# Dapagliflozin for the treatment of type 2 diabetes

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**Declared competing interests of authors**

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**Rider on responsibility for report**

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

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**Contributions of authors**

Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted Section 5. Kieran Rothnie and Miriam Brazzelli reviewed the methods of the clinical effectiveness evidence synthesis. Norman Waugh and Sam Philip provided clinical advice and drafted the background and the critique of the manufacturer's decision problem. Neil Scott critiqued the statistical methods used and checked all the numerical results, tables, and figures. Cynthia Fraser critiqued the methods used for identifying relevant studies in the literature. Miriam Brazzelli supervised the work throughout the project. All authors assisted in preparing the final manuscript and commenting on early drafts.

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| | |
|---|---|
| **AIC** | Academic in confidence |
| **ALT** | Alanine aminotransferase |
| **APD** | Automated peritoneal dialysis |
| **AST** | Aspartate aminotransferase |
| **BMI** | Body mass index |
| **BMS/AZ** | Bristol-Myers Squibb and AstraZeneca |
| **BNF** | British National Formulary |
| **CADTH** | Canadian Agency for Drugs and Technologies in Health |
| **CAPD** | Continuous ambulatory peritoneal dialysis |
| **CG** | Clinical guidance |
| **CHF** | Congestive heart failure |
| **CHMP** | Committee for Medical Products of Human Use |
| **CIC** | Commercial in confidence |
| **DAPA** | Dapagliflozin |
| **DCEM** | Dapagliflozin cost effectiveness model |
| **DPP-4** | Dipeptidyl peptidase-4 |
| **DSU** | Decision support unit |
| **EMA** | European Medicines Agency |
| **EQ-5D** | Euroqol 5 dimensions |
| **ERG** | Evidence review group |
| **ESRD** | End stage renal disease |
| **FDA** | Food and Drug Administration |
| **GI** | Genital infection |
| **GLP-1** | Glucagon-like peptide-1 |
| **HbA1c** | Glycosylated haemoglobin |
| **HCSPPI** | Hospital and community services pay and prices index |
| **HD** | Hospital-based dialysis |
| **HDL** | High density lipoprotein |
| **HRQoL** | Health related quality of life |
| **ICER** | Incremental cost effectiveness ratio |
| **IHD** | Ischaemic heart disease |
| **INS** | Insulin |
| **LDL** | Low density lipoprotein |
| **LL** | Lower limit |
| **MET** | Metformin |

| | |
|---|---|
| **MI** | Myocardial infarction |
| **MIMS** | Monthly Index of Medical Specialities |
| **MTC** | Mixed treatment comparison |
| **NICE** | National Institute for health and Clinical Excellence |
| **NMA** | Network meta-analysis |
| **NPH** | Neutral Hagedorn Insulin |
| **OR** | Odds ratio |
| **PSS** | Personal social services |
| **PSSRU** | Personal Social Services Research Unit |
| **QALY** | Quality adjusted life year |
| **RCT** | Randomised controlled trial |
| **SBP** | Systolic blood pressure |
| **SGLT2** | Sodium glucose co-transporter 2 |
| **STA** | Single technology appraisal |
| **SU** | Sulphonylurea |
| **T1DM** | Type 1 diabetes mellitus |
| **T2DM** | Type 2 diabetes mellitus |
| **TC** | Total cholesterol |
| **TTO** | Time trade off |
| **TZD** | Thiazolidinedione |
| **UKPDS** | UK prospective diabetes study |
| **UