63 | 7.523 | -0.061 | Dominated |

For reasons that are not clear, no probabilistic model for the comparison of empagliflozin 10 mg with canagliflozin 300 mg appears to have been presented for this patient population.

### 5.2.10 Sensitivity analyses

Two sensitivity analyses are presented. One models BMI converging over a period of around 10 years. This tends to slightly reduce the QALY gains of the more effective treatment so worsening the ICERs from those reported above. But results are largely qualitatively the same as the base case analyses. For reasons of space the full results are presented in appendix ECON1, with only a summary being presented below.

The other sensitivity analysis assumes no SBP reduction from sitagliptin, while retaining the SBP reduction from empagliflozin[1]. The other comparators are not considered within this sensitivity

[1] This is based upon an examination of the simulation *BI-Empagliflozin re-Analysis NICE-UK-Population IV, Empa 25mg vs. Sita 100mg (NoSBP Effect in Sita)*, the treatment algorithm modules *BI_RA_Empa25_INS_BaseCase* and *BI_RA_Sita100_INS_vs_Empa25_No_SBP_Effect* within it and their

analyses. These sensitivity analyses are only performed when there was no NMA evidence of a difference in SBP effect between empagliflozin and sitagliptin: as add-on to metformin plus a thiazolidinedione and as add-on to insulin.

*Sensitivity analysis: BMI convergence: Add-on to metformin*
Results are qualitatively unchanged, though there are slight increases in the net costs of the comparators over empagliflozin 25 mg. Empagliflozin 25 mg remains dominant over the comparators within the modelling.

*Sensitivity analysis: BMI convergence: Add-on to metformin plus sulfonylurea*
For the analyses based upon the comparator clinical effectiveness estimates from the empagliflozin 10mg comparisons the sensitivity analysis changes the ordering of treatment by total costs. Canagliflozin 100 mg becomes the least costly and as a consequence it dominates empagliflozin 10 mg, saving £15 but also resulting in an additional 0.025 QALYs. Canagliflozin 300 mg is estimated to have a cost effectiveness of £15,433 per QALY compared to canagliflozin 100 mg, and to dominate empagliflozin 25 mg by saving £228 and resulting in an additional 0.089 QALYs.

For the analyses based upon the comparator clinical effectiveness estimates from the empagliflozin 25mg comparisons the sensitivity analysis again changes the ordering of treatment by total costs. Canagliflozin 100 mg becomes the least costly but does not dominate empagliflozin 10 mg. Empagliflozin 10 mg is estimated to yield an additional 0.012 QALYs at a cost of £94, yielding a cost effectiveness estimate of £7,833 per QALY. But canagliflozin 300 mg when compared to empagliflozin 10 mg costs an additional £100 with an additional 0.058 QALYs so yields a cost effectiveness estimate of only £1,724 per QALY so extendedly dominates it. Canagliflozin 300 mg also dominates empagliflozin 25 mg due to savings of £742 and gains of 0.151 QALYs.

*Sensitivity analysis: BMI convergence: Add-on to metformin plus thiazolidinedione*
The net QALY gains are slightly reduced. As a consequence, for the analyses based upon the comparator clinical effectiveness estimates from the empagliflozin 10 mg comparisons the ICER for canagliflozin 100 mg compared to sitagliptin 100 mg worsens from £4,115 per QALY to £5,333 per QALY. Empagliflozin 25 mg remains dominated by canagliflozin 100 mg, being associated with an additional £164 cost and a 0.034 QALY loss. The cost effectiveness of canagliflozin 300 mg compared to canagliflozin 100 mg worsens from £10,143 per QALY to £16,167 per QALY, and ignoring dominance the estimate of its cost effectiveness compared to empagliflozin 25 mg improves

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corresponding first line treatment modules *BI_RA_Empa25_INS* and *BI_RA_Sita100_INS_vs_Empa25_No_SBP_Effect*.

from £4,755 per QALY to £3,690 per QALY. Empagliflozin 10 mg remains dominated by canagliflozin 300 mg, being associated with a small additional £27 cost and a 0.082 QALY loss.

For the analyses based upon comparator clinical effectiveness estimates from the empagliflozin 25 mg comparisons the cost effectiveness of canagliflozin 100 mg compared to sitagliptin 100 mg is estimated as £5,550 per QALY. Empagliflozin 25 mg is dominated by canagliflozin 100 mg, being associated with an additional £175 cost and a 0.033 QALY loss. The cost effectiveness of canagliflozin 300 mg compared to canagliflozin 100 mg is estimated as £16,250 per QALY, and ignoring dominance the estimate of its cost effectiveness compared to empagliflozin 25 mg is £3,772 per QALY. Empagliflozin 10 mg is dominated by canagliflozin 300 mg, being associated with a small additional £26 cost and a 0.081 QALY loss.

*Sensitivity analysis: BMI convergence: Add-on to insulin*

For the analyses based upon the comparator clinical effectiveness estimates from the empagliflozin 10 mg comparisons the net QALY amounts are slightly reduced. Canagliflozin 300 mg compared to canagliflozin 100 mg results in an additional 0.033 QALYs at an additional cost of £361, resulting in a cost effectiveness estimate of £10,939 per QALY, compared to the £9,579 per QALY of the manufacturer base case. Ignoring dominance and considering canagliflozin 300 mg compared to empagliflozin 25 mg, an additional 0.039 QALYs are anticipated at an additional cost of £198, resulting in a cost effectiveness estimate of £5,077 per QALY.

Similarly effects occur for the analyses based upon the comparator clinical effectiveness estimates from the empagliflozin 25 mg comparisons. Canagliflozin 300 mg compared to canagliflozin 100 mg results in an additional 0.027 QALYs at an additional cost of £146, resulting in a cost effectiveness estimate of £5,407 per QALY, compared to the £4,333 per QALY of the manufacturer base case. Ignoring dominance and considering canagliflozin 300 mg compared to empagliflozin 25 mg, an additional 0.042 QALYs are anticipated at an additional cost of £85, resulting in a cost effectiveness estimate of £2,024 per QALY.

*Sensitivity analysis: No sitagliptin SBP effect: Add-on to metformin plus thiazolidinedione*

These sensitivity analyses do not consider canagliflozin and are only presented as pairwise comparisons between empagliflozin and sitagliptin.

Removing the SBP effect suggests that the net cost of empagliflozin 10 mg over sitagliptin 100 mg falls from £522 to £159 and the patient impact changes from a loss of 0.011 QALYs to a gain of 0.025 QALYs. Empagliflozin 10 mg is estimated to move from being dominated by sitagliptin 100 mg to it having a cost effectiveness of £6,360 per QALY compared to sitagliptin 100 mg.

The net cost of empagliflozin 25 mg over sitagliptin 100 mg falls from £210 to a saving of £149 and the patient impact changes from a gain 0.008 QALYs to a gain of 0.043 QALYs. Empagliflozin 25 mg is estimated to move from a cost effectiveness estimate of £26,250 per QALY compared to sitagliptin 100 mg to dominate it.

*Sensitivity analysis: No sitagliptin SBP effect: Add-on to insulin*
These sensitivity analyses do not consider canagliflozin and are only presented as pairwise comparisons between empagliflozin and sitagliptin.

Removing the SBP effect suggests that the net cost of empagliflozin 10mg over sitagliptin 100 mg falls from £179 to a cost saving of £208 and the patient impact changes from a loss of 0.023 QALYs to a gain of 0.040 QALYs. Empagliflozin 10 mg is estimated to move from being dominated by sitagliptin 100 mg to dominating it.

The net saving of empagliflozin 25 mg over sitagliptin 100 mg increase from a saving of £208 to a saving of £434 and the patient impact changes from a gain 0.040 QALYs to a gain of 0.058 QALYs.

### 5.2.11 Model validation and face validity check

The ERG asked three related questions at clarification. Note that the third question does not limit itself to asking about only UKPDS equations. The manufacturer gave the following responses:

- **Q1:** Please outline which of the equations of the UKPDS 68 are applied within the CORE modelling exercise.
  - *UKPDS 68 – Eq. 1 for IHD, Eq. 3 for CHF, Eq. 8 for Event Fatality, Eq. 9 for Diabetes Mortality*
- **Q2**: Please outline which of the equations of the UKPDS 82 are applied within the CORE modelling exercise. If any of tables 4, 5 or 6 of the electronic supplementary material to the UKPDS 82 are used, please provide more details of how the various risk factors: LDL, high density lipoprotein (HDL), etc. are modelled as evolving over time.
  - *Within this CORE modelling analysis, UKPDS 82 equations were not applied (in the CDM simulation interface the option "Apply UKPDS 82 equations" was not activated). UKPDS 68 is considered the most externally validated set of risk equations.*
- **Q3:** Please outline any additional equations that are applied within the CORE modelling exercise, coupled with a citation of the relevant paper.

- *UKPDS risk engines - UKPDS 56 for 1st myocardial infarction, UKPDS 60 for 1st Stroke*

Given the responses to the first two questions, the response to the third question is deficient. CORE requires that the evolution of the risk factors be modelled and also involves modelling considerably more complications than those listed.

It had been the ERG understanding that the evolution of the risk factors of HbA1c, SBP, lipids ratio and smoking status within CORE were determined by the UKPDS 68 [6] equations 11, 12, 13 and 14. But given the response to ERG clarification question 1 this appears to be no longer the case.

The response to the ERG clarification questions only provides the sources of the equations for the modelling of:

- First myocardial infarction
- First stroke
- Onset of IHD
- Onset of CHF
- Diabetes event related fatality
- Diabetes related mortality

These are all drawn from UKPDS publications. There is no obvious rationale for preferring UKPDS 56 for modelling the 1st myocardial infarction or the UKPDS 60 for modelling the 1st stroke over equations 2 and 4 of the UKPDS 68. Without being able to comment upon the impact of choosing different equations upon the output of CORE, it would seem more reasonable to try to use as many of the UKPDS 68 equations as possible in order to increase the overall coherence of the equations being used.

There is a lack of information about the CORE model equations, though in fairness had these been itemised in response to the ERG clarification questions there may have been relatively little the ERG could have done with these in the time available other than report them. But it does mean that any ERG commentary upon the validity of the CORE model structure is limited to a summary of the Mt. Hood validation papers provided by the manufacturer. These are summarised in appendix ECON1. While it has to be borne in mind that CORE is a commercial product and that both papers are either co-authored or authored by one of the main CORE modellers, these suggest that the CORE model is among the better models for the modelling of the complications of type 2 diabetes. Note that these exercises only address the modelling of complications. The costs and quality of life values that should be applied are entirely separate from this.

## 5.3 ERG cross check and critique

### 5.3.1 Base case results

The results presented within the submission cross check with the results of the base cases as presented within CORE. But cloning the manufacturer base cases and running them again within CORE results in different values. The reasons for this are unclear. It does not appear to be due to differences in the sequences of random numbers used within CORE for assessing the probabilities of events and such like because the manufacturer pairwise base case analyses for a given population all result in the same outputs for e.g. the empagliflozin 10mg arm despite these being run over a number of different pairwise comparisons.

It should be borne in mind that CORE has no audit trail. Running an analysis, changing a cost associated with it, and re-running the analysis will result in two different sets of outputs with both being visible within CORE. But it is only possible to see the set of costs that have been used for the final analysis. There is no way to roll back to the original set of costs. As a consequence, if a clone of a simulation results in different output values it is impossible to know what inputs may have differed between the original analysis and its clone.

The ERG reruns mainly result in changes to the total costs by arm but have only marginal impacts upon the total QALYs by arm. But the costs across all comparators tend to change by similar amounts and the net costs are not affected as much. While the ICERs do change, the results of the ERG reruns are qualitatively the same as those of the manufacturer. The results of the ERG reruns of the manufacturer base case are presented in appendix ECON3 for completeness, with the changes in the ICERs being noted.

### 5.3.2 Data Inputs: Correspondence between clinical section and economic section

The ERG has made the following cross checks between the clinical effectiveness estimates and the economics of the submission. The values cross check between the sections, though there are some additional notes. The exceptions to this are the rates for GTIs, non-severe hypoglycaemia and severe hypoglycaemia.

**Table 20. Table 3 of economic submission correspondence with clinical effectiveness section**

| +MET | Clinical | Timepoint | Notes |
|---|---|---|---|
| HBA1c | Table 7 | Week 52 | .. |
| SBP | Table 11 | Week 52 | .. |

| | | | |
|---|---|---|---|
| BMI | Table 9 | Week 52 | Assumes a patient height of 1.71m to translate kg changes of table 9 to BMI changes. |
| Non-severe hypos | Table 14 | Week 24 | Nothing relative to placebo for week 52 available, though some week 52 relative risk data for empagliflozin 25mg and sitagliptin 100mg relative to sulfonylurea in table 15.<br><br>Due to a lack of data the rate for canagliflozin is assumed to be the same as that for empagliflozin. This leads to some inconsistencies when modelling e.g. empagliflozin 10mg vs canagliflozin 100mg compared to empagliflozin 10mg vs canagliflozin 300mg. This in turn slightly complicates the presentation of results across all comparators. |
| Severe hypos | .. | .. | Assumed to be zero for all comparisons. Table 15 suggests a lower relative risk for empagliflozin 25mg compared to sitagliptin 100mg. |
| UTIs | Table 16 | Week 24 | Nothing relative to placebo for week 52 available, though some week 52 relative risk data in table 17.<br><br>In common with non-severe hypos the rate for canagliflozin is assumed to be the same as that for empagliflozin. |
| GTI. | .. | .. | Nothing presented within NMA report.<br><br>Table 3 suggests rates of 0.08 and 0.10 for empagliflozin 10mg and 25mg, 0.06 for canagliflozin 100mg and 300mg, 0.12 for dapagliflozin 10mg and zero for sitagliptin 100mg. These values appear to differ from those within the original submission, which also did not consider dapagliflozin. |

**Table 21. Table 4 of economic submission correspondence with clinical effectiveness section**

| Variable | Clinical | Timepoint | Notes |
|---|---|---|---|
| HBA1c | Table 20 | Week 52 | .. |
| SBP | Table 24 | Week 52 | .. |
| BMI | Table 22 | Week 52 | Assumes a patient height of 1.71m to translate kg changes of table 22 to BMI changes. |
| Non-severe hypos | Table 26 | Week 24 | Nothing relative to placebo for week 52 available.<br><br>Due to a lack of data the rate for sitagliptin is assumed to be the same as that for empagliflozin. This leads to some |

| | | | |
|---|---|---|---|
| | | | inconsistencies when modelling the different empagliflozin doses similar to those outlined previously. |
| Severe hypos | .. | .. | Assumed to be zero for all comparators. Table 15 suggests a lower relative risk for empagliflozin 25mg compared to sitagliptin 100mg. |
| UTIs | .. | .. | Assumed to be 13/100 patient years for all comparators. |
| GTI. | .. | .. | Nothing presented within NMA report.<br><br>Table 4 suggests rates of 0.06 and 0.05 for empagliflozin 10mg and 25mg, 0.06 for canagliflozin 100mg and 300mg and zero for sitagliptin 100mg. These values appear to differ from those within the original submission. |

**Table 22. Table 5 of economic submission correspondence with clinical effectiveness section**

| Variable | Clinical | Timepoint | Notes |
|---|---|---|---|
| HBA1c | Table 28 | Week 24 | The values reported are versus control of MET+TZD (applies generally) |
| SBP | Table 30 | Week 24 | Due to a lack of data the rate for sitagliptin is assumed to be the same as that for empagliflozin. This leads to some inconsistencies when modelling the different empagliflozin doses similar to those outlined previously. |
| BMI | Table 29 | Week 24 | Assumes a patient height of 1.71m to translate kg changes of table 29 to BMI changes. |
| Non-severe hypos | .. | .. | Assumed to be 6.5 for all comparators. |
| Severe hypos | .. | .. | Assumed to be zero for all comparators. |
| UTIs | .. | .. | Assumed to be 2.17/100 patient years for all comparators. |
| GTI. | .. | .. | Nothing presented within NMA report.<br><br>Table 5 suggests rates of 0.18 and 0.08 for empagliflozin 10mg and 25mg, 0.06 for canagliflozin 100mg and 300mg and zero for sitagliptin 100mg. These values appear to differ from those within the original submission. |

**Table 23. Table 6 of economic submission correspondence with clinical effectiveness section**

| Variable | Clinical | Timepoint | Notes |
|---|---|---|---|
| HBA1c | Table 32 | Week 24 | Table 33 also provides comparative week 52 data with dapagliflozin, with a marginally smaller effect for |

| | | | |
|---|---|---|---|
| | | | empagliflozin 10mg and a slightly larger effect for empagliflozin 25mg. |
| SBP | Table 36 | Week 24 | Table 37 also provides comparative week 52 data with dapagliflozin, with a slightly smaller effect for empagliflozin 10mg and a slightly larger effect for empagliflozin 25mg.<br><br>Due to a lack of data the rate for sitagliptin is assumed to be the same as that for empagliflozin. This leads to some inconsistencies when modelling the different empagliflozin doses similar to those outlined previously. |
| BMI | Table 34 | Week 24 | Assumes a patient height of 1.71m to translate kg changes of table 29 to BMI changes.<br><br>Table 35 also provides comparative week 52 data with dapagliflozin, with a marginally small effect for empagliflozin 10mg and a slightly larger effect for empagliflozin 25mg |
| Non-severe hypos | Table 39 | Week 24 | Due to a lack of data the rate for sitagliptin is assumed to be the same as that for empagliflozin. This leads to some inconsistencies when modelling the different empagliflozin doses similar to those outlined previously. |
| Severe hypos | .. | .. | Assumed to be the placebo rate of 4.33 for all comparators. Table 40 provides data on the risk of severe hypos at week 24 with a very low relative risk for dapagliflozin 10mg, relative risks rising in order for empagliflozin 10mg, canagliflozin 100mg, canagliflozin 300mg and then empagliflozin 25mg. |
| UTIs | Table 41 | Week 24 | Appears to assume a placebo rate of 0.065 rather than the 0.03 reported in table 42. |
| GTI. | .. | .. | Nothing presented within NMA report.<br><br>Table 6 suggests rates of 0.09 and 0.21 for empagliflozin 10mg and 25mg, 0.06 for canagliflozin 100mg and 300mg, 0.06 for dapagliflozin 10mg and zero for sitagliptin 100mg. These values appear to differ from those within the original submission. |

*Non-Severe hypoglycaemia*

The ERG has not managed to replicate the rates of non-severe hypoglycaemic events given within tables 3, 4 and 6 of the economics of the submission. Applying the relative risks of clinical effectiveness section tables 14, 26 and 39 to the clinical effectiveness section placebo rates of tables

18, 27 and 42 respectively appears to result in values that are roughly half those reported in tables 3, 4 and 6 of the economics of the submission. This suggests that the placebo rates of tables 18, 27 and 42 may be 24 week rates which are required to be doubled to be in line with the one year cycle of CORE. The original and the revised placebo rates appear to result in the following.

**Table 24. Non-severe hypoglycaemic event rates: add-on to metformin**

| | RR vs Placebo | Submission Table 3 | Rate Original | Rate Revised |
|---|---|---|---|---|
| Sulphonylurea | 1.62 | .. | 1.62 | 3.24 |
| Empagliflozin 10 mg | 2.71 | 5.87 | 2.71 | 5.42 |
| Empagliflozin 25 mg | 1.99 | 4.31 | 1.99 | 3.98 |
| Dapagliflozin 10 mg | 1.35 | 2.93 | 1.35 | 2.70 |
| Sitagliptin 100 mg | 0.45 | 0.98 | 0.45 | 0.90 |

**Table 25. Non-severe hypoglycaemic event rates: add-on to metformin plus sulfonylurea**

| | RR vs Placebo | Submission Table 6 | Rate Original | Rate Revised |
|---|---|---|---|---|
| Empagliflozin 10 mg | 1.62 | 28.08 | 12.96 | 25.92 |
| Empagliflozin 25 mg | 1.34 | 23.23 | 10.72 | 21.44 |
| Canagliflozin 100 mg | 1.81 | 31.37 | 14.48 | 28.96 |
| Canagliflozin 300 mg | 1.51 | 26.17 | 12.08 | 24.16 |

**Table 26. Non-severe hypoglycaemic event rates: add-on to insulin**

| | RR vs Placebo | Submission Table 6 | Rate Original | Rate Revised |
|---|---|---|---|---|
| Empagliflozin 10 mg | 1.03 | 53.56 | 24.72 | 49.44 |
| Empagliflozin 25 mg | 1.20 | 62.40 | 28.8 | 57.60 |
| Dapagliflozin 10 mg | 1.09 | 56.68 | 26.16 | 52.32 |
| Canagliflozin 100 mg | 1.47 | 76.44 | 35.28 | 70.56 |
| Canagliflozin 300 mg | 1.42 | 73.84 | 34.08 | 68.16 |

The ERG calculated values are broadly in line with those of tables 3, 4, 5 and 6 of the economics of the submission. But discrepancies remain, and the ERG is not confident that is has replicated the manufacturer method for estimating the rates of non-severe hypoglycaemic events.

*Severe hypoglycaemia*

Within the clinical effectiveness section there are relative risks for overall hypoglycaemia and relative risks for non-severe hypoglycaemia. There are also placebo rates for overall hypoglycaemia and

relative risks for non-severe hypoglycaemia. Only non-severe hypoglycaemic events have been modelled.

For add on to metformin the central estimates for the relative risks of overall hypoglycaemia for canagliflozin 100 mg and 300 mg compared to empagliflozin 25 mg are slightly above unity, though the confidence intervals are wide. Ignoring severe hypoglycaemia within this comparison may have had little impact, and any bias seems likely to have been to the detriment of empagliflozin.

For add on to metformin plus sulfonylurea the central estimates for the relative risks of overall hypoglycaemia for canagliflozin 100 mg and 300 mg compared to empagliflozin 25 mg are slightly above unity, though the confidence intervals are wide. They also lie very slightly above the corresponding relative risks for non-severe hypoglycaemia. Ignoring severe hypoglycaemia within this comparison may have had little impact, and any bias seems likely to have been to the detriment of empagliflozin 25 mg.

For add on to insulin there are explicit relative risks for severe hypoglycaemia. Within this comparison the relative risk point estimates favour canagliflozin 100 mg and 300 mg over empagliflozin 25 mg, though for empagliflozin 10 mg the situation is reversed. Unfortunately, the only rates for placebo that are given are for overall hypoglycaemia and for non-severe hypoglycaemia. Subtracting the placebo non-severe hypoglycaemia rate from the placebo overall hypoglycaemia rate of table 42 of the clinical effectiveness section could give an indication of the implied manufacturer estimate of the placebo severe hypoglycaemia rate. But it is not clear what contributes to these figures. Employing the same method as for the non-severe hypoglycaemic events suggests the following severe hypoglycaemic event rates per 100 patient years.

**Table 27. Severe hypoglycaemic event rates: add-on to insulin**

| | RR vs Placebo | Submission Table 6 | Rate Original | Rate Revised |
|---|---|---|---|---|
| Empagliflozin 10 mg | 0.34 | 0.00 | 0.68 | 1.36 |
| Empagliflozin 25 mg | 1.32 | 0.00 | 2.64 | 5.28 |
| Dapagliflozin 10 mg | 0.04 | 0.00 | 0.08 | 0.16 |
| Canagliflozin 100 mg | 0.70 | 0.00 | 1.40 | 2.80 |
| Canagliflozin 300 mg | 1.10 | 0.00 | 2.20 | 4.40 |

As would be expected, given the relative risks the inclusion of severe hypoglycaemic events would be expected to improve the cost effectiveness of canagliflozin 300 mg versus empagliflozin 25 mg. But the ERG views the omission of any severe hypoglycaemic episodes as being justified.

### 5.3.3 Data Inputs: Correspondence between written submission and sources cited

*Quality of life values: Complications of diabetes*

It appears that the CORE default values for the main complications of diabetes are drawn from the UKPDS 62, while the submission has revised the values for incident myocardial infarction, stroke and amputation events as outlined below based upon values drawn from Sullivan et al (2011).

The values drawn from Sullivan et al broadly cross check with those of the *CCC_full_regression_results* worksheet of the electronic supplementary data to Sullivan et al. This is with the possible exception of the value for blindness in one eye. Table 64 of the previous submission gave this as -0.0642 which the ERG has not been able to source, though the *CCC_full_regression_results* worksheet does provide an estimate of -2.16E-10 for Blindness and Vision Defects. The amputation event disutility of -0.280 is also not clearly referenced and the ERG cannot find any -0.280 decrement within the *CCC_full_regression_results* worksheet. Paralysis appears to have the worst decrement of -0.247, which may call into question the decrement of -0.280 for amputation.

Due to a lack of documentation, the ERG is unsure whether within CORE the utility decrements or the quality of life values should be inputted for incident events. All the values for incident events have been changed from the CORE defaults by the manufacturer, and the ERG does not have access to the CORE default values for incident events. If within CORE the quality of life values should be inputted for incident events rather than the quality of life decrements associated with the incident events, the analyses of the submission will greatly exaggerate the impact of incident events. This seems unlikely to apply, but should be confirmed with the manufacturer and the IMS CORE team.

If the utility decrements associated with incident events are correctly implemented within CORE, the revisions from the CORE default values to those derived from Sullivan et al tend to lessen the impact of events during the year in which they occur. This applies particularly to myocardial infarction events. The impact of severe vision loss is slightly greater than that of the UKPDS 62.

Note that it appears that the original submission used the values from the UKPDS 62, and only applied the values drawn from Sullivan et al as a sensitivity analysis. The original submission noted that:

> *…alternative values were available from a sponsored study. An average value per patient with diabetes with or without complications was provided as part of this catalogue. Additionally, values were estimated that represented the marginal decrement in EQ-5D index*

*scores for each condition after controlling for age, comorbidity, gender, race, ethnicity, income and education. These values could be used as disutilities to apply whenever a patient had experienced a complication on the top of their main condition .... The limitation with these utilities was that, although community-based UK preferences were applied to EQ-5D descriptive questionnaire responses, the population responding the questionnaire was from the US-based Medical Expenditure Panel Survey (MEPS). Therefore, following recommendations from a UK clinical expert, this additional set of utilities was used as sensitivity analysis. Although these values were considered not to be wholly representative of the UK population compared with the utility values considered in the base case, they did allow disutilities associated to complications and an age-related disutility to be taken into account.*

It should be borne in mind that the utility decrements for complications during their incident year as drawn from Sullivan et al are typically smaller than those of the UKPDS 62. This will tend to worsen the cost effectiveness of the more effective treatment. Since the analyses tend to find canagliflozin 300mg to be the most cost effective treatment, the utility decrements of Sullivan et al will slightly favour empagliflozin and reduce the incremental total QALYs estimated for canagliflozin 300mg over empagliflozin.

*Quality of life values: Adverse events*

The submission applies the following quality of life decrements for adverse events.

**Table 28. Quality of life associated with adverse events**

| | QoL |
|---|---|
| Severe hypo | -0.0118 |
| Non-severe hypo | -0.0035 |
| GTI event | -0.0028 |
| UTI event | -0.0028 |
| Post UTI event | 0.8168 |

The quality of life decrements for the events are the same as those used in the original submission. The quality of life decrements for GTI and UTI events are drawn from the STA of dapagliflozin, and cross check with the values used in the dapagliflozin STA as reported in the FAD. But the FAD went on to note that:

*The Committee concluded that, although the loss in utility associated with urinary tract and genital infections was likely to be greater than that proposed by the manufacturers, it was*

*satisfied that this did not significantly impact on the relative cost effectiveness of dapagliflozin as dual therapy or add-on to insulin*[2].

It is unclear to the ERG is whether these decrements are QoL decrements or are QALY decrements. If they are QoL decrements it seems likely that they should be adjusted by the average duration of the event as a proportion of one year to arrive at a QALY decrement which would tend to reduce their impact upon results.

The post UTI quality of life is based upon 0.814 minus 0.0028. The ERG calculates this as 0.811. More questionable is whether a UTI would have a potentially indefinite quality of life impact, given their short duration of a few days. The value of 0.8168 cross checks with that implemented within CORE and actually lies above the 0.814 value for those not experiencing any complications. The ERG cannot comment upon how this is implemented within CORE, but it appears to raise the prospect the impact of a UTI being to decrease quality of life during the incident year but to increase it potentially indefinitely thereafter.

It may be more reasonable to set this value to 0.814. For most analyses the rates of UTIs are assumed to be equal between the treatments. But dapagliflozin 10 mg has a worse UTI profile than empagliflozin, while for the +MET analyses sitagliptin 100 mg has a slightly better UTI profile than empagliflozin.

Unfortunately, the considerations around the post UTI quality of life only occurred to the ERG after having set the ERG analyses running in CORE. As a consequence, these retain the 0.8168 value of the manufacturer base case. This may bias the analyses in favour of dapagliflozin 10 mg and against sitagliptin 100 mg in the add-on to metformin analyses, and in favour of dapagliflozin 10 mg in the add-on to insulin analyses. The comparisons of empagliflozin with canagliflozin should be largely unaffected by this.

*Quality of life and BMI*

The CORE default value of -0.0038125 is applied, with the CORE user model stating that this is derived from Bagust and Beale (2005).[7] Within Bagust and Beale, in order to permit a comparison between a VAS based analysis and the EQ-5D based analysis, the EQ-5D UK social tariff utilities are rebased so as to lie on the interval [0,100]. Since the EQ-5D UK social tariff utilities lie on the interval [-0.6,1.0] which is 1.6 wide, this transformation takes the form TTO*=(TTO+0.6)/1.6*100. As Bagust and Beale note, "*for obesity the coefficient in table 3 (-0.0061) is transformed to its*

[2] http://www.nice.org.uk/guidance/ta288/resources/guidance-dapagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf

*equivalent on a 0-100 scale (-0.38)*". Dividing the adjusted -0.38 of the text and table 5 of Bagust and Beale by 100 yields the corollary on the [0,1] interval: -0.0038. This is in line with the CORE default coefficient of -0.0038125. The calculation of the CORE default coefficient is further confirmed by noting that -0.0038125*1.6 = -0.0061.

But it would seem that the coefficient that is required is that which corresponds with the [-0.6,1.0] interval of the EQ-5D social tariff: -0.0061. This is the coefficient that was applied by the authors in the economic model that they analysed the CODE-2 EQ-5D data for [*personal communication: Prof. A. Bagust, 5 Nov 2014*].

*Direct drug costs*

The annual costs of the comparators are the same for each of the four main groupings of comparisons which have been made, with only the costs of the concomitant treatments varying between the lines of treatment. The costs of the comparators as reported in the submission and as estimated by the ERG from the BNF and the drug tariff[3] are as below.

**Table 29. Comparator drug costs**

| | Submission | BNF | Drug tariff |
|---|---|---|---|
| Empagliflozin 10 | £477.30 | .. | £477.30 |
| Empagliflozin 25 | £477.30 | .. | £477.30 |
| Canagliflozin 100 mg | £477.26 | £477.26 | .. |
| Canagliflozin 300 mg | £608.63 | £608.63 | .. |
| Dapagliflozin 10mg | £477.30 | £477.30 | £477.30 |
| Sitagliptin 100 mg | £433.86 | £433.86 | £433.86 |

The costs of the concomitant treatments have not been cross checked by the ERG, but appear broadly reasonable with the following annual costs being implied:

- £8.95 for metformin
- £28.55 for metformin plus sulfonylurea
- £45.08 for metformin plus a thiazolidinedione
- £396.21 for NPH insulin plus consumables

A minor concern might be the assumption of NPH insulin, since in the UK it has been overtaken in use by long-acting analogues such as glargine. The original manufacturer submission also provided a cost estimate for glargine of £557.55. Higher insulin costs will tend to improve the cost effectiveness

[3] BNF and drug tariff accessed 29 October 2014, with the November 2014 drug tariff being accessed.

of the treatment with the largest reduction in HbA1c, the point estimates for this tending to favour canagliflozin 300mg.

*Costs of complications*

The original submission suggests that the main costs of complications have been sourced from the UKPDS 65. This outlines a range of non-inpatient and inpatient costs associated with complications in their incident year and thereafter. The ERG has not been able to find the base year for prices within the UKPDS 65, but it does note that:

> *The cost of each episode of hospitalization was estimated by multiplying the length of stay by the average cost of the respective specialty, based on an average (after adjusting for inflation) of the Department of Health's NHS Trust Financial Returns (TFR2) for 1997/8 and 1998/9.*

In the light of this, the ERG has assumed that the inflation adjustment is to the 1997/8 prices to bring them into line with 1998/9 prices. But the text is ambiguous. Having been accepted for publication in 2002 it is possible that the inflation adjustment is to both the 1997/8 prices and the 1998/9 prices to bring them into line with 2001/2 prices.

The non-inpatient costs reported for no complications, macro-vascular complications and micro-vascular complications are as below.

**Table 30. UKPDS 65 : non-inpatient costs**

| | 4 mth prob | 4 mth cost | Mean annual |
|---|---|---|---|
| No complication | 76% | £70 | £159 |
| Incident year | | | |
| macro-vascular | 91% | £116 | £315 |
| micro-vascular | 97% | £94 | £273 |
| Subsequent year | | | |
| Macro-vascular | 86% | £101 | £258 |
| micro-vascular | 83% | £82 | £204 |

These costs can be added to the inpatient costs estimated within the UKPDS 65 to give the gross cost, and uprated for inflation using the PSSRU HCSC index[4] as below. In the following the probabilities are the probability of incurring an inpatient cost for the complication, while the costs of the column to the right of this are the inpatient costs conditional upon them having been incurred. The mean cost is the product of these two columns, with the gross cost adding the relevant outpatient costs from the table above. The last column summarises the values taken from table 8 of the submission.

[4] Based upon an index of 180.4 in 1998/9 rising to 289.1 in 2012/13 to yield an adjustment factor of 1.60.

**Table 31. UKPDS 65 costs**

| | UKPDS 65 annual quantities | | | | | Submission | |
|---|---|---|---|---|---|---|---|
| | Prob. | Cost | Mean | Gross | Inflated | Original | Current |
| No complication | 6% | £2,543 | £157 | £316 | £506 | £483 | £0 |
| Incident year | | | | | | | |
| Fatal MI | 74% | £1,567 | £1,152 | £1,467 | £2,351 | £2,511 | .. |
| Non-fatal MI | 80% | £5,104 | £4,070 | £4,385 | £7,027 | £8,179 | £8,179 |
| Fatal stroke | 80% | £4,227 | £3,383 | £3,698 | £5,926 | £6,774 | £6,774 |
| Non-fatal stroke | 35% | £6,822 | £2,367 | £2,682 | £4,298 | £10,932 | £10,932 |
| IHD | 41% | £4,760 | £1,959 | £2,274 | £3,644 | £7,628 | £3,644 |
| CHF | 53% | £4,227 | £2,221 | £2,536 | £4,064 | £6,773 | £6,773 |
| Blind in one eye | 20% | £4,370 | £872 | £1,145 | £1,835 | £7,003 | £7,003 |
| Amputation | 100% | £8,459 | £8,459 | £8,732 | £13,993 | £13,556 | £13,556 |
| Subsequent year | | | | | | | |
| Non-fatal MI | 13% | £3,603 | £464 | £722 | £1,157 | £5,773 | £5,733 |
| Non-fatal stroke | 8% | £2,970 | £249 | £507 | £812 | £4,760 | £4,760 |
| IHD | 13% | £3,814 | £493 | £751 | £1,204 | £6,112 | £1,204 |
| CHF | 15% | £4,097 | £631 | £889 | £1,425 | £6,566 | £6,566 |
| Blind in one eye | 10% | £2,945 | £281 | £485 | £777 | £4,719 | £4,720 |
| Amputation | 8% | £3,639 | £300 | £504 | £808 | £5,831 | .. |

The reasons for the revision by the manufacturer of the IHD costs of the original submission to those of the current submission are unclear, particularly given that the other costs have been retained.

There are a number of elements in the above that do not appear to be within CORE:

- The annual cost for patients with no complications.
- The cost of a fatal MI, which may mean that these are associated with the higher cost of a non-fatal MI in its first year.
- The cost of an amputation subsequent to the first year, meaning that these may be associated with the higher cost of an amputation in its first year or, given the text of the submission, with no cost.

Note also that the UKPDS 65 costs for blindness are for blindness in one eye whereas the CORE descriptor is severe visual loss which may not exactly correspond. But the ERG does not have access to the programming underlying CORE and cannot cross check these elements.

The costs of the complications are very much higher in the submission than would appear to be implied by the UKPDS 65. The discrepancies appear likely to be the result of the estimates within the

submission being based upon the annual inpatient cost rather than the annual inpatient cost conditioned by the probability of that cost being incurred for an event[5].

Higher costs of complications will tend to improve the ICER for the more effective treatment. Since canagliflozin 300mg is typically estimated to be the most cost effective treatment, any exaggeration of the costs of the complications of diabetes may tend to have biased the analysis against empagliflozin.

### 5.3.4 Data Inputs: Correspondence between written submission and electronic model

The ERG has extracted the settings of the manufacturer base case analyses from CORE and the corresponding CORE treatment algorithms and parameter input modules. These have then been cross checked against the values of the written submission of tables 2, 3, 4, 5, 6, 7, the values of the table on drug costs within section 4.4.2 and the values for the direct costs for CVD complications, renal complications, neuropathy, foot ulcer, amputation and management costs of table 8.

The values cross check with the following exceptions in table 6:

- It appears that for the comparison of empagliflozin 25 mg with canagliflozin 300 mg the rate of UTI infections for the canagliflozin 300 mg arm within CORE is 22.25 compared to the 9.30 of table 6.
- For the comparison of empagliflozin 10 mg with canagliflozin 300 mg within the ERG userspace there are two identically named treatment modules within CORE. These give the number of UTIs as 22.25 and 9.30, compared with to the 10.73 of table 6.

It is peculiar and slightly worrying that there are two identically named treatment modules within the ERG1 userspace. Since the manufacturer base case results do not correspond with the results of the ERG reruns, it is not possible for the ERG to determine which has been used to generate the base case results of the manufacturer.

### 5.3.5 ERG commentary on model structure, assumptions and data inputs

*CORE model implementation*

The CORE model has the option to select 2nd order sampling. Given the responses to the ERG clarification questions Q1-Q4 as presented in appendix ECON4, the ERG understanding is that this turns on 2nd order sampling and so makes the model probabilistic. Sampling of the costs of complications may not have occurred, but this option appears to cause the other model elements including the treatment effects to be sampled. As a consequence, in the opinion of the ERG this

[5] More detail on the method is supplied in the UKPDS 65 Statistical Analysis section.

modelling is best viewed as being probabilistic rather than deterministic. The setting for the base case "deterministic" analyses and the probabilistic analyses of the manufacturer differ as below.

**Table 32. CORE model settings applied by the manufacturer**

| | Base case | Base case PSA |
|---|---|---|
| BMI adjustment for QALY | yes | yes |
| 2nd order with sampling | yes | yes |
| Patient number | 1,000 | 50,000 |
| Time horizon | 80 years | 80 years |
| Number of bootstrap iterations | 1,000 | 500 |

In the light of the above, it appears that the "deterministic" base cases of the manufacturer are actually probabilistic runs of CORE with 1,000 patients per iterations and 1,000 iterations. Given this it seems likely that CORE will not have converged over the 1,000 patients for the set of parameter estimates drawn from the 2$^{nd}$ order uncertainty for that iteration.

The ERG understanding is that the CORE model default for deterministic model runs is 1,000 patients over 1,000 bootstraps. If 2$^{nd}$ order sampling is not selected the 1,000 bootstraps all run using the same set of parameter estimates, and these are averaged to give the total costs and QALYs by arm and the resulting ICER; i.e. in effect 1,000,000 patients are run through the model which is sufficient to achieve convergence.

This requirement for a sufficient number of patients to be run through CORE for a given set of parameter values for CORE to reliably converge seems likely to be the reason for the number of patients being increased to 50,000 within what are labelled the PSA analyses. Reducing the number of bootstraps to 500 is likely to be the flip side of this, reducing the lengthy computation time to a more manageable duration.

Given the above, there are concerns around model convergence and the reliability of results within the "deterministic" analyses of the manufacturer.

The responses to the ERG clarification questions Q4 and Q5 as presented in appendix ECON4 appears to suggest that the "deterministic" modelling over 1,000 patients and 1,000 bootstraps was correct to select the option of 2$^{nd}$ order sampling, despite the ERG understanding as per responses to Q1-Q4. It is unclear to the ERG whether the manufacturer views selecting the option of 2$^{nd}$ order sampling for the deterministic analyses as having been correct or incorrect.

*Choice of comparators: GLP-1 analogues*

The GLP-1 analogues have not been considered in spite of their inclusion in the scope. The ERG considers the omission of these as comparators to be reasonable. The GLP-1 analogues are more expensive and have to be injected, and as a consequence a gliptin or a flozin would be tried before a GLP-1 analogue.

*Choice of comparators: sulfonylurea for add-on to metformin*

The NMA of the clinical effectiveness section provides estimates for sulfonylureas. These have not been considered within the economics, despite being within the scope. Sulfonylureas are cheap and based upon the clinical effectiveness estimates presented appear to be of similar clinical effectiveness in terms of HbA1c, though the impacts upon SBP may be more questionable and they often cause weight gain..

Not including the sulfonylureas, given their low drug costs, risks seriously biasing the analyses. However the ERG considers that sulphonylureas should be tried before flozins or gliptins, in which case a flozin would be tried only if a sulphonylurea could not be tolerated.

*Maintenance of clinical effect through time*

The switch of therapy once a patient rises above 7.5% HbA1c appears to be associated with weight gain and a change in costs but nothing else, with this applying at change of therapy to all arms. It would seem more natural to assume some clinical effects from a change in therapy, in that much of the justification for a change in therapy once HbA1c rises above 7.5% would seem to be aiming to get it back down to below 7.5% again. Letting the risk factors evolve without further changes at change of therapy may tend to increase the number of complications which are modelled as occurring. This may tend to favour the more effective treatment.

*Modelling of BMI: Base case and sensitivity analyses*

For the base cases the differences in weight that are modelled at one year are maintained for the patient lifetime. This may not be realistic and will tend to exaggerate the QALY gains from the treatments associated with the greatest weight loss. Whether empagliflozin is estimated to result in a lower weight than canagliflozin or vice versa switches depending upon which therapies the comparators are being added to.

The ERG clarification question Q8 asked: *Please outline how within CORE the convergence of BMI of section 6.1 was implemented; i.e. please walk the ERG through what needs to be done in CORE to effect this.* The ERG has been expecting an explanation of how to implement a convergence of BMI within CORE as per section 6.1 of the manufacturer submission. But only an outline of the outputs of

CORE was presented, though this did confirm that for the base case analyses CORE models the difference in BMI between the arms as continuing indefinitely[6]. As a consequence the ERG remains unclear how to implement this within CORE so has limited sensitivity analyses around this element to not applying the QALY decrement associated with BMI changes.

*Treatments after therapy switch within CORE*

The modelling should apply the same treatment module after change of therapy in both arms. The manufacturer modelling applies a different treatment module for the next line of treatment within the empagliflozin arm from that of the non-empagliflozin arm. The inputs to these treatment modules appears to be the same for both arms, but within CORE there are many hidden tables that lie underneath the main input parameters and it is not a simple matter to cross check these.

To cross check this the ERG has revised the modelling to apply the same treatment after change of therapy in both arms, revising the next line of treatment within the non-empagliflozin arm to be the same as that in the empagliflozin arm, for:

- the comparison of empagliflozin 10 mg with dapagliflozin 10 mg as an add-on to metformin;
- the comparison of empagliflozin 10 mg with canagliflozin 100 mg as an add-on to metformin plus sulfonylurea;
- the comparison of empagliflozin 25 mg with sitagliptin 100 mg as an add-on to metformin plus thiazolidinedione; and,
- the comparison of empagliflozin 25 mg with dapagliflozin 10 mg as an add-on to insulin.

The values that result correspond with the values of the ERG model reruns of appendix ECON3.

## 5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the CORE economics module to apply the UKPDS 65 costs as calculated by the ERG and the UKPDS 62 quality of life decrements in favour of those drawn from Sullivan et al (2011) by the manufacturer[7].

For the comparisons as add-on to insulin the ERG has also revised the rates of UTIs for canagliflozin 300 mg to be equal to 10.73 per 100 patient years for the comparison with empagliflozin 10 mg and to 9.30 per 100 patient years for the comparison with empagliflozin 25 mg[8].

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[6] This is slightly modified if treatment change to insulin occurs at different times between the two arms, in that the second step in the BMI will occur at different times. But essentially it appears that both before and after this second step the BMI difference between the two arms modelled is maintained.

[7] These are available within the ERG1 CORE userspace as *ERG_RA_Economics_BC*

As reviewed above, due to it appearing to not affect the results for the four instances that were examined, the ERG has not revised the treatment algorithms so that the empagliflozin arm has the same named second line treatment as within the comparator arm treatment algorithm.

Given the centrality of the BMI utility decrement to other NICE assessments of treatments for diabetes, sensitivity analyses around this parameter are required. The simplest way to implement this within CORE is rerun the analyses with CORE set to not apply any quality of life decrement to weight changes. This provides the QALY changes associated with moving from a coefficient of -0.0038125 to zero.

Due to time constraints, the ERG has not revised the BMI disutilities table of CORE, with every 0.1 BMI point above 25 having to be specified, and then rerun all the analyses. The QALY changes associated with moving from a coefficient of -0.0038125 to zero have rather been adjusted by a factor of 1.6 to derive the QALYs associated with a coefficient of -0.0061. But some rounding errors may results from this.

In the light of the manufacturer response to the ERG clarification questions as outlined in appendix ECON4, the ERG has run the above analyses with the 2nd order sampling of CORE set to "No". There was insufficient time to run any probabilistic analyses.

*ERG analyses with new economics*

*Base case rerun results: Add-on to metformin*

The following presents the base case deterministic results for the patient population having therapy added to metformin.

[8] These are available in *ERG_RA_Cana300_INS_vs_Empa_10_UTI1073* and *ERG_RA_Cana300_INS_vs_Empa_25_UTI93*

**Table 33. Results: add-on to MET: empag. 10mg comparator effectiveness estimates:**[9]

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,969 | £5,982 | £5,892 | £5,757 | £5,892 | £6,458 |
| Management | £1,045 | £1,048 | £1,043 | £1,041 | £1,043 | £1,048 |
| Complications | £34,753 | £34,616 | £34,740 | £34,756 | £34,691 | £34,686 |
| Total | £41,767 | £41,646 | £41,675 | £41,554 | £41,626 | £42,192 |
| LYs (undisc.) | 20.142 | 20.212 | 20.100 | 20.019 | 20.100 | 20.214 |
| QALYs | | | | | | |
| No BMI effect | 8.178 | 8.203 | 8.161 | 8.136 | 8.161 | 8.202 |
| BMI coef. -0.0038 | 8.049 | 8.078 | 8.033 | 7.969 | 8.028 | 8.082 |
| BMI coef. -0.0061 | 7.972 | 8.003 | 7.956 | 7.869 | 7.948 | 8.010 |

**Table 34. Cost effectiveness: add-on to MET: empag. 10mg comparator effectiveness**

| | | | No BMI coef. | | ICERs for BMI coef. of | | |
|---|---|---|---|---|---|---|---|
| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
| Sitagliptin 100mg | £41,554 | | 8.136 | | | | |
| Canagliflozin 100mg | £41,626 | £72 | 8.161 | 0.025 | £2,880 | £1,220 | £907 |
| Empagliflozin 25mg | £41,646 | £20 | 8.203 | 0.042 | £476 | £400 | £365 |
| Dapagliflozin 10mg | £41,675 | £29 | 8.161 | -0.042 | Dominated | Dominated | Dominated |
| Empagliflozin 10mg | £41,767 | £121 | 8.178 | -0.025 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £42,192 | £546 | 8.202 | -0.001 | Dominated | £136,500 | £78,000 |

**Table 35. Results: add-on to MET: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,969 | £5,982 | £5,892 | £5,757 | £5,890 | £6,454 |
| Management | £1,045 | £1,048 | £1,043 | £1,041 | £1,043 | £1,047 |
| Complications | £34,753 | £34,616 | £34,740 | £34,756 | £34,724 | £34,556 |

[9] Recall that the clinical effectiveness estimates of the comparators differ slightly depending upon whether the pairwise comparison is with empagliflozin 10mg or is with empagliflozin 25mg. For elements such as GTIs where three is no evidence of a difference, the comparator is assumed to have the same rate as empagliflozin. But this gives two sets of effectiveness estimates for the comparators, and as a consequence these have to be presented separately. But typically there are minimal differences in cost effectiveness estimates between these two sets of analyses.

| | | | | | | |
|---|---|---|---|---|---|---|
| Total | £41,767 | £41,646 | £41,675 | £41,554 | £41,657 | £42,057 |
| LYs (undisc.) | 20.142 | 20.212 | 20.100 | 20.019 | 20.092 | 20.194 |
| QALYs | | | | | | |
| No BMI effect | 8.178 | 8.203 | 8.161 | 8.136 | 8.16 | 8.196 |
| BMI coef. -0.0038 | 8.049 | 8.078 | 8.033 | 7.969 | 8.028 | 8.076 |
| BMI coef. -0.0061 | 7.972 | 8.003 | 7.956 | 7.869 | 7.949 | 8.004 |

**Table 36. Cost effectiveness: add-on to MET: empagliflozin 25mg comparator effectiveness**

| | | | No BMI coef. | | ICERs for BMI coef. of | | |
|---|---|---|---|---|---|---|---|
| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
| Sitagliptin 100mg | £41,554 | | 8.136 | | | | |
| Empagliflozin 25mg | £41,646 | £92 | 8.203 | 0.067 | £1,373 | £844 | £686 |
| Canagliflozin 100mg | £41,657 | £11 | 8.160 | -0.043 | Dominated | Dominated | Dominated |
| Dapagliflozin 10mg | £41,675 | £29 | 8.161 | -0.042 | Dominated | Dominated | Dominated |
| Empagliflozin 10mg | £41,767 | £121 | 8.178 | -0.025 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £42,057 | £411 | 8.196 | -0.007 | Dominated | Dominated | £411,000 |

*Base case rerun results: Add-on to metformin plus sulphonylurea*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus sulphonylurea.

**Table 37. Results: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,814 | £5,808 | £5,627 | £5,826 | £6,316 |
| Management | £1,000 | £999 | £995 | £1,003 | £1,006 |
| Complications | £32,665 | £32,592 | £32,980 | £32,610 | £32,274 |
| Total | £39,479 | £39,399 | £39,602 | £39,439 | £39,596 |
| LYs (undisc.) | 18.958 | 18.935 | 18.808 | 19.021 | 19.085 |
| QALYs | | | | | |
| No BMI effect | 7.841 | 7.834 | 7.782 | 7.864 | 7.894 |
| BMI coef. -0.0038 | 7.574 | 7.568 | 7.478 | 7.587 | 7.631 |
| BMI coef. -0.0061 | 7.414 | 7.408 | 7.296 | 7.421 | 7.473 |

**Table 38. Cost effectiveness: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | No BMI coef. | ICERs for BMI coef. of |
|---|---|---|

| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
|---|---|---|---|---|---|---|---|
| Empagliflozin 25mg | £39,399 | | 7.834 | | | | |
| Canagliflozin 100mg | £39,439 | £40 | 7.864 | 0.030 | £1,333 | £2,105 | £3,226 |
| Empagliflozin 10mg | £39,479 | £40 | 7.841 | -0.023 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £39,596 | £157 | 7.894 | 0.030 | £5,233 | £3,568 | £2,996 |
| Sitagliptin 100mg | £39,602 | £6 | 7.782 | -0.112 | Dominated | Dominated | Dominated |

Given the focus in the ERG reporting of the manufacturer results upon the comparison of canagliflozin 300 mg with empagliflozin 25 mg, for BMI coefficients of zero and -0.0038 the cost effectiveness of canagliflozin 300 mg compared to empagliflozin 25 mg is £3,283 per QALY and £3,127 per QALY respectively. For a BMI coefficient of -0.0061 canagliflozin 300 mg extendedly dominates canagliflozin 100 mg, and has a cost effectiveness estimate against empagliflozin 25 mg of £3,040 per QALY.

Basing the results upon the empagliflozin 25 mg comparison estimates, with the exclusion of a very minor difference in the sitagliptin 100 mg total QALYs, results in the same as the above.

*Base case rerun results: Add-on to metformin plus thiazolidinedione*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus thiazolidinedione.

**Table 39. Results: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,759 | £5,871 | £5,724 | £5,877 | £6,359 |
| Management | £998 | £1,000 | £1,003 | £1,002 | £1,003 |
| Complications | £32,765 | £32,762 | £32,665 | £32,643 | £32,510 |
| Total | £39,522 | £39,633 | £39,392 | £39,522 | £39,872 |
| LYs (undisc.) | 18.883 | 18.938 | 18.995 | 18.978 | 19.014 |
| QALYs | | | | | |
| No BMI effect | 7.814 | 7.836 | 7.858 | 7.850 | 7.865 |
| BMI coef. -0.0038 | 7.551 | 7.570 | 7.561 | 7.593 | 7.622 |
| BMI coef. -0.0061 | 7.393 | 7.410 | 7.383 | 7.439 | 7.476 |

**Table 40. Cost effectiveness: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | No BMI coef. | ICERs for BMI coef. of |
|---|---|---|

| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
|---|---|---|---|---|---|---|---|
| Sitagliptin 100mg | £39,392 | | 7.858 | | | | |
| Canagliflozin 100mg | £39,522 | £130 | 7.850 | -0.008 | Dominated | £4,063 | £2,321 |
| Empagliflozin 10mg | £39,522 | £130 | 7.814 | -0.044 | Dominated | Dominated | Dominated |
| Empagliflozin 25mg | £39,633 | £241 | 7.836 | -0.022 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £39,872 | £480 | 7.865 | 0.007 | £68,571 | £12,069 | £9,358 |

Canagliflozin 300 mg when compared to empagliflozin 25 mg has a cost effectiveness estimate of £68,571 per QALY if there is no impact upon quality of life from weight changes. A BMI coefficient of -0.0038 reduces this to £7,869 per QALY, while a BMI coefficient of -0.0061 reduces it further to £5,139 per QALY, due to the greater weight loss associated with canagliflozin 300 mg

Superseded

The cost effectiveness results that use the clinical effectiveness estimates for the comparators based upon the empagliflozin 25 mg comparison appear to be identical to the above. It would be anticipated that there should be some minor differences for sitagliptin due to the slight differences in non-severe hypoglycaemia. But these differences are slight and may be sufficiently slight not to be reflected in the above.

See erratum

*Base case rerun results: Add-on to insulin*

The following presents the base case deterministic results for the patient population having therapy added to insulin.

**Table 41. Results: add-on to INS: empag. 10mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £6,737 | £7,129 | £7,132 | £6,976 | £7,145 | £7,633 |
| Management | £999 | £998 | £998 | £998 | £1,001 | £1,003 |
| Complications | £32,844 | £32,896 | £32,878 | £32,836 | £32,805 | £32,656 |
| Total | £40,580 | £41,023 | £41,008 | £40,810 | £40,951 | £41,292 |
| LYs (undisc.) | 18.902 | 18.884 | 18.909 | 18.903 | 18.965 | 19.030 |
| QALYs | | | | | | |
| No BMI effect | 7.814 | 7.804 | 7.810 | 7.817 | 7.832 | 7.858 |
| BMI coef. -0.0038 | 7.536 | 7.533 | 7.544 | 7.516 | 7.566 | 7.596 |
| BMI coef. -0.0061 | 7.369 | 7.370 | 7.384 | 7.335 | 7.406 | 7.439 |

**Table 42. Cost effectiveness: add-on to INS: empag. 10mg comparator effectiveness**

| | | | No BMI coef. | | ICERs for BMI coef. of | | |
|---|---|---|---|---|---|---|---|
| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
| Empagliflozin 10mg | £40,580 | | 7.814 | | | | |
| Sitagliptin 100mg | £40,810 | £230 | 7.817 | 0.003 | £76,667 | Dominated | Dominated |
| Canagliflozin 100mg | £40,951 | £371 | 7.832 | 0.018 | £20,611 | £12,367 | £9,973 |
| Dapagliflozin 10mg | £41,008 | £57 | 7.810 | -0.022 | Dominated | Dominated | Dominated |
| Empagliflozin 25mg | £41,023 | £72 | 7.804 | -0.028 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £41,292 | £341 | 7.858 | 0.026 | £13,115 | £11,367 | £10,525 |

Note that in the above, the cost effectiveness estimate of £20,611 for canagliflozin 100 mg is against empagliflozin 10 mg, on the grounds that the cost effectiveness estimate for sitagliptin 100 mg against empagliflozin 10 mg of £76,667 per QALY is outside acceptable bounds.

Canagliflozin 300 mg is estimate to yield an additional 0.044 QALY, 0.060 QALYs and 0.070 QALYs for BMI coefficients of zero, -0.0038 and -0.0061 at an additional cost of £712 when compared with empagliflozin 10 mg. These translate into cost effectiveness estimates of £16,182 per QALY, £11,827 per QALY and £10,230 per QALY.

Canagliflozin 300 mg is estimate to yield an additional 0.054 QALY, 0.063 QALYs and 0.068 QALYs for BMI coefficients of zero, -0.0038 and -0.0061 at an additional cost of £269 when compared with empagliflozin 25 mg. These translate into cost effectiveness estimates of £4,981 per QALY, £4,270 per QALY and £3,933 per QALY.

**Table 43. Results: add-on to INS: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £6,737 | £7,129 | £7,132 | £6,977 | £7,137 | £7,634 |
| Management | £999 | £998 | £998 | £999 | £1,000 | £1,004 |
| Complications | £32,844 | £32,896 | £32,878 | £33,007 | £32,643 | £32,590 |
| Total | £40,580 | £41,023 | £41,008 | £40,983 | £40,780 | £41,228 |
| LYs (undisc.) | 18.902 | 18.884 | 18.909 | 18.904 | 18.926 | 19.037 |
| QALYs | | | | | | |
| No BMI effect | 7.814 | 7.804 | 7.810 | 7.814 | 7.824 | 7.864 |
| BMI coef. -0.0038 | 7.536 | 7.533 | 7.544 | 7.514 | 7.558 | 7.602 |
| BMI coef. -0.0061 | 7.369 | 7.370 | 7.384 | 7.334 | 7.398 | 7.445 |

**Table 44. Cost effectiveness: add-on to INS: empag. 25mg comparator effectiveness**

| | | | No BMI coef. | | ICERs for BMI coef. of | | |
|---|---|---|---|---|---|---|---|
| | Costs | net | QALYs | net | None | -0.0038 | -0.0061 |
| Empagliflozin 10mg | £40,580 | | 7.814 | | | | |
| Canagliflozin 100mg | £40,780 | £200 | 7.824 | 0.010 | £20,000 | £9,091 | £6,849 |
| Sitagliptin 100mg | £40,983 | £203 | 7.814 | -0.010 | Dominated | Dominated | Dominated |
| Dapagliflozin 10mg | £41,008 | £228 | 7.810 | -0.014 | Dominated | Dominated | Dominated |
| Empagliflozin 25mg | £41,023 | £243 | 7.804 | -0.020 | Dominated | Dominated | Dominated |
| Canagliflozin 300mg | £41,228 | £448 | 7.864 | 0.040 | £11,200 | £10,182 | £9,655 |

Canagliflozin 300 mg is estimate to yield an additional 0.050 QALY, 0.066 QALYs and 0.076 QALYs for BMI coefficients of zero, -0.0038 and -0.0061 at an additional cost of £648 when compared with empagliflozin 10 mg. These translate into cost effectiveness estimates of £12,960 per QALY, £9,818 per QALY and £8,571 per QALY.

Canagliflozin 300 mg is estimate to yield an additional 0.060 QALY, 0.069 QALYs and 0.074 QALYs for BMI coefficients of zero, -0.0038 and -0.0061 at an additional cost of £205 when compared with empagliflozin 25 mg. These translate into cost effectiveness estimates of £3,417 per QALY, £2,971 per QALY and £2,755 per QALY.

## 5.5 Conclusions of the cost effectiveness section

The submission of the manufacturer is broadly in line with the scope, though there are some omissions in terms of comparators.

The comparison for add-on to metformin does not consider the sulfonylureas despite these being within the scope. It can be argued that the sulfonylureas are precursors in treatment, not comparators.

The GLP-1 analogues are not considered for any of the comparisons despite these being within the scope. In the opinion of the ERG this is justified because a gliptin or a flozin should be tried first before moving on to one of the much more expensive GLP-1 analogues, which have to be injected.

The manufacturer submission only tabulated the CORE modelling results as pairwise comparisons. In the opinion of the ERG it is more correct to tabulate all comparators alongside one another.

It appears that both the “deterministic” and the probabilistic modelling of the manufacturer adopted 2$^{nd}$ order sampling. If so, this means that no cost effectiveness estimates based upon the central

clinical effectiveness estimates have been presented by the manufacturer. It may also raise concerns about the reliable convergence of the cost effectiveness estimates of the manufacturer "deterministic" analyses.

In the opinion of the ERG, the estimates for the cost and the quality of life impacts of the complications of diabetes were not in line with those of the main cited references. But the biases that result tend to pull in opposite directions and so to some degree cancel out. The estimate for the quality of life impact from weight changes also appears not to be in line with the cited publication. Revising these elements results in deterministic cost effectiveness estimates which while quantitatively different from those of the manufacturer are broadly qualitatively the same.

The manufacturer submission only presented the probabilistic modelling for a subset of the pairwise comparisons that were undertaken. Given the uncertainty around the reliability and practical significance of some of the net QALY estimates, presenting the probabilistic modelling results may be particularly relevant to this assessment. The ACD also recommended that they be undertaken. CORE is unfortunately limited in its output, meaning that the probabilistic modelling can only be presented for the pairwise comparisons and that CEAFs cannot be constructed.

# 6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the ERG revised analyses are tabulated in section 5.4 above.

The ERG analyses revise the costs of complications and the utilities used, and also do not select 2nd order sampling as an option within CORE. Due to the time they take to run in CORE the ERG has not been able to perform any probabilistic analyses.
The ERG has revised the CORE economics module to apply the UKPDS 65 costs as calculated by the ERG and the UKPDS 62 quality of life decrements in favour of those drawn from Sullivan et al (2012) by the manufacturer.

For the comparisons as add-on to insulin the ERG has also revised the rates of UTIs for canagliflozin 300mg to be equal to 10.73 for the comparison with empagliflozin 10mg and to 9.30 for the comparison with empagliflozin 25 mg.

The ERG has undertaken analyses for quality of life decrements per BMI point of zero, 0.0038 and 0.0061. The 0.0061 value is preferred by the ERG. Note that these analyses assume that the initial net effect upon BMI is maintained for the patient lifetime. Convergence of a patient's BMIs between the arms over time would tend to cause the cost effectiveness estimates to fall somewhere between those that assume no BMI impact upon quality of life and those that assume the 0.0061 per BMI point.

*As add-on to metformin*
Empagliflozin is no longer estimated to be the least costly, with sitagliptin 100 mg now being so. Canagliflozin 100 mg and empagliflozin 25 mg are estimated to have broadly the same total costs, but empagliflozin 25mg is more effective. This leads to empagliflozin 25 mg either dominating or extendedly dominating canagliflozin 100 mg. As the BMI quality of life decrement is increased from zero to 0.0061 the cost effectiveness of empagliflozin 25 mg compared to sitagliptin 100 mg improves from around £1,373 per QALY to £686 per QALY. The other comparators are dominated by empagliflozin 25 mg if there is no quality of life decrement associated with BMI, though canagliflozin is of broadly the same effectiveness but more costly. As the BMI quality of life decrement is increased, canagliflozin 300 mg ceases to be formally dominated by empagliflozin 25 mg but does not approach conventional cost effectiveness thresholds.

*As add-on to metformin plus sulfonylurea*

Empagliflozin 25 mg is estimated to be the least costly, but canagliflozin 100 mg is only £40 more costly and yields an additional 0.030 QALYs if there is no quality of life impact from BMI, suggesting a cost effectiveness estimate of £1,333 per QALY. If the quality of life decrement of BMI is 0.0061 this estimate worsens to £3,226 per QALY. Empagliflozin 10 mg is associated with a higher cost and a QALY loss compared to canagliflozin 100 mg. Canagliflozin 300 mg is associated with an additional cost of £157 compared to canagliflozin 100 mg. But there is a gain of 0.030 QALYs and a cost effectiveness of £5,233 per QALY if there is no BMI quality of life impact, this improving to £2,996 per QALY for a BMI decrement of 0.0061.

For the pairwise comparison of empagliflozin 25 mg with canagliflozin 300 mg, if there is no BMI quality of life impact the cost effectiveness of canagliflozin 300 mg is estimated to be £3,283 per QALY with this improving to £3,040 per QALY for a BMI decrement of 0.0061.

*As add-on to metformin plus thiazolidinedione*

Sitagliptin 100mg is estimated to be the least costly, with canagliflozin 100mg being £130 more costly and slightly inferior if there is no quality of life impact from BMI. But a BMI decrement of 0.0061 causes a gain of 0.052 QALYs resulting in a cost effectiveness estimate of £2,321 per QALY.

Empagliflozin 10 mg and empagliflozin 25 mg are estimated to be £130 and £241 more costly than sitagliptin 100 mg, so cost neutral and £111 more costly than canagliflozin 100 mg. If there is no quality of life impact from BMI they are associated with losses of 0.044 QALYs and 0.022 QALYs compared to sitagliptin 100 mg. With a BMI decrement of 0.0061 canagliflozin 100 mg becomes the appropriate comparator, and they are associated with losses of 0.046 QALYs and 0.028 QALYs. Canagliflozin 300 mg is estimated to cost an additional £480 compared to sitagliptin and yield an additional 0.007 QALYs if there is no BMI quality of life impact, resulting in a cost effectiveness estimate of £68,571 per QALY. The BMI quality of life decrement of 0.0061 causes canagliflozin 100 mg to become the appropriate comparator, with the cost effectiveness of canagliflozin 300 mg relative to it being £9,358 per QALY.

*As add-on to insulin*

Empagliflozin is estimated to be the least costly, with canagliflozin 100 mg being between £200 and £371 more costly. A gain of between 0.010 QALYs and 0.018 QALYs from canagliflozin 100 mg is anticipated if there are no BMI quality of life impacts, resulting in cost effectiveness estimates of around £20,000 per QALY. The gains increase to between 0.029 QALYs and 0.037 QALYs for a BMI coefficient of 0.0061, resulting in cost effectiveness estimates of between £6,849 per QALY and £9,973 per QALY.

Canagliflozin 300 mg is estimated to be the most effective, with an additional cost of between £341 and £448 compared to canagliflozin 100 mg. Given gains of between 0.026 QALYs and 0.040 QALYs if there is no BMI quality of life impact these translate into cost effectiveness estimates of between £11,200 per QALY and £13,115 per QALY. For a BMI quality of life decrement of 0.0061 these cost effectiveness estimates improve to between £9,655 per QALY and £10,525 per QALY.

Comparing canagliflozin with empagliflozin 10 mg sees an additional cost of £712. With BMI quality of life impacts of zero and 0.0061 the gains are estimated to be 0.044 QALYs and 0.070 QALYs, resulting in cost effectiveness estimates of £16,182 per QALY and £10,230 per QALY.

Comparing canagliflozin with empagliflozin 25 mg sees an additional cost of £269. With BMI quality of life impacts of zero and 0.0061 the gains are estimated to be 0.054 QALYs and 0.068 QALYs, resulting in cost effectiveness estimates of £4,981 per QALY and £3,933 per QALY.

# 7 End of life

Not applicable.

# 8 Overall conclusions

The ERG was unable to exactly replicate the results of the manufacturer, despite cloning and re-running the manufacturer analyses within CORE. The differences that result do not change the qualitative nature of the CORE modelling results, but this is peculiar particularly in the light of it appearing unlikely that the differences are due to differences in random sampling.

The comparison between the results of the manufacturer and the results of the ERG are complicated by both sets of manufacturer analyses adopting the 2nd order sampling option of CORE. The ERG does not understand why the two sets of analyses run by the manufacturer both applied 2nd order sampling, the "deterministic" modelling over 1,000 patients over 1,000 bootstraps and the probabilistic modelling over 50,000 patients over 500 bootstraps. It is possible that the selection of 2nd order sampling for the "deterministic" modelling was a mistake.

The ERG analyses do not adopt the 2nd order sampling option of CORE. If the selection of 2nd order sampling by the manufacturer for the deterministic modelling was correct, the ERG approach is incorrect. The other differences with the manufacturer modelling are:

- The ERG has revised the utility inputs to reflect those of the UKPDS 62. This will tend to be to the benefit of the treatment that is more effective in terms of preventing complications.
- The ERG has revised the modelling inputs to return the costs of complications to those implied by the UKPDS 65. This will tend to be to the detriment of the treatment that is more effective in terms of preventing complications.
- The ERG has made some minor corrections to the inputs for the modelling of empagliflozin against canagliflozin 300mg for the comparisons as add-on to insulin. This will tend to be to the benefit of canagliflozin 300mg when compared to empagliflozin 25mg.
- The ERG has simulated no quality of life impact from changes in a patient's BMI, a quality of life reduction of 0.0038 per BMI point gained and a quality of life reduction of 0.0061 per BMI point gained. The 0.0038 reduction facilitates a comparison with the manufacturer results, while the 0.0061 reduction is the ERG preferred estimate.

These differences aside, the modelling of the ERG is much as per that of the manufacturer.

One difference is in the presentation of results, with the ERG choosing to rank treatments in order of increasing cost and present a tabulation of cost effectiveness across all comparators. The manufacturer chooses to only tabulate the pairwise comparisons, which the ERG found quite difficult to read and absorb. The ERG approach highlights dominance, quality of life gains where dominance does not occur and perhaps with greater certainty the anticipated differences in total costs.

As already noted, the ERG has not performed any probabilistic analyses. This is due to the time these take to run in CORE. The manufacturer presented a partial set of probabilistic analyses, with the empagliflozin versus canagliflozin analyses being absent from the add-on to metformin and add-on to insulin analyses. Perhaps due to the limitations of the CORE model outputs, these were also only presented for the pairwise comparison. As in the manufacturer "deterministic" analyses, there was no overall presentation of the probabilistic results across all comparators with an accompanying CEAF.

If the deterministic estimates are viewed as suggesting meaningful differences between the comparators, the conclusions of the deterministic analyses may be quite stark regardless of whether those of the manufacturer or the ERG are preferred. The broad thrust of the results of both the manufacturer and the ERG are similar. They may suggest that a key question is the extent that the modelled benefits of canagliflozin 300mg over empagliflozin 25mg are reliably estimated and meaningful, and do they justify the additional cost of canagliflozin 300 mg.

But it can be argued that the differences between some comparators within the analyses are relatively small, particularly in terms of the QALY differences. Modelling from interim outputs to the patient relevant complications of diabetes over a lifetime horizon makes the absolute size of these quite uncertain. In this context, probabilistic modelling that encompasses all comparators simultaneously could better inform decision making. Given the structure of CORE, the pairwise probabilistic modelling between the main comparators of interest may be have to be a sufficient second best.

The ERG was not able to replicate the manufacturer analyses that modelled a convergence over time in each patient's BMI. For the ERG preferred BMI coefficient of 0.0061 this would be anticipated to result in cost effectiveness estimates somewhere between those that assume no BMI quality of life impact and those that assume a 0.0061 reduction per point increase in the BMI.

# 9 Discussion

The clinical effectiveness of empagliflozin is not in doubt. The Boehringer NMA suggests that it is similar in effects to other flozins, and an independent academic NMA finds the same for use in dual therapy.

In the modelling, the differences in lifetime costs and lifetime QALYs are often very small, leading to unstable ICERs. The manufacturer comments on this in a footnote to table 1 of the submission; "*The incremental QALY of 0.001 represents an equivalent of 0.4 days and is probably not clinically meaningful".*

It is doubtful if even some larger differences are clinically meaningful. In the comparison of additions to metformin, against empagliflozin 25mg, the QALY differences range from 0.009 (about 3 days) to 0.096 (35 days). In comparisons of additions to metformin and SU, QALY differences range from 0.002 (0.7 days) to 0.15 (56 days), with lifetime cost differences ranging from £16 to £390.

What should be regarded as the minimum QALY difference that is clinically meaningful?

The cost differences over a lifetime are based on current drug costs. In reality, costs will fall once patents expire, and costs of gliptins such as sitagliptin will fall before those of the flozins do.

In the Boehringer submission, Table 3 gives reduction of HbA1c of 0.52% with sitagliptin 100mg. All the values in Table 3 correspond to Table 7 of the BI NMA report – the changes are all against placebo. This reduction is rather less than seen in the trials reviewed in the assessment report that underpinned the clinical guideline (CG 87) on type 2 diabetes. In two trials of adding sitagliptin to metformin in dual therapy, the reductions in HbA1c were 0.67% (Nauck 2007)[8] and 0.79% (Scott 2007)[9] (Details in HTA 2010/14/ number 36).[10] The baseline HbA1cs were similar to those in the empagliflozin modelling. The NMA also mentions a recent sitagliptin trial (Lavalle-Gonzalez 2013),[11] against canagliflozin where the HbA1c reduction with sitagliptin was 0.73%.

In a trial of adding sitagliptin to metformin and glimepiride in triple therapy, where a smaller reduction might be expected, the reduction with sitagliptin was 0.59% (Hermansen 2007)[12] which is similar to the assumption of 0.6% reduction with sitagliptin in the BI triple therapy modelling.

So taking both lifetime costs and HbA1c reductions into account, sitagliptin might have been expected to do a bit better in the dual therapy modelling, though gliptins tend to be weight neutral whereas flozins promote some weight loss, and flozins also have a modest effect on blood pressure.

Relative potencies of the flozins.

In addition to the SGLT2 transport system in the kidney, there is also a related transport system in the gut, SGLT1. Most SGLT2 inhibitors have no significant effect of SGLT1, but one of the class, canagliflozin, does affect SGLT1, and it has been suggested by Polidori and colleagues[13] that canagliflozin may reduce blood glucose by a dual action in both gut and kidney. However that suggestion followed a very short-term study of canagliflozin in healthy individuals, and the gut effect was seen only with higher doses (>200 mg).

Superseded

A very recent study by Polidori and colleagues from Janssen Research and Development looked at the SGLT1 effect in people with type 2 diabetes[14] found that canagliflozin 300 mg, but not a 150 mg dose, reduced post-prandial plasma glucose, by about 0.5 mmol/l (from graph) for about 2 hours after administration. Would a change of that magnitude be enough to make a clinically meaningful difference in HbA1c, experienced once a day?

See erratum

If the SGLT1 effect is clinically significant in people with type 2 diabetes, then one might expect canagliflozin 300 mg (but not 100 mg) to be more potent than other SGLT2 inhibitors without the SGTL1 effect. This was not found in the BI NMA, as shown in the extract below.

Table 45 Mean difference in HbA1c at 52 weeks in patients no longer responding adequately to metformin

| Treatment Regimen | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|
| Canagliflozin 300 mg | -0.07 (-0.24, 0.10) | -0.03 (-0.15, 0.08) |

In the independent NMA (Shyangdan et al, submitted for publication), slightly large differences between canagliflozin and empagliflozin in dual therapy were noted, but confidence intervals again overlapped with no difference. So the SGLT1 effect in dual therapy remains of unproven statistical significance.

Ideally, the sitagliptin versus empagliflozin question in dual therapy would be settled by a good quality trial looking at all outcomes and quality of life.

There is quite considerable variability within the modelled ICERs. The results of the NMA are appropriate as estimates for use in the cost effectiveness modelling, though it remains unclear to the ERG how the estimates for UTIs and GTIs have been derived.

While the CORE model is a black box to the ERG, the published results of the Mount Hood challenges suggest that it is among the better models for estimating the incidence of the complications of type 2 diabetes. ERG revisions to costs and utility inputs change cost effectiveness estimates, but probably do not change the qualitative conclusions that can be drawn from them.

The most challenging comparison for empagliflozin in the cost effectiveness modelling appears to be relative to canagliflozin 300mg. The modelled additional benefits from canagliflozin 300mg while small are not trivial. A key question will be the degree to which the assessment committee views these as being accurately estimated, bearing in mind the lack of significant differences in glucose-lowering effectiveness as discussed above. Consideration of this will also be qualified by the degree to which experts suggest canagliflozin is either the main comparator or is currently just one of several comparators that are in routine use within the NHS. The estimated differences between empagliflozin and the other comparators which have been examined suggest smaller differences, but with empagliflozin often being estimated to be cost effective relative to these comparators.

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# 11 Appendices

## 11.1 Appendix I. Summary of first ERG report

**Scope of manufacturer submission**

The industry submission from Boehringer Ingelheim covers use of empagliflozin in;

- dual therapy in people with diabetes that is not sufficiently controlled on metformin
- triple therapy in people whose diabetes is not well controlled on dual therapy with metformin and either a sulphonylurea or pioglitazone
- people whose diabetes is not well-controlled despite therapy with insulin and one or two oral agents

The submission identifies the main comparators as the other flozins, and the dipeptidyl peptidase-4 (DPP-4) inhibitors, referred to hereafter as the gliptins. In the modelling, the gliptin used as comparator is sitagliptin, because that is the one most commonly used in the UK.

The main difference between the scope of the Boehringer submission and the final scope issued by NICE was the omission of any comparison with the glucagon-like peptide-1 (GLP-1) analogue. Boehringer argue, and the ERG agrees, that the GLP-1 analogues belong at a different place in the treatment pathway. The ERG also agrees with the omission by Boehringer of insulin as a comparator, despite its listing as a comparator in the NICE scope.

**Clinical evidence submitted by the manufacturer.**

The manufacturer submitted data from seven trials and an extension study. The ERG regarded the most important of the trials as being;

- empagliflozin in dual therapy with metformin
- empagliflozin in triple therapy with metformin and a sulphonylurea (unspecified)
- empagliflozin used with regimens containing basal insulin
- empagliflozin used with regimens with multiple daily insulin injections (MDI)

The trials used two doses of empagliflozin, 10 mg and 25 mg daily.

Compared to placebo, empagliflozin reduced HbA1c;

- in dual therapy by 0.57% and 0.64% for 10 mg and 25 mg respectively, at 24 weeks
- in triple therapy, by 0.64% and 0.59% at 24 weeks
- in basal insulin regimens, by 0.46% and 0.62% at 78 weeks
- in MDI insulin regimens, by 0.38% and 0.46% at 52 weeks

In a trial in patients with renal impairment, HbA1c was reduced by 0.52% and 0.68% in those with mild renal impairment, and by 0.42% by the 25 mg dose in those with moderate renal impairment.

Empagliflozin was also associated with weight loss (via losing glucose and hence calories in the urine);

- in dual therapy, by 1.6 kg for the 10mg dose and 2.0 kg for the 25 mg dose, compared to placebo
- in triple therapy, by 1.8 and 2.0 kg
- in basal insulin regimens, by 3.6 kg and 3.1 kg (i.e. those on the larger dose lost less)
- with MDI insulin, by 1.5 and 1.6 kg

There were reductions in systolic blood pressure (SBP) ranging from 1.4mm Hg in the MDI trial, to 4.8 mg Hg in the dual therapy trial. In a short-duration (12 weeks) trial in patients with hypertension, SBP reductions were 3.4 and 4.2mm Hg for the two doses.
There were only small differences between the two doses of empagliflozin, with the lower dose sometimes reported to have greater effects.

Because there were no head to head trials of empagliflozin against the gliptins or other flozins, the submission provided data for modelling from a series of network meta-analyses. In brief, the results showed roughly equal effectiveness in glycaemic control amongst the flozins and the gliptins.

**ERG Commentary**

The main weakness in the evidence base was that all but one of the trials compared empagliflozin with placebo rather than active comparators such as a gliptin. One trial compared empagliflozin with glimepiride, a sulphonylurea, in dual therapy with metformin, but the ERG considered that this was less relevant because sulphonylureas should be a precursor to flozins, given the very low cost of the former. In the trial against glimepiride there was little difference in HbA1c (0.1%) but those on the sulphonylurea gained weight where those on the flozin lost weight, giving a difference of 4.5 kg at 2 years.

The ERG had some concerns with the network meta-analysis (NMA) in which some errors were detected, but correcting these made little difference – no difference in HbA1c results and only slight differences in hypoglycaemic episodes. The ERG therefore agrees with Boehringer that empagliflozin is comparable in clinical effectiveness with canagliflozin, dapagliflozin and sitagliptin.
No data on lipid changes were included in the clinical effectiveness submission.

The main adverse effects were urinary tract infections (UTIs) and genital infections, both seen mainly in women (women with UTIs about 12% on empagliflozin versus 8% on placebo). Hypoglycaemia was reported infrequently, and the definition used was ≤ 3.9mml/l which includes some of the normal range for plasma glucose. The ERG thinks it would be reasonable to say that empagliflozin does not cause hypoglycaemia.

The ERG had access to an independent academic NMA which confirmed that the three flozins were similar in effectiveness.

**Economic model used by Boehringer: ERG critique**

The model submitted was the Empagliflozin Cost Effectiveness Model (ECEM) written in visual basic, which is not on the NICE approved software list. As far as we know, this model has never been used in any previous NICE appraisals.

The ERG has cross checked a number of elements of the visual basic (VB) implementation of the ECEM. This has identified what may be a number of serious issues: random sampling at the patient level, modelling of the evolution of the risk factors, model convergence, model sensitivity to the random seeds chosen, questionable handling of the application of quality of life values to weight changes and a possible halving of the quality adjusted life year (QALY) decrements associated with adverse events and the complications of diabetes. If the manufacturer confirms that many of these are indeed errors, it will largely invalidate the submitted results. The ECEM has also been constructed so that it can only simulate 100 individual patients if 300 probabilistic sensitivity analysis (PSA) iterations are being conducted. These are unusually low numbers and may limit the ability of the ECEM to reliably discriminate between the overall impacts of different therapies.

Due to the extent and complexity of the coding of this new model, the ERG has not had time to parse all of VB code and there may be other problems not detected. It appears that there may have been a lack of validation and stress testing of the model, which may call into question the robustness and reliability of the remaining code.

These problems have implications for both the economic modelling included in the Boehringer submission, and for ERG analyses. If the problems are confirmed, neither can be regarded as reliable.

**Summary of cost-effectiveness evidence submitted by the manufacturer**

The Boehringer submission compares the cost-effectiveness of empagliflozin with sitagliptin, canagliflozin and dapagliflozin, in dual and triple oral therapy, and in insulin-containing regimens. Data on clinical effectiveness was taken from the NMA. Both doses of empagliflozin, canagliflozin

100mg daily, and dapagliflozin were costed at £477 per annum, with sitagliptin at £433 and canagliflozin 300 mg daily at £608. Modelling involved treatment effects for the evolutions of HbA1c, systolic blood pressure and weight.

Because the clinical effectiveness data from the NMA showed similar clinical effectiveness, differences in QALYs gained were very small, and often too small to matter. A QALY difference of 0.01 represents 3.65 days of perfect health. Cost differences over the 40 years modelled were also usually small, for example a few hundred pounds. Incremental cost-effectiveness analyses (ICERs) were therefore subject to considerable uncertainty and empagliflozin fluctuated from being dominated by sitagliptin to being dominant over sitagliptin.

**ERG commentary on cost-effectiveness analysis**

Serious problems with the model raise doubts about the estimates of cost-effectiveness and the uncertainty surrounding them. This does not necessarily mean that the conclusion of equivalence (based on clinical trial data and the NMA, and similar pricing) is incorrect, but the model is incapable of showing this in a robust way. For example, there is an error in converting utility per BMI point change into utility per 1 kg change, and this affects the estimation of the effect of weight change in the model.

The Boehringer submission states that;

"*The overall differences in QALYs and costs were marginal in all analyses and no treatment was clearly the optimum choice.*"

The ERG agrees with this summary. A few changes were made by the ERG and some model re-runs carried out, but differences were unimportant, with differences in QALYs ranging from 0.001 to 0.019.

**Conclusions**

The evidence from the trials of empagliflozin show that it is clinically effective in improving glycaemic control, though not dramatically so, with mean reductions in HbA1c ranging from 0.38 to 0.64%, when 0.5% is usually regarded as clinically meaningful. Empagliflozin also provides modest reductions in blood pressure and weight. Its clinical effectiveness is similar to other drugs already approved, canagliflozin, dapagliflozin, and sitagliptin.

Costs are similar, except for the higher dose of canagliflozin. Given that and the similar clinical effects, and despite concerns with model and modelling, the ERG expects empagliflozin to be as cost-effective as the comparators.

## 11.2 Appendix II. Problems with the original Boehringer NMAs

These included

- Although the search strategy was comprehensive the flow from recovered studies to included studies lacked clarity; e.g. the review process involved for applying study eligibility criteria was unspecified, eligibility criteria for comparators was somewhat ambiguous and did not include SU, the number of specified excluded studies was surprisingly small and the information on reasons for study exclusions lacked detail.

- Details of the data extraction process were not reported. For such a large amount of extracted data some assurance should be provided regarding steps taken to avoid human error.

- There was no assessment or mention of the quality of studies included in the NMA (Appendix 5 was blank). The MS may have been assumed that all RCTs were of acceptable quality but ERG could find no explicit statement to this effect.

- No sensitivity analyses or statistical tests were conducted for any of NMAs undertaken.

- There is some concern regarding the inclusion of studies in the major network for metformin based dual therapies; this is considered in more detail below.

- For the dual therapy NMA there were worrying discrepancies between input data, identification of treatments, and WINBUGS codes. These human errors probably result from insufficient checking during data extraction. Discrepancies encompassed: the exclusion from the WINBUGS code of studies listed as providing relevant data, the inclusion in the WINBUGS code of data from an unlisted and unidentified study, incorrect identification of treatment as saxagliptin rather than sitagliptin, inconsistent use of data from studies listed as providing zero event results for safety outcomes. ERG had insufficient time to check more of the coding, more errors might have been found. Note that not all the WinBUGS coding had been provided.

## 11.3 Appendix III. NMA results

In the tables, empagliflozin (10 or 25 mg dose) is the intervention while placebo or another SGLT-2i or sulphonylurea or sitagliptin is the comparator. For the outcomes [i] change in HbA1c (as a percentage), [ii] change in body weight (kg) and [iii] change in SBP (mm Hg), a negative mean difference infers more patient benefit from the intervention (i.e. empagliflozin) than the comparator. For the outcomes hypoglycaemia and urinary tract infection a relative risk less than 1 infers that patients are at reduced risk of unwanted events with empagliflozin while RR > 1 infers increased risk of these events for patients receiving empagliflozin.

In the tables that follow the reported results for mean difference outcomes or for relative risk outcomes are summarised in a separate table for therapy and weeks follow up (24 or 52 weeks follow up).

## OUTCOMES REPORTED AS MEAN DIFFERENCE

**Figure 6. Dual therapy– 24 weeks; patients no longer responding adequately to metformin (MET)**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.57 | -0.70, | -0.44 | -1.76 | -2.49 | -1.02 | -4.21 | -6.02 | -2.38 |
| Versus SU | 0.15 | 0.02 | 0.28 | -4.10 | -4.84 | -3.30 | -4.55 | -6.51 | -2.6 |
| Versus Dapagliflozin 10 | -0.05 | -0.2 | 0.09 | 0.28 | -0.54 | 1.12 | -0.3 | -2.42 | 1.84 |
| Versus Canagliflozin 100 | 0.01 | -0.14 | 0.16 | 0.22 | -0.66 | 1.17 | -0.32 | -2.48 | 1.84 |
| Versus Canagliflozin 300 | 0.13 | -0.02 | 0.28 | 0.87 | -0.01 | 1.81 | 0.99 | -1.19 | 3.13 |
| Versus sitagliptin 100 | 0.01 | -0.13 | 0.14 | -1.92 | -2.68 | -1.07 | -2.06 | -4.34 | 0.22 |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.64 | -0.73 | -0.56 | -2.28 | -2.83 | -1.72 | -5.01 | -6.42 | -3.62 |
| Versus SU | 0.08 | 0.00 | 0.16 | -4.62 | -5.11 | -4.03 | -5.37 | -6.57 | -4.16 |
| Versus Empagliflozin 10 | -0.07 | -0.2 | 0.05 | -0.52 | -1.24 | 0.22 | -0.81 | -2.63 | 0.99 |
| Versus Dapagliflozin 10 | -0.12 | -0.23 | -0.02 | -0.23 | -0.89 | 0.43 | -1.1 | -2.73 | 0.53 |
| Versus Canagliflozin 100 | -0.06 | -0.17 | 0.05 | -0.29 | -1.01 | 0.49 | -1.13 | -2.77 | 0.53 |
| Versus Canagliflozin 300 | 0.06 | -0.05 | 0.16 | 0.36 | -0.37 | 1.14 | 0.17 | -1.46 | 1.82 |
| Versus sitagliptin 100 | -0.07 | -0.15 | 0.02 | -2.44 | -3.01 | -1.76 | -2.87 | -4.72 | -1.01 |
| SU V PBO | -0.72 | -0.79 | -0.66 | 2.34 | 1.93 | 2.68 | 0.35 | -0.89 | 1.59 |
| Sitagliptin 100 V PBO | -0.58 | -0.64, | -0.52 | 0.16 | -0.28 | 0.53 | -2.15 | -3.65 | -0.63 |
| Dapagliflozin 10 V PBO | -0.52 | -0.60, | -0.44 | -2.05 | -2.46 | -1.63 | -3.91 | -5.28 | -2.55 |
| Canagliflozin 100 V PBO | -0.58 | -0.67, | -0.49 | -2.63 | -3.25 | -2.06 | -3.89 | -5.3 | -2.46 |
| Canaglifozin 300 V PBO | -0.70 | -0.79, | -0.61 | -2.63 | -3.25 | -2.06 | -5.19 | -6.6 | -3.77 |

## OUTCOMES REPORTED AS RELATIVE RISK

**Figure 7. Relative risk of hypoglycaemia (overall) at 24 weeks in dual, triple and insulin add on therapies**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | 2.07 | 0.34 | 7.71 |
| Dual | empag 25 | Sulphonylurea | 1.22 | 0.19 | 5.26 |
| Dual | empag 25 | Empagliflozin 10 mg | 0.76 | 0.15 | 3.45 |
| Dual | empag 25 | Dapagliflozin 2.5 mg | 2.38 | 0.26 | 20.00 |
| Dual | empag 25 | Dapagliflozin 5 mg | 1.00 | 0.14 | 5.26 |
| Dual | empag 25 | Dapagliflozin 10 mg | 1.64 | 0.24 | 7.69 |
| Dual | empag 25 | Sitagliptin 100 mg | 4.35 | 0.67 | 20.00 |
| Dual | empag 10 | placebo | 2.74 | 0.54 | 9.07 |
| Dual | empag 10 | Sulphonylurea | 1.61 | 0.29 | 6.25 |
| Dual | empag 10 | Empagliflozin 25 mg | 1.32 | 0.29 | 6.67 |
| Dual | empag 10 | Dapagliflozin 2.5 mg | 3.13 | 0.40 | 25.00 |
| Dual | empag 10 | Dapagliflozin 5 mg | 1.33 | 0.21 | 6.25 |
| Dual | empag 10 | Dapagliflozin 10 mg | 2.17 | 0.36 | 9.09 |
| Dual | empag 10 | Sitagliptin 100 mg | 5.88 | 1.02 | 25.00 |
| Triple | empag 25 | placebo | 1.27 | 0.74 | 2.17 |
| Triple | empag 25 | Empagliflozin 10 mg | 0.76 | 0.47 | 1.23 |
| Triple | empag 25 | Canagliflozin 100 mg | 0.71 | 0.26 | 2.00 |
| Triple | empag 25 | Canagliflozin 300 mg | 0.86 | 0.30 | 2.56 |
| Triple | empag 10 | placebo | 1.67 | 1.01 | 2.75 |
| Triple | empag 10 | Empagliflozin 25 mg | 1.32 | 0.81 | 2.13 |
| Triple | empag 10 | Canagliflozin 100 mg | 0.93 | 0.35 | 2.63 |
| Triple | empag 10 | Canagliflozin 300 mg | 1.12 | 0.40 | 3.33 |
| insulin + on | empag 25 | placebo | 1.22 | 0.96 | 1.53 |
| insulin + on | empag 25 | Empagliflozin 10 mg | 1.18 | 0.93 | 1.49 |
| insulin + on | empag 25 | Dapagliflozin 2.5 mg | 0.85 | 0.60 | 1.20 |
| insulin + on | empag 25 | Dapagliflozin 5 mg | 1.03 | 0.72 | 1.49 |
| insulin + on | empag 25 | Dapagliflozin 10 mg | 1.12 | 0.78 | 1.64 |
| insulin + on | empag 25 | Canagliflozin 100 mg | 0.85 | 0.64 | 1.11 |
| insulin + on | empag 25 | Canagliflozin 300 mg | 0.87 | 0.65 | 1.14 |
| insulin + on | empag 25 | Sitagliptin 100 mg | 0.61 | 0.45 | 0.80 |
| insulin + on | empag 10 | placebo | 1.03 | 0.80 | 1.32 |
| insulin + on | empag 10 | Empagliflozin 10 mg | 0.85 | 0.67 | 1.06 |
| insulin + on | empag 10 | Dapagliflozin 2.5 mg | 0.71 | 0.50 | 1.02 |
| insulin + on | empag 10 | Dapagliflozin 5 mg | 0.88 | 0.60 | 1.27 |
| insulin + on | empag 10 | Dapagliflozin 10 mg | 0.95 | 0.65 | 1.39 |
| insulin + on | empag 10 | Canagliflozin 100 mg | 0.72 | 0.53 | 0.96 |
| insulin + on | empag 10 | Canagliflozin 300 mg | 0.73 | 0.54 | 0.98 |
| insulin + on | empag 10 | Sitagliptin 100 mg | 0.51 | 0.38 | 0.68 |

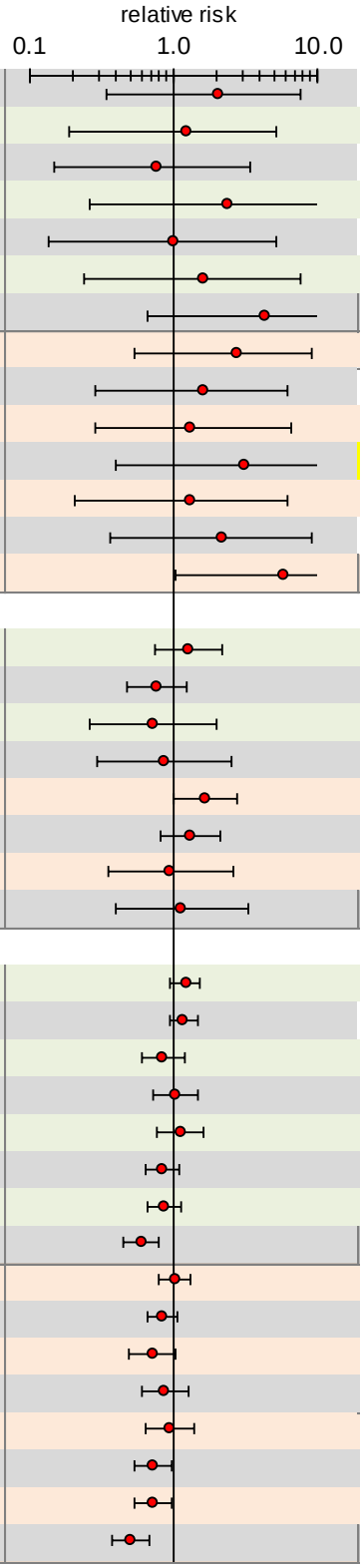


**Figure 8. Relative risk of non-severe hypoglycaemia at 24 weeks in dual, triple and insulin add on therapies**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | 1.99 | 0.32 | 7.57 |
| Dual | empag 25 | Sulphonylurea | 1.22 | 0.18 | 5.26 |
| Dual | empag 25 | Empagliflozin 10 mg | 0.75 | 0.14 | 3.33 |
| Dual | empag 25 | Dapagliflozin 2.5 mg | 2.22 | 0.24 | 20.00 |
| Dual | empag 25 | Dapagliflozin 5 mg | 0.93 | 0.12 | 5.00 |
| Dual | empag 25 | Dapagliflozin 10 mg | 1.47 | 0.20 | 7.14 |
| Dual | empag 25 | Sitagliptin 100 mg | 4.35 | 0.64 | 20.00 |
| Dual | empag 10 | placebo | 2.71 | 0.52 | 9.04 |
| Dual | empag 10 | Sulphonylurea | 1.67 | 0.29 | 6.25 |
| Dual | empag 10 | Empagliflozin 25 mg | 1.33 | 0.30 | 7.14 |
| Dual | empag 10 | Dapagliflozin 2.5 mg | 3.03 | 0.37 | 25.00 |
| Dual | empag 10 | Dapagliflozin 5 mg | 1.27 | 0.20 | 6.25 |
| Dual | empag 10 | Dapagliflozin 10 mg | 1.96 | 0.32 | 8.33 |
| Dual | empag 10 | Sitagliptin 100 mg | 5.88 | 1.02 | 25.00 |
| Triple | empag 25 | placebo | 1.34 | 0.78 | 2.27 |
| Triple | empag 25 | Empagliflozin 10 mg | 0.83 | 0.50 | 1.32 |
| Triple | empag 25 | Canagliflozin 100 mg | 0.74 | 0.26 | 2.13 |
| Triple | empag 25 | Canagliflozin 300 mg | 0.89 | 0.31 | 2.70 |
| Triple | empag 10 | placebo | 1.62 | 0.97 | 2.66 |
| Triple | empag 10 | Empagliflozin 25 mg | 1.22 | 0.76 | 2.00 |
| Triple | empag 10 | Canagliflozin 100 mg | 0.89 | 0.32 | 2.50 |
| Triple | empag 10 | Canagliflozin 300 mg | 1.08 | 0.38 | 3.23 |
| insulin + on | empag 25 | placebo | 1.20 | 0.94 | 1.54 |
| insulin + on | empag 25 | Empagliflozin 10 mg | 1.18 | 0.92 | 1.52 |
| insulin + on | empag 25 | Dapagliflozin 2.5 mg | 0.82 | 0.56 | 1.20 |
| insulin + on | empag 25 | Dapagliflozin 5 mg | 1.02 | 0.69 | 1.49 |
| insulin + on | empag 25 | Dapagliflozin 10 mg | 1.11 | 0.75 | 1.67 |
| insulin + on | empag 25 | Canagliflozin 100 mg | 0.82 | 0.61 | 1.10 |
| insulin + on | empag 25 | Canagliflozin 300 mg | 0.85 | 0.63 | 1.14 |
| insulin + on | empag 25 | placebo | 1.03 | 0.79 | 1.32 |
| insulin + on | empag 10 | Empagliflozin 25 mg | 0.85 | 0.66 | 1.10 |
| insulin + on | empag 10 | Dapagliflozin 2.5 mg | 0.70 | 0.48 | 1.03 |
| insulin + on | empag 10 | Dapagliflozin 5 mg | 0.87 | 0.59 | 1.30 |
| insulin + on | empag 10 | Dapagliflozin 10 mg | 0.94 | 0.63 | 1.43 |
| insulin + on | empag 10 | Canagliflozin 100 mg | 0.70 | 0.52 | 0.95 |
| insulin + on | empag 10 | Canagliflozin 300 mg | 0.72 | 0.53 | 0.98 |

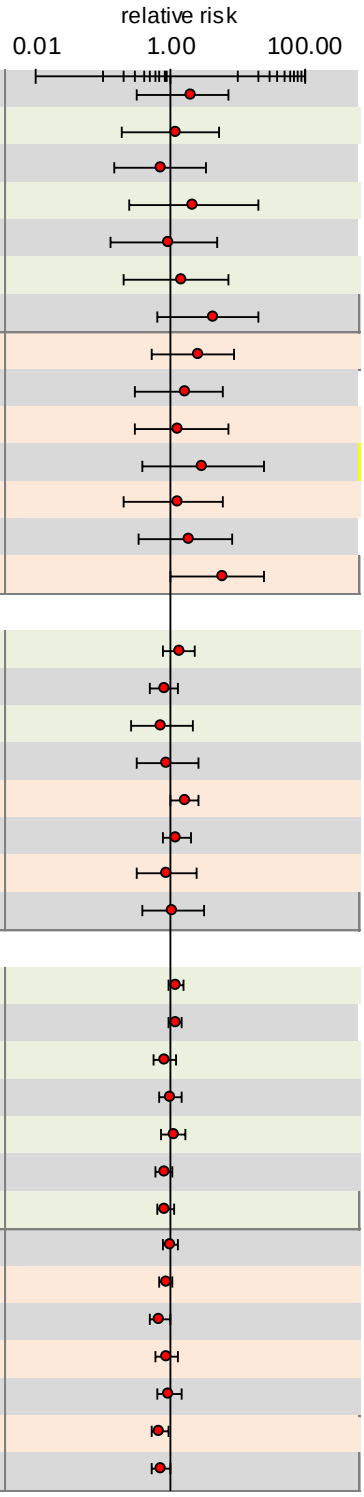


**Figure 9. Relative risk of severe hypoglycaemia at 24 weeks in insulin add on therapy**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| insulin + on | empag 25 | placebo | 1.32 | 0.25 | 4.71 |
| insulin + on | empag 25 | Empagliflozin 10 mg | 3.85 | 0.41 | 36.39 |
| insulin + on | empag 25 | Dapagliflozin 2.5 mg | 33.33 | 0.55 | 2033.33 |
| insulin + on | empag 25 | Dapagliflozin 5 mg | 0.72 | 0.08 | 8.33 |
| insulin + on | empag 25 | Dapagliflozin 10 mg | 33.33 | 0.55 | 2055.56 |
| insulin + on | empag 25 | Canagliflozin 100 mg | 1.89 | 0.30 | 9.09 |
| insulin + on | empag 25 | Canagliflozin 300 mg | 1.19 | 0.20 | 5.26 |
| insulin + on | empag 10 | placebo | 0.34 | 0.05 | 2.27 |
| insulin + on | empag 10 | Empagliflozin 25 mg | 0.26 | 0.01 | 6.04 |
| insulin + on | empag 10 | Dapagliflozin 2.5 mg | 7.14 | 0.07 | 755.10 |
| insulin + on | empag 10 | Dapagliflozin 5 mg | 0.19 | 0.01 | 3.23 |
| insulin + on | empag 10 | Dapagliflozin 10 mg | 7.14 | 0.07 | 767.86 |
| insulin + on | empag 10 | Canagliflozin 100 mg | 0.48 | 0.01 | 7.24 |
| insulin + on | empag 10 | Canagliflozin 300 mg | 0.30 | 0.02 | 11.63 |

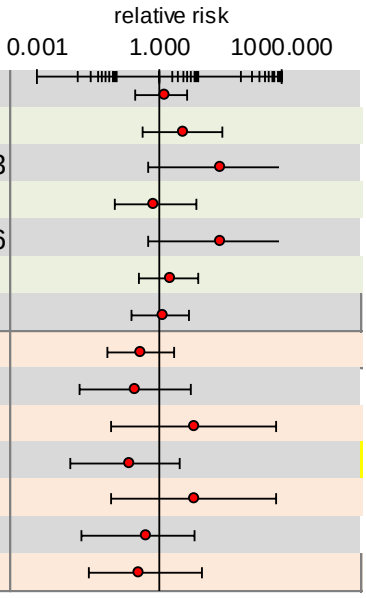



**Figure 10. Relative risk of urinary tract infections at 24 weeks in dual and insulin add on therapies**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | placebo | 1.13 | 0.31 | 4.35 |
| Dual | empag 25 | Empagliflozin 10 mg | 0.97 | 0.27 | 3.57 |
| Dual | empag 25 | Dapagliflozin 2.5 mg | 2.04 | 0.31 | 14.29 |
| Dual | empag 25 | Dapagliflozin 5 mg | 1.06 | 0.23 | 5.56 |
| Dual | empag 25 | Dapagliflozin 10 mg | 0.72 | 0.16 | 3.33 |
| Dual | empag 25 | Sitagliptin 100 mg | 1.15 | 0.23 | 6.25 |
| Dual | empag 10 | placebo | 1.18 | 0.31 | 4.16 |
| Dual | empag 10 | Empagliflozin 25 mg | 1.03 | 0.28 | 3.70 |
| Dual | empag 10 | Dapagliflozin 2.5 mg | 2.13 | 0.34 | 14.29 |
| Dual | empag 10 | Dapagliflozin 5 mg | 1.12 | 0.24 | 5.00 |
| Dual | empag 10 | Dapagliflozin 10 mg | 0.74 | 0.17 | 3.33 |
| Dual | empag 10 | Sitagliptin 100 mg | 1.19 | 0.25 | 5.56 |
| | | | | | |
| insulin + on | empag 25 | placebo | 1.43 | 0.65 | 3.08 |
| insulin + on | empag 25 | Empagliflozin 10 mg | 0.88 | 0.41 | 1.85 |
| insulin + on | empag 25 | Dapagliflozin 2.5 mg | 0.86 | 0.24 | 2.94 |
| insulin + on | empag 25 | Dapagliflozin 5 mg | 0.75 | 0.21 | 2.50 |
| insulin + on | empag 25 | Dapagliflozin 10 mg | 0.76 | 0.21 | 2.56 |
| insulin + on | empag 10 | placebo | 1.65 | 0.78 | 3.41 |
| insulin + on | empag 10 | Empagliflozin 25 mg | 1.15 | 0.55 | 2.44 |
| insulin + on | empag 10 | Dapagliflozin 2.5 mg | 0.98 | 0.28 | 3.45 |
| insulin + on | empag 10 | Dapagliflozin 5 mg | 0.85 | 0.26 | 2.86 |
| insulin + on | empag 10 | Dapagliflozin 10 mg | 0.87 | 0.26 | 2.86 |

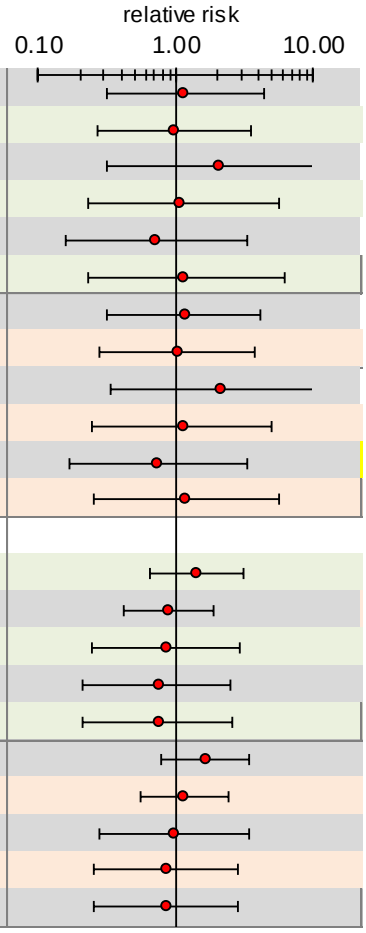


**Figure 11. Relative risk of hypoglycaemia at 52 weeks in dual therapy**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | Sulphonylurea | 0.09 | 0.05 | 0.14 |
| Dual | empag 25 | Dapagliflozin 10 mg | 1.39 | 0.64 | 3.13 |
| Dual | empag 25 | Canagliflozin 100 mg | 0.65 | 0.33 | 1.28 |
| Dual | empag 25 | Canagliflozin 300 mg | 0.74 | 0.36 | 1.47 |
| Dual | empag 25 | Sitagliptin 100 mg | 0.68 | 0.34 | 1.30 |

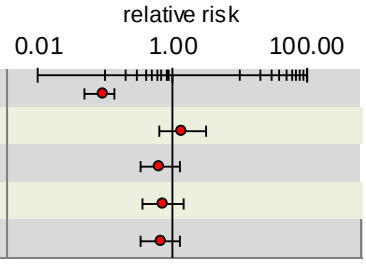



**Figure 12. Relative risk of non-severe hypoglycaemia at 52 weeks in dual therapy**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | Sulphonylurea | 0.10 | 0.05 | 0.16 |
| Dual | empag 25 | Sitagliptin 100 mg | 0.67 | 0.33 | 1.30 |

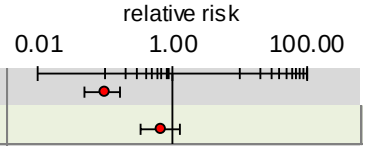
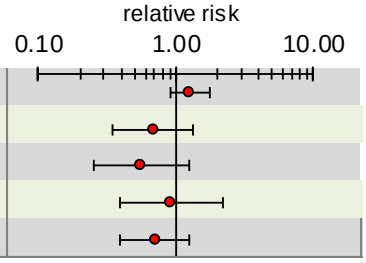



**Figure 13. Relative risk of urinary tract infection at 52 weeks in dual therapy**

| | empag | comparator | RR | LCI | UCI |
|---|---|---|---|---|---|
| Dual | empag 25 | Sulphonylurea | 1.25 | 0.90 | 1.74 |
| Dual | empag 25 | Dapagliflozin 10 mg | 0.69 | 0.35 | 1.33 |
| Dual | empag 25 | Canagliflozin 100 mg | 0.56 | 0.25 | 1.23 |
| Dual | empag 25 | Canagliflozin 300 mg | 0.91 | 0.39 | 2.17 |
| Dual | empag 25 | Sitagliptin 100 mg | 0.70 | 0.39 | 1.25 |



## PLACEBO RESPONSE RATES REPORTED REQUIRED FOR CORE MODEL

**Table 46. Dual therapy; Hypoglycaemia and urinary tract infections**

| | | Overall hypoglycemia | Non severe hypoglycemia | Urinary tract infections |
|---|---|---|---|---|
| Placebo | Proportion | 0.01 | 0.01 | 0.03 |
| | 95% Credible interval | (0.01 to 0.02) | (0.01 to 0.02) | (0.02 to 0.04) |

**Table 47. Triple therapy; Hypoglycaemia and urinary tract infections**

| | | Overall hypoglycaemia | Non severe hypoglycaemia | Urinary tract infections |
|---|---|---|---|---|
| Placebo | Proportion | 0.08 | 0.08 | 0.06 |
| | 95% Credible interval | (0.04 to 0.13) | (0.04 to 0.13) | (0.05 to 0.09) |

**Table 48. Insulin add on therapy; Hypoglycaemia**

| | | Overall hypoglycaemia | Non severe hypoglycaemia | Urinary tract infections |
|---|---|---|---|---|
| Placebo | Proportion | 0.26 | 0.24 | 0.03 |
| | 95% Credible interval | (0.25 to 0.28) | (0.23 to 0.26) | (0.02 to 0.05) |

**Figure 14. Dual therapy 52 weeks – patients no longer responding adequately to metformin (MET)**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.58 | -0.72 | -0.45 | -1.75 | -2.27 | -1.22 | -2.89 | -4.84 | -0.94 |
| Versus SU | -0.06 | -0.21 | 0.08 | -4.22 | -4.8 | -3.63 | -4.2 | -6.58 | -1.79 |
| Versus Dapagliflozin 10 | -0.11 | -0.27 | 0.04 | 0.47 | -0.24 | 1.17 | 0.9 | -1.91 | 3.78 |
| Versus Canagliflozin 100 | -0.06 | -0.23 | 0.11 | 0.24 | -0.51 | 0.99 | -0.63 | -3.42 | 2.15 |
| Versus Canagliflozin 300 | 0.07 | -0.1 | 0.24 | 0.59 | -0.17 | 1.34 | 0.54 | -2.26 | 3.35 |
| Versus sitagliptin 100 | -0.07 | -0.24 | 0.1 | -1.81 | -2.6 | -1.03 | -3.49 | -6.62 | -0.34 |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.62 | -0.73 | -0.5 | -2.33 | -2.83 | -1.83 | -4.49 | -6.44 | -2.57 |
| Versus SU | -0.1 | -0.17 | -0.02 | -4.8 | -5.1 | -4.5 | -5.8 | -7.19 | -4.41 |
| Versus Empagliflozin 10 | -0.03 | -0.16 | 0.1 | -0.58 | -1.1 | -0.06 | -1.6 | -3.56 | 0.34 |
| Versus Dapagliflozin 10 | -0.15 | -0.26 | -0.03 | -0.12 | -0.65 | 0.41 | -0.7 | -2.78 | 1.41 |
| Versus Canagliflozin 100 | -0.09 | -0.21 | 0.03 | -0.35 | -0.9 | 0.21 | -2.23 | -4.24 | -0.23 |
| Versus Canagliflozin 300 | 0.03 | -0.08 | 0.15 | 0 | -0.55 | 0.56 | -1.07 | -3.07 | 0.94 |
| Versus sitagliptin 100 | -0.1 | -0.22 | 0.02 | -2.4 | -2.99 | -1.8 | -5.09 | -7.56 | -2.63 |
| SU V PBO | -0.52 | -0.64 | -0.4 | 2.47 | 1.91 | 3.03 | 1.31 | -1.06 | 3.67 |
| Sitagliptin 100 V PBO | -0.52 | -0.67 | -0.37 | 0.07 | -0.69 | 0.83 | 0.6 | -2.55 | 3.74 |
| Dapagliflozin 10 V PBO | -0.47 | -0.58 | -0.36 | -2.21 | -2.87 | -1.55 | -3.8 | -6.65 | -0.94 |
| Canagliflozin 100 V PBO | -0.52 | -0.68 | -0.37 | -1.98 | -2.71 | -1.25 | -2.25 | -5.05 | 0.51 |
| Canaglifozin 300 V PBO | -0.65 | -0.8 | -0.5 | -2.33 | -3.06 | -1.6 | -3.42 | -6.2 | -0.66 |

**Figure 15. Triple therapy 24 weeks; patients no longer responding adequately to metformin + sulphonylurea**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.65 | -0.79 | -0.51 | -1.77 | -2.19 | -1.36 | -2.7 | -4.66 | -0.73 |
| Versus Empagliflozin 25 | -0.05 | -0.19 | 0.09 | 0.23 | -0.2 | 0.66 | -0.58 | -2.55 | 0.58 |
| Versus Canagliflozin 100 | 0.11 | -0.14 | 0.35 | -0.51 | -1.26 | 0.25 | -0.37 | -3.65 | 0.37 |
| Versus Canagliflozin 300 | 0.36 | 0.15 | 0.57 | -0.09 | -0.76 | 0.59 | -0.98 | -4.26 | 0.98 |
| Versus Sitagliptin 100 | 0.16 | -0.05 | 0.37 | -2.76 | -3.45 | -2.06 | -7.02 | -10.8 | 7.02 |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.6 | -0.74 | -0.46 | -2 | -2.44 | -1.57 | -2.09 | -4.05 | -0.17 |
| Versus Empagliflozin 10 | 0.05 | -0.09 | 0.19 | -0.23 | -0.66 | 0.2 | 0.58 | -1.36 | -0.58 |
| Versus Canagliflozin 100 | 0.16 | -0.09 | 0.4 | -0.74 | -1.5 | 0.02 | 0.22 | -3.01 | -0.22 |
| Versus Canagliflozin 300 | 0.41 | 0.2 | 0.62 | -0.32 | -1 | 0.36 | -0.4 | -3.64 | 0.4 |
| Versus Sitagliptin 100 | 0.21 | 0 | 0.42 | -2.99 | -3.68 | -2.29 | -6.42 | -10.1 | 6.42 |
| Sitagliptin 100 V PBO | -0.81 | -0.97 | -0.65 | 0.99 | 0.44 | 1.54 | 4.33 | 1.15 | 7.43 |
| Canagliflozin 100 V PBO | -0.76 | -0.96 | -0.56 | -1.26 | -1.88 | -0.63 | -2.3 | -4.92 | 0.36 |
| Canaglifozin 300 V PBO | -1.01 | -1.16 | -0.85 | -1.69 | -2.21 | -1.15 | -1.7 | -4.27 | 0.92 |

**Figure 16. Triple therapy 52 weeks; patients no longer responding adequately to metformin + sulphonylurea**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.71 | -0.88 | -0.54 | -2.00 | -2.49 | -1.51 | -2.8 | -4.89 | -0.72 |
| Versus Empagliflozin 25 | -0.02 | -0.19 | 0.15 | 0.05 | -0.49 | 0.59 | -0.09 | -2.19 | 1.98 |
| Versus Canagliflozin 100 | 0.04 | -0.23 | 0.31 | -0.72 | -1.68 | 0.23 | 1 | -2.59 | 4.59 |
| Versus Canagliflozin 300 | 0.26 | -0.01 | 0.53 | 0.28 | -0.68 | 1.24 | 0.2 | -3.28 | 3.69 |
| Versus Sitagliptin 100 | -0.11 | -0.41 | 0.19 | -2.37 | -3.4 | -1.35 | -5.79 | -9.74 | -1.86 |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.69 | -0.86 | -0.52 | -2.05 | -2.56 | -1.55 | -2.72 | -4.94 | -0.48 |
| Versus Empagliflozin 10 | 0.02 | 0.19 | -0.15 | -0.05 | -0.59 | 0.49 | 0.09 | -1.98 | 2.19 |
| Versus Canagliflozin 100 | 0.06 | 0.33 | -0.21 | -0.77 | -1.75 | 0.19 | 1.1 | -2.6 | 4.77 |
| Versus Canagliflozin 300 | 0.28 | 0.55 | -0.1 | 0.22 | -0.74 | 1.2 | 0.28 | -3.27 | 3.88 |
| Versus Sitagliptin 100 | -0.09 | 0.21 | -0.39 | -2.42 | -3.45 | -1.38 | -5.7 | -9.69 | -1.68 |
| Sitagliptin 100 V PBO | -0.6 | -0.85 | -0.35 | 0.37 | -0.53 | 1.27 | 2.99 | -0.35 | 6.33 |
| Canagliflozin 100 V PBO | -0.75 | -0.96 | -0.54 | -1.28 | -2.11 | -0.44 | -3.82 | -6.75 | -0.85 |
| Canaglifozin 300 V PBO | -0.97 | -1.18 | -0.76 | -2.28 | -3.11 | -1.46 | -3.00 | -5.81 | -0.21 |

**Figure 17. Insulin add on therapy 24 weeks; patients no longer responding to insulin with other treatment**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.5 | -0.61 | -0.39 | -1.44 | -3.1 | -0.16 | -2.86 | -4.5 | -1.17 |
| Versus Empagliflozin 25 | 0.07 | -0.04 | 0.19 | 0.24 | -1.62 | 1.41 | -0.59 | -2.3 | 1.06 |
| Versus Dapagliflozin 2.5 | -0.1 | -0.29 | 0.09 | -0.09 | -2.64 | 2.15 | -2.17 | -5.29 | 1.04 |
| Versus Dapagliflozin 5 | 0 | -0.19 | 0.19 | -0.01 | -2.56 | 2.18 | -0.48 | -3.54 | 2.67 |
| Versus Dapagliflozin 10 | 0.07 | -0.12 | 0.26 | 0.61 | -1.92 | 2.79 | 0.27 | -3.06 | 3.36 |
| Versus Canagliflozin 100 | 0.14 | -0.06 | 0.34 | 0.4 | -2.21 | 2.64 | -0.26 | -3.62 | 3.08 |
| Versus Canagliflozin 300 | 0.23 | 0.03 | 0.43 | 0.89 | -1.68 | 3.14 | 1.53 | -1.73 | 5.12 |
| Versus Sitagliptin 100 | 0.1 | -0.08 | 0.28 | -1.44 | -4.03 | 0.79 | NR | NR | NR |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.57 | -0.69 | -0.46 | -1.68 | -3.01 | 0 | -2.27 | -3.88 | -0.51 |
| Versus Empagliflozin 25 | -0.07 | -0.19 | 0.04 | -0.24 | -1.41 | 1.62 | 0.59 | -1.06 | 2.30 |
| Versus Dapagliflozin 2.5 | -0.17 | -0.36 | 0.02 | -0.33 | -2.53 | 2.22 | -1.57 | -4.74 | 1.60 |
| Versus Dapagliflozin 5 | -0.07 | -0.26 | 0.11 | -0.26 | -2.45 | 2.38 | 0.11 | -2.79 | 3.14 |
| Versus Dapagliflozin 10 | 0 | -0.19 | 0.18 | 0.36 | -1.85 | 2.99 | 0.82 | -2.3 | 4.18 |
| Versus Canagliflozin 100 | 0.07 | -0.14 | 0.26 | 0.15 | -2.04 | 2.78 | 0.36 | -3.03 | 3.68 |
| Versus Canagliflozin 300 | 0.15 | -0.04 | 0.35 | 0.65 | -1.53 | 3.28 | 2.18 | -1.27 | 5.61 |
| Versus Sitagliptin 100 | 0.03 | -0.15 | 0.2 | -1.69 | -3.9 | 0.91 | NR | NR | NR |
| Dapagliflozin 2.5 V PBO | -0.4 | -0.55 | -0.25 | -1.36 | -3.24 | 0.53 | -0.69 | -3.45 | 2 |
| Dapagliflozin 5 V PBO | -0.5 | -0.65 | -0.35 | -1.44 | -3.3 | 0.43 | -2.4 | -4.98 | 0.28 |
| Dapagliflozin 5 V PBO | -0.57 | -0.72 | -0.42 | -2.05 | -3.97 | -0.14 | -3.13 | -5.85 | -0.39 |
| Canagliflozin 100 V PBO | -0.64 | -0.8 | -0.47 | -1.84 | -3.74 | 0.02 | -2.63 | -5.42 | 0.18 |
| Canaglifozin 300 V PBO | -0.73 | -0.89 | -0.57 | -2.33 | -4.24 | -0.48 | -4.4 | -7.34 | -1.56 |
| Sitagliptin 100 V PBO | -0.6 | -0.74 | -0.46 | 0 | -1.88 | 1.86 | NR | NR | NR |

**Figure 18. Insulin add on therapy 52 weeks; patients no longer responding to insulin with other treatment**

| COMPARISON | MEAN DIFFERENCE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HbA1c (%) | | | BODY WEIGHT (kg) | | | SBP (mm Hg) | | |
| | ES | LCI | UCI | ES | LCI | UCI | ES | LCI | UCI |
| Empaglifozin 10 | | | | | | | | | |
| Versus PBO | -0.48 | -0.64 | -0.33 | -1.41 | -1.82 | -1.00 | -2.45 | -4.03 | -0.88 |
| Versus Empagliflozin 25 | 0.16 | 0.00 | 0.32 | 0.40 | -0.06 | 0.86 | 0.05 | -1.52 | 1.61 |
| Versus Dapagliflozin 2.5 | -0.08 | -0.30 | 0.14 | -0.06 | -0.74 | 0.62 | -1.79 | -4.91 | 1.28 |
| Versus Dapagliflozin 5 | 0.01 | -0.20 | 0.23 | 0.02 | -0.65 | 0.70 | -0.07 | -3.16 | 3.01 |
| Versus Dapagliflozin 10 | 0.08 | -0.13 | 0.30 | 0.63 | -0.05 | 1.31 | 0.65 | -2.42 | 3.74 |
| Empagliflozin 25 | | | | | | | | | |
| Versus PBO | -0.64 | -0.80 | -0.49 | -1.81 | -2.26 | -1.36 | -2.51 | -4.07 | -0.93 |
| Versus Empagliflozin 10 | -0.16 | -0.32 | 0.00 | -0.40 | -0.86 | 0.06 | -0.05 | -1.61 | 1.52 |
| Versus Dapagliflozin 2.5 | -0.24 | -0.46 | -0.02 | -0.46 | -1.17 | 0.25 | -1.84 | -4.97 | 1.22 |
| Versus Dapagliflozin 5 | -0.14 | -0.36 | 0.07 | -0.38 | -1.08 | 0.33 | -0.12 | -3.21 | 2.95 |
| Versus Dapagliflozin 10 | -0.07 | -0.29 | 0.14 | 0.23 | -0.48 | 0.93 | 0.6 | -2.47 | 3.7 |
| Dapagliflozin 2.5 V PBO | -0.40 | -0.55 | -0.25 | -1.35 | -1.90 | -0.81 | -0.66 | -3.32 | 2.06 |
| Dapagliflozin 5V PBO | -0.5 | -0.65 | -0.35 | -1.43 | -1.97 | -0.90 | -2.38 | -5.01 | 0.27 |
| Dapagliflozin 10 V PBO | -0.57 | -0.72 | -0.42 | -2.04 | -2.58 | -1.49 | -3.11 | -5.76 | -0.44 |

## 11.4 Appendix IV. ECON1: Manufacturer one way sensitivity analyses: BMI convergence

Note that the following results have been taken from the word version of the submission and not directly from CORE. As a consequence there may be some rounding of figures which may cause any ICERs which are reported to be slightly inaccurate.

*Manufacturer OWSA results: Add-on to metformin*

The following presents the base case deterministic results for the patient population having therapy added to metformin.

**Table 49. Cost effectiveness: add-on to MET: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,495 | | 7.993 | | |
| Dapagliflozin 10mg | £61,614 | £119 | 7.960 | -0.033 | Dominated |
| Canagliflozin 100mg | £61,703 | £208 | 7.952 | -0.041 | Dominated |
| Empagliflozin 10mg | £61,761 | £266 | 7.963 | -0.030 | Dominated |
| Sitagliptin 100mg | £61,778 | £283 | 7.899 | -0.094 | Dominated |
| Canagliflozin 300mg | £61,877 | £382 | 7.984 | -0.009 | Dominated |

**Table 50. Cost effectiveness: add-on to MET: empagliflozin 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,495 | | 7.993 | | |
| Dapagliflozin 10mg | £61,582 | £87 | 7.964 | -0.029 | Dominated |
| Canagliflozin 100mg | £61,643 | £148 | 7.949 | -0.044 | Dominated |
| Empagliflozin 10mg | £61,761 | £266 | 7.963 | -0.030 | Dominated |
| Sitagliptin 100mg | £61,778 | £283 | 7.899 | -0.094 | Dominated |
| Canagliflozin 300mg | £61,829 | £334 | 7.986 | -0.007 | Dominated |

*Manufacturer OWSA results: Add-on to metformin plus sulphonylurea*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus sulphonylurea.

**Table 51. Cost effectiveness: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £58,757 | | 7.568 | | |
| Empagliflozin 10mg | £58,772 | £15 | 7.543 | -0.025 | Dominated |
| Canagliflozin 300mg | £59,220 | £463 | 7.598 | 0.030 | £15,433 |
| Sitagliptin 100mg | £59,364 | £144 | 7.466 | -0.132 | Dominated |
| Empagliflozin 25mg | £59,448 | £228 | 7.509 | -0.089 | Dominated |

**Table 52. Cost effectiveness: add-on to MET+SU: empag. 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £58,772 | | 7.543 | | |
| Empagliflozin 10mg | £58,866 | £94 | 7.555 | 0.012 | £7,833 |
| Canagliflozin 300mg | £58,966 | £100 | 7.613 | 0.058 | £1,724 |
| Sitagliptin 100mg | £59,448 | £482 | 7.509 | -0.104 | Dominated |
| Empagliflozin 25mg | £59,708 | £742 | 7.462 | -0.151 | Dominated |

The comparison based upon empagliflozin 25mg assumptions for the comparators does not consider extended dominance. It appears that empagliflozin 10mg is extended dominated by canagliflozin 300mg. Canagliflozin 300mg results in an additional cost of £194 over canagliflozin 100mg but also results in an additional 0.007 QALYs, yielding a cost effectiveness estimate of £2,771 per QALY.

*Manufacturer OWSA results: Add-on to metformin plus thiazolidinedione*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus thiazolidinedione.

**Table 53. Cost effectiveness: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Sitagliptin 100mg | £58,610 | | 7.553 | | |
| Canagliflozin 100mg | £58,722 | £112 | 7.574 | 0.021 | £5,333 |
| Empagliflozin 25mg | £58,896 | £174 | 7.540 | -0.034 | Dominated |
| Canagliflozin 300mg | £59,110 | £388 | 7.598 | 0.024 | £16,167 |
| Empagliflozin 10mg | £59,137 | £27 | 7.516 | -0.082 | Dominated |

**Table 54. Cost effectiveness: add-on to MET+TZD: empag. 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Sitagliptin 100mg | £58,610 | | 7.553 | | |
| Canagliflozin 100mg | £58,721 | £111 | 7.573 | 0.02 | £5,550 |
| Empagliflozin 25mg | £58,896 | £175 | 7.540 | -0.033 | Dominated |
| Canagliflozin 300mg | £59,111 | £390 | 7.597 | 0.024 | £16,250 |
| Empagliflozin 10mg | £59,137 | £26 | 7.516 | -0.081 | Dominated |

*Manufacturer OWSA results: Add-on to insulin*

The following presents the base case deterministic results for the patient population having therapy added to insulin.

**Table 55. Cost effectiveness: add-on to INS: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,231 | | 7.540 | | |

| | | | | | |
|---|---|---|---|---|---|
| Dapagliflozin 10mg | £60,372 | £141 | 7.538 | -0.002 | Dominated |
| Empagliflozin 25mg | £60,394 | £163 | 7.534 | -0.006 | Dominated |
| Empagliflozin 10mg | £60,539 | £308 | 7.523 | -0.017 | Dominated |
| Sitagliptin 100mg | £60,564 | £333 | 7.511 | -0.029 | Dominated |
| Canagliflozin 300mg | £60,592 | £361 | 7.573 | 0.033 | £10,939 |

**Table 56. Cost effectiveness: add-on to INS: empag. 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,333 | | 7.549 | | |
| Dapagliflozin 10mg | £60,342 | £9 | 7.540 | -0.009 | Dominated |
| Empagliflozin 25mg | £60,394 | £61 | 7.534 | -0.015 | Dominated |
| Canagliflozin 300mg | £60,479 | £146 | 7.576 | 0.027 | £5,407 |
| Sitagliptin 100mg | £60,539 | £60 | 7.523 | -0.053 | Dominated |
| Empagliflozin 10mg | £60,564 | £85 | 7.511 | -0.065 | Dominated |

## *11.5* Appendix V. ECON2: Mt. Hood challenge published results

Diabetes models are, if their developers submit them, tested in the Mount Hood Challenge. In the 4th challenge, the principal author of which is one of the main CORE modellers, one test for the models was to simulate 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 and SBP as presented within the mixed treatment comparison of the submission, and
- weight changes

The CARDS trial results for the control arm and the intervention arm are presented alongside the modelled results below.

**Table 57. 4th Mt. Hood challenge results**

| | Acute coronary event | | Stroke | |
|---|---|---|---|---|
| | Control | Inter. | Control | Inter. |
| **CARDS study** | **5.1** | **3.2** | **3.2** | **1.4** |
| Models | | | | |
| 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 OM | 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.

The 5th challenge, the paper of which is authored by one of the main CORE modellers, required modellers to simulate the outcomes of three recent trials:

- ASPEN – 4 year use of atorvastatin to lower lipids
- ADVANCE –preterax and diamicron to lower HbA1c to below 6.5%
- ACCORD – intensive therapy versus standard therapy to lower blood pressure, with an additional examination of intensive glucose lowering therapy

**Table 58. ASPEN results**

| | | Primary composite end point | CVD mortality (Prim/Sec) | Non-CVD mortality (Prim/Sec) | Fatal/nonfatal MI (Prim/Sec) | Fatal/ nonfatal stroke | Angina | Primary event | Secondary event |
|---|---|---|---|---|---|---|---|---|---|
| **ASPEN** | **Control** | **15.0%** | **3.1% (2.5/5.6)** | **2.6% (2.3/3.6)** | **5.5% (3.6/12.6)** | **3.1%** | **3.2%** | **10.8%** | **30.8%** |
| | **Inter.** | **13.7%** | **3.1% (2.0/7.1)** | **2.6% (2.1/4.8)** | **4.0% (2.9/8.3)** | **3.0%** | **2.8%** | **10.4%** | **26.2%** |
| CORE | Control | | 3.9% (2.2/10.7) | 5.7% (5.1/8.5) | 5.8% (4.8/11.4) | 2.5% | | | |
| | Inter. | | 3.4% (1.8/10.3) | 5.5% (4.9/8.4) | 4.5% (3.6/9.1) | 2.0% | | | |
| MICHIGAN | Control | 3.3% | | 2.3% (2.5/–) | 3.9% (3.2/–) | | 3.4% | 2.7% | |
| | Inter. | 2.7% | | 2.8% (2.5/–) | 6.1% (5.5/–) | | 3.0% | 2.1% | |
| ECHO | Control | 14.8% | 5.0% (4.0/8.0) | 5.1% (4.0/11.2) | 8.5% (7.1/14.9) | | | 12.7% | 23.9% |
| | Inter. | 12.3% | 4.3% (3.3/7.4) | 4.9% (3.9/10.3) | 6.7% (5.6/11.9) | | | 10.5% | 20.4% |
| UKPDS OM | Control | 11.1% | 4.1% | 7.4% | 6.1% | 2.8% | 1.9% | | |
| | Inter. | 9.6% | 4.1% | 7.0% | 5.2% | 2.5% | 2.3% | | |
| UKPDS RE | Control | | | | | | | 8.7% | |
| . | Inter. | | | | | | | 7.4% | |
| CDC-RTI | Control | 14.3% | 5.5% (3.3/13.9) | 6.4% (6.3/6.6) | 9.4% (8.0/14.4) | | | 12.2% | 22.4% |
| | Inter. | 12.4% | 5.0% (2.8/13.7) | 6.4% (6.4/6.6) | 8.1% (6.4/14.4) | | | 10.0% | 21.5% |
| CARDIFF | Control | | (1.7/3.1) | (4.1/6.0) | (3.1/5.8) | | | | |
| | Inter. | | (1.5/3.5) | (4.1/6.0) | (2.7/5.8) | | | | |

**Table 59. ADVANCE results – primary endpoints**

| | | CVD mortality | All micro/ macro events | Major macro events | Nonfatal MI | Nonfatal stroke | Major micro events | Neph. | Retin. |
|---|---|---|---|---|---|---|---|---|---|
| **ADVANCE** | **Control** | **5.2%** | **20.0%** | **10.6%** | **2.8%** | **3.8%** | **10.9%** | **5.2%** | **6.3%** |
| | **Inter.** | **4.5%** | **18.1%** | **10.0%** | **2.7%** | **3.8%** | **9.4%** | **4.1%** | **6.0%** |
| CORE | Control | 4.6% | 17.5% | 12.2% | 4.9% | 2.7% | 5.4% | 2.8% | 2.6% |
| | Inter. | 4.2% | 15.7% | 11.3% | 4.6% | 2.6% | 4.4% | 2.3% | 2.1% |
| MICHIGAN | Control | 5.7% | 55.9% | 16.7% | 7.7% | 4.7% | 46.0% | 25.8% | 27.4% |
| | Inter. | 5.6% | 56.1% | 16.4% | 7.4% | 4.7% | 46.6% | 26.3% | 27.8% |
| ECHO | Control | 7.5% | 30.1% | 18.0% | 7.9% | 3.5% | | 4.3% | 10.8% |
| | Inter. | 6.6% | 24.1% | 16.1% | 7.2% | 3.0% | | 2.7% | 6.9% |
| UKPDS OM | Control | 6.5% | | 11.4% | | | | | |
| | Inter. | 6.4% | | 10.5% | | | | | |
| UKPDS RE | Control | | | 14.5% | | | | | |
| . | Inter. | | | 13.1% | | | | | |
| CDC-RTI | Control | 11.4% | 29.5% | 19.2% | | | 10.3% | 3.2% | 7.1% |
| | Inter. | 11.0% | 26.0% | 17.8% | | | 8.2% | 2.4% | 5.8% |
| CARDIFF | Control | 2.4% | | | 2.1% | 1.6% | | | |
| | Inter. | 2.2% | | | 2.2% | 1.6% | | | |
| EBMI | Control | | | 12.0% | | | | | 21.0% |
| | Inter. | | | 11.2% | | | | | 21.0% |

**Table 60. ADVANCE – secondary endpoints**

| | | Death Any cause | CVD events | Coronary events | Cerebrovasc. events | Major cerebro. | Heart failre events | PVD | New MA | New/worse neuropathy |
|---|---|---|---|---|---|---|---|---|---|---|
| **ADVANCE** | **Control** | **22.4%** | **9.6%** | **10.3%** | **6.1%** | **5.9%** | **4.4%** | **4.1%** | **6.6%** | **25.7%** |
| | **Inter.** | **22.1%** | **8.9%** | **10.1%** | **5.6%** | **6.3%** | **4.3%** | **3.9%** | **6.2%** | **23.7%** |
| CORE | Control | 15.9% | 13.4% | 13.2% | 9.4% | 3.1% | 3.1% | 3.4% | 2.5% | 6.6% |
| | Inter. | 14.9% | 13.1% | 12.4% | 8.7% | 2.9% | 2.9% | 3.3% | 1.9% | 5.4% |
| MICHIGAN | Control | | 10.1% | | | | | | | 16.7% |
| | Inter. | | 10.3% | | | | | | | 15.9% |
| ECHO | Control | 21.5% | 17.3% | | 12.6% | 4.2% | | 3.0% | 10.1% | 2.0% |
| | Inter. | 19.4% | 16.3% | | 11.3% | 3.6% | | 2.7% | 10.1% | 1.4% |
| UKPDS OM | Control | | 17.8% | | 7.7% | | 3.7% | 3.2% | | |
| | Inter. | | 17.3% | | 7.2% | | 3.3% | 2.9% | | |
| CDC-RTI | Control | | 16.7% | | | | | | | |
| | Inter. | | 16.4% | | | | | | | |
| CARDIFF | Control | | | | | | | 1.2% | | |
| | Inter. | | | | | | | 1.0% | | |
| EBMI | Control | 28.7% | 25.2% | | 5.6% | | 8.8% | 9.2% | 2.7% | 9.6% |
| | Inter. | 27.7% | 24.4% | | 4.8% | | 8.8% | 9.1% | 2.7% | 8.6% |

**Table 61. ACCORD results- blood pressure intervention**

| | | Primary End point | Death Any cause | CVD Mortality | Fatal stroke | Major Coron. Dis. | NonFatal MI | Any stroke | Heart Failure |
|---|---|---|---|---|---|---|---|---|---|
| **ACCORD** | **Control** | **2.10%** | **1.20%** | **0.5%** | | **2.40%** | **1.30%** | **0.5%** | **0.8%** |
| | **Inter.** | **1.90%** | **1.30%** | **0.5%** | | **2.30%** | **1.10%** | **0.3%** | **0.7%** |
| CORE | Control | 1.20% | 2.70% | 0.4% | 0.03% | 0.9% | 0.5% | 0.3% | 0.6% |
| | Inter. | 1.00% | 2.60% | 0.4% | 0.02% | 0.9% | 0.4% | 0.2% | 0.5% |
| MICHIGAN | Control | 2.80% | 1.70% | 1.00% | 0.2% | 2.40% | 1.30% | 0.9% | |
| | Inter. | 2.30% | 1.70% | 0.9% | 0.2% | 2.00% | 1.00% | 0.7% | |
| ECHO | Control | 2.60% | 2.00% | 1.00% | 0.2% | 2.30% | 1.10% | 0.6% | 0.7% |
| | Inter. | 2.20% | 2.00% | 0.9% | 0.1% | 2.00% | 1.00% | 0.4% | 0.6% |
| UKPDS OM | Control | 1.90% | 2.70% | 1.00% | | 2.00% | | 0.5% | 0.7% |
| | Inter. | 1.70% | 2.70% | 1.00% | | 1.80% | | 0.4% | 0.6% |
| UKPDS RE | Control | 2.10% | | | | | | | |
| . | Inter. | 1.90% | | | | | | | |
| CDC-RTI | Control | 1.90% | 2.90% | 1.60% | 0.4% | | | 0.4% | 0.00% |
| | Inter. | 1.70% | 2.90% | 1.50% | 0.4% | | | 0.3% | 0.00% |
| CARDIFF | Control | 1.10% | 1.10% | 0.4% | 0.1% | 0.00% | 0.4% | 0.4% | 0.2% |
| | Inter. | 1.00% | 1.20% | 0.4% | 0.0% | 0.00% | 0.4% | 0.3% | 0.2% |
| EBMI | Control | | 5.15% | | | 2.51% | | 0.61% | 2.38% |
| | Inter. | | 5.09% | | | 2.52% | | 0.36% | 2.43% |

**Table 62. ACCORD results- glucose lowering intervention**

| | | Duration Years | Primary | AC Mortality | CVD Mortality | NonFatal MI | NonFatal Stroke |
|---|---|---|---|---|---|---|---|
| **ACCORD** | **Control** | | **7.2%** | **4.0%** | **1.3%** | **4.6%** | **1.2%** |
| | **Inter.** | **3.5** | **6.9%** | **5.0%** | **1.7%** | **3.6%** | **1.3%** |
| CORE | Control | | | 10.2% | 1.9% | 2.2% | 1.0% |
| | Inter. | 4.0 | | 10.1% | 1.5% | 1.9% | 0.9% |
| ECHO | Control | | 9.0% | 10.0% | 4.1% | 3.8% | 1.5% |
| | Inter. | 3.5 | 8.1% | 9.4% | 3.6% | 3.5% | 1.3% |
| UKPDS OM | Control | | 7.4% | 11.1% | 4.7% | | |
| | Inter. | 3.5 | 6.7% | 10.6% | 4.6% | | |
| UKPDS RE | Control | | 7.1% | | | | |
| . | Inter. | 3.5 | 6.3% | | | | |
| CDC-RTI | Control | | | 11.3% | 6.1% | | |
| | Inter. | 4.0 | | 11.2% | 5.9% | | |
| CARDIFF | Control | | | 4.8% | 1.3% | 1.7% | 0.9% |
| | Inter. | 4.0 | | 4.8% | 1.1% | 1.6% | 0.8% |
| EBMI | Control | | | 12.4% | | 4.5% | 1.8% |
| | Inter. | 3.5 | | 17.3% | | 3.4% | 1.6% |

## 11.6 Appendix VI ECON3: ERG reruns of manufacturer base cases

*Base case rerun results: Add-on to metformin*

The following presents the base case deterministic results for the patient population having therapy added to metformin.

**Table 63. Results: add-on to MET: empag. 10mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,901 | £5,919 | £5,888 | £5,712 | £5,888 | £6,410 |
| Management | £1,030 | £1,032 | £1,029 | £1,025 | £1,028 | £1,032 |
| Complications | £54,768 | £54,528 | £54,645 | £55,001 | £54,776 | £54,414 |
| Total | £61,699 | £61,479 | £61,562 | £61,738 | £61,692 | £61,856 |
| LYs (undiscounted) | 19.907 | 19.974 | 19.89 | 19.763 | 19.872 | 19.961 |
| QALYs | 7.962 | 7.994 | 7.963 | 7.898 | 7.953 | 7.989 |

**Table 64. Cost effectiveness: add-on to MET: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,479 | | 7.994 | | |
| Dapagliflozin 10mg | £61,562 | £83 | 7.963 | -0.031 | Dominated |
| Canagliflozin 100mg | £61,692 | £213 | 7.953 | -0.041 | Dominated |
| Empagliflozin 10mg | £61,699 | £220 | 7.962 | -0.032 | Dominated |
| Sitagliptin 100mg | £61,738 | £259 | 7.898 | -0.096 | Dominated |
| Canagliflozin 300mg | £61,856 | £377 | 7.989 | -0.005 | Dominated |

**Table 65. Results: add-on to MET: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £5,901 | £5,919 | £5,888 | £5,712 | £5,885 | £6,408 |
| Management | £1,030 | £1,032 | £1,029 | £1,025 | £1,028 | £1,031 |
| Complications | £54,768 | £54,528 | £54,645 | £55,001 | £54,693 | £54,333 |
| Total | £61,699 | £61,479 | £61,562 | £61,738 | £61,606 | £61,772 |
| LYs (undiscounted) | 19.907 | 19.974 | 19.89 | 19.763 | 19.852 | 19.947 |
| QALYs | 7.962 | 7.994 | 7.963 | 7.898 | 7.948 | 7.985 |

**Table 66. Cost effectiveness: add-on to MET: empagliflozin 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £61,479 | | 7.994 | | |
| Dapagliflozin 10mg | £61,562 | £83 | 7.963 | -0.031 | Dominated |
| Canagliflozin 100mg | £61,606 | £127 | 7.948 | -0.046 | Dominated |
| Empagliflozin 10mg | £61,699 | £220 | 7.962 | -0.032 | Dominated |
| Sitagliptin 100mg | £61,738 | £259 | 7.898 | -0.096 | Dominated |
| Canagliflozin 300mg | £61,772 | £293 | 7.985 | -0.009 | Dominated |

*Base case rerun results: Add-on to metformin plus sulphonylurea*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus sulphonylurea.

**Table 67. Results: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,777 | £5,769 | £5,570 | £5,786 | £6,362 |
| Management | £989 | £988 | £983 | £990 | £994 |
| Complications | £51,960 | £51,894 | £52,788 | £51,962 | £51,597 |
| Total | £58,726 | £58,651 | £59,341 | £58,738 | £58,953 |
| LYs (undiscounted) | 18.805 | 18.774 | 18.616 | 18.827 | 18.915 |
| QALYs | 7.570 | 7.563 | 7.465 | 7.567 | 7.615 |

**Table 68. Cost effectiveness: add-on to MET+SU: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Empagliflozin 25mg | £58,651 | | 7.563 | | |
| Empagliflozin 10mg | £58,726 | £75 | 7.57 | 0.007 | £10,714 |
| Canagliflozin 100mg | £58,738 | £12 | 7.567 | -0.003 | Dominated |
| Canagliflozin 300mg | £58,953 | £227 | 7.615 | 0.045 | £5,044 |
| Sitagliptin 100mg | £59,341 | £388 | 7.465 | -0.15 | Dominated |

The estimate of £10,714 per QALY compares with an estimate of £9,571 per QALY in the manufacturer analyses. The estimate of £5,044 per QALY compares with an estimate of £4,933 per QALY in the manufacturer analyses.

The above does not consider extended dominance. It appears that empagliflozin 10mg is extended dominated by canagliflozin 300mg. Canagliflozin 300mg results in an additional cost of £302 over empagliflozin 25mg but also results in an additional 0.052 QALYs, yielding a cost effectiveness

estimate of £5,808 per QALY. This compares with an estimate of £5,558 per QALY in the manufacturer analyses.

Basing the results upon the empagliflozin 25mg comparison estimates for the comparators marginally increases the total QALYs associated with sitagliptin to 7.466 but does not change costs and has no qualitative impact upon the above.

*Base case rerun results: Add-on to metformin plus thiazolidinedione*

The following presents the base case deterministic results for the patient population having therapy added to metformin plus thiazolidinedione.

**Table 69. Results: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | Empag. | | Sita. | Canag. | |
|---|---|---|---|---|---|
| | 10mg | 25mg | 100mg | 100mg | 300mg |
| Costs | | | | | |
| Treatment | £5,792 | £5,819 | £5,678 | £5,829 | £6,359 |
| Management | £986 | £987 | £989 | £989 | £991 |
| Complications | £52,347 | £52,014 | £51,927 | £51,877 | £51,720 |
| Total | £59,125 | £58,820 | £58,594 | £58,695 | £59,070 |
| LYs (undiscounted) | 18.718 | 18.763 | 18.816 | 18.785 | 18.843 |
| QALYs | 7.542 | 7.56 | 7.552 | 7.578 | 7.613 |

**Table 70. Cost effectiveness: add-on to MET+TZD: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Sitagliptin 100mg | £58,594 | | 7.552 | | |
| Canagliflozin 100mg | £58,695 | £101 | 7.578 | 0.026 | £3,885 |
| Empagliflozin 25mg | £58,820 | £125 | 7.56 | -0.018 | Dominated |
| Canagliflozin 300mg | £59,070 | £375 | 7.613 | 0.035 | £10,714 |
| Empagliflozin 10mg | £59,125 | £55 | 7.542 | -0.071 | Dominated |

The estimate of £3,885 per QALY compares with an estimate of £4,115 per QALY in the manufacturer analyses. The estimate of £10,714 per QALY compares with an estimate of £10,413 per QALY in the manufacturer analyses.

Comparing canagliflozin 300mg with empagliflozin 25mg, there is a net additional cost of £250 and a net gain of 0.053 QALYs. This results in a cost effectiveness estimate for canagliflozin 300mg versus empagliflozin 25mg of £4,717 per QALY. This compares with an estimate of £4,755 per QALY in the manufacturer analyses.

The cost effectiveness results that use the clinical effectiveness estimates for the comparators based upon the empagliflozin 25mg comparison appear to be identical to the above. It would be anticipated that there should be some minor differences for sitagliptin due to the slight differences in non-severe hypoglycaemia. But these differences are slight and may be sufficiently slight not to be reflected in the above.

*Base case rerun results: Add-on to insulin*

The following presents the base case deterministic results for the patient population having therapy added to insulin.

**Table 71. Results: add-on to INS: empag. 10mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |
| Costs | | | | | | |
| Treatment | £7,045 | £7,094 | £7,094 | £6,951 | £7,132 | £7,678 |
| Management | £985 | £987 | £987 | £987 | £988 | £991 |
| Complications | £52,464 | £52,298 | £52,238 | £52,565 | £52,064 | £51,892 |
| Total | £60,494 | £60,379 | £60,319 | £60,503 | £60,184 | £60,561 |
| LYs (undiscounted) | 18.712 | 18.738 | 18.747 | 18.751 | 18.762 | 18.847 |
| QALYs | 7.522 | 7.534 | 7.544 | 7.511 | 7.544 | 7.582 |

**Table 72. Cost effectiveness: add-on to INS: empag. 10mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,184 | | 7.544 | | |
| Dapagliflozin 10mg | £60,319 | £135 | 7.544 | 0.000 | Dominated |
| Empagliflozin 25mg | £60,379 | £195 | 7.534 | -0.010 | Dominated |
| Empagliflozin 10mg | £60,494 | £310 | 7.522 | -0.022 | Dominated |
| Sitagliptin 100mg | £60,503 | £319 | 7.511 | -0.033 | Dominated |
| Canagliflozin 300mg | £60,561 | £377 | 7.582 | 0.038 | £9,921 |

The cost effectiveness estimate of £9,921 per QALY for canagliflozin 300mg compared to canagliflozin 100mg compares with an estimate of £9,579 per QALY within the manufacturer submission. The net costs of the other treatments over canagliflozin 100mg are slightly reduced.

**Table 73. Results: add-on to INS: empag. 25mg comparator effectiveness**

| | Empag. | | Dapa. | Sita. | Canag. | |
|---|---|---|---|---|---|---|
| | 10mg | 25mg | 10mg | 100mg | 100mg | 300mg |

| | | | | | | |
|---|---|---|---|---|---|---|
| Costs | | | | | | |
| Treatment | £7,045 | £7,094 | £7,094 | £6,944 | £7,136 | £7,680 |
| Management | £985 | £987 | £987 | £986 | £988 | £991 |
| Complications | £52,464 | £52,298 | £52,238 | £52,566 | £52,170 | £51,752 |
| Total | £60,494 | £60,379 | £60,319 | £60,496 | £60,294 | £60,423 |
| LYs (undiscounted) | 18.712 | 18.738 | 18.747 | 18.706 | 18.779 | 18.845 |
| QALYs | 7.522 | 7.534 | 7.544 | 7.498 | 7.55 | 7.582 |

**Table 74. Cost effectiveness: add-on to INS: empag. 25mg comparator effectiveness**

| | Costs | net | QALYs | net | ICER |
|---|---|---|---|---|---|
| Canagliflozin 100mg | £60,294 | | 7.55 | | |
| Dapagliflozin 10mg | £60,319 | £25 | 7.544 | -0.006 | Dominated |
| Empagliflozin 25mg | £60,379 | £85 | 7.534 | -0.016 | Dominated |
| Canagliflozin 300mg | £60,423 | £129 | 7.582 | 0.032 | £4,031 |
| Sitagliptin 100mg | £60,496 | £73 | 7.498 | -0.084 | Dominated |
| Empagliflozin 10mg | £60,494 | £71 | 7.522 | -0.060 | Dominated |

The cost effectiveness estimate of £4,031 per QALY for canagliflozin 300mg compared to canagliflozin 100mg compares with an estimate of £4,333 per QALY within the manufacturer submission. The net costs of the other treatments over canagliflozin are slightly reduced.

## 11.7 Appendix VII. ECON4: Manufacturer response to clarification questions around sampling

The ERG has been reviewing the differences in the model settings and the differences in how CORE has been run for the deterministic analysis versus the PSA analyses. The differences seem to be the following, as taken from the comparison of empagliflozin 10mg with dapagliflozin 10mg:

| | **Base case** | **Base case PSA** |
|---|---|---|
| BMI adjustment for QALY | yes | yes |
| 2nd order with sampling | yes | yes |
| Patient number | 1,000 | 50,000 |
| Time horizon | 80 years | 80 years |
| Number of bootstrap iterations | 1,000 | 500 |

**Q1:** The ERG's understanding was that sampling of 2nd order uncertainty was what was required for a PSA. But this option appears to have been set to yes for both sets of analyses.

- Please clarify what is sampled (if anything – e.g. 1st order uncertainty) when 2nd order with sampling is set to No.

  *When 2nd order sampling is set to "No", no parameters are sampled. However, in the 1st order simulation there is variability of patients that results from random assigning to patients such attributes as gender, race, and presence of each of baseline risk factors. In addition, there will be 1st order variability due to different random walks for each patient.*

- Please clarify what is sampled when 2nd order with sampling is set to Yes.

  *When 2nd order with sampling is set to "Yes" then the probabilities for cardiovascular complications and mortality are sampled. Further, all those parameters are sampled for which the corresponding standard error values are > 0. These include:*

  - *Patient age*
  - *Patient duration of diabetes*
  - *Baseline risk factors (HbA1c, SBP, etc.)*
  - *Treatment effects on risk factors*
  - *Direct complication costs*
  - *Indirect complication costs*
  - *Utilities*

  *Please also note that the sampling of costs depends on whether uncertainty is defined in the Economics module of CDM. For the point estimate analyses ("deterministic") and for PSA we used two different variants of the Economics module, i.e.*

*BI_RA_Economics_BC for point estimates, and BI_RA_Economics_BC (PSA) for PSA. The economics module BI_RA_Economics_BC does not have variability in costs.*

**Q2:** The ERG's understanding was that increasing the patient numbers mainly addressed 1st order uncertainty and model convergence for a given set of parameter values. Is this the case?

*Yes, increasing the number of patients lowers 1st order variations (also called Monte Carlo Error (MCE)). PSA demands in particular that MCE is low in order to enable the assessment of parameter uncertainty in the 2nd order simulation.*

**Q3** For the above Base Case PSA does CORE simulate 50,000 heterogeneous patients with the same parameter value(s) for e.g. HBA1c reduction and then resample this HBA1c parameter value and simulate another 50,000 heterogeneous patients using this parameter value (in reality a set of parameter values)? And continue doing this for a given number of PSA iterations?

*Yes, 50,000 patients are run with the same parameter values sampled from distributions. Then parameters are re-sampled and the next 50,000 patients are run through the model. This is repeated for as many times as bootstrap iterations are defined for the PSA.*

**Q4**: What is the role of the bootstraps iterations? Are these synonymous with the PSA iterations mentioned in Q3 above or do they perform some other function?

*Yes they are synonymous to PSA iterations. (See answer for Q3)*

**Q5**: The ERG does not understand how to implement a deterministic analysis; i.e. one without sampling of 2nd order uncertainty, within CORE. What settings should be used for this?

*The 2nd order simulation can be disabled by unchecking the "2nd order with sampling" check box in the simulations. However, for deterministic analyses (point estimates) the "2nd order with sampling" was checked.*

*Using 2nd order sampling in deterministic analysis (point estimates) would normally produce slightly different mean incremental outcomes, due to such factors as heterogeneity of patients, asymmetry of distributions, and non-linearity in the model.*

*The "2nd order with sampling" was activated in the point estimates analyses in order for the model to produce more realistic point estimates reflecting the above factors (i.e. heterogeneity, asymmetry, and non-linearity).*

**Q6** The ERG does not understand how to implement a probabilistic analysis; i.e. one with sampling of 2nd order uncertainty, within CORE. What settings should be used for this?

T*o run a PSA, check the "2nd order with sampling" check box in the simulation inputs and populate the cohort, treatment and economic settings with standard error (SE) values if not yet populated.*

*In this particular analysis if you would like to run a PSA please make sure that you also use the economics module BI_RA_Economics_BC (PSA) in which sampling of costs is defined.*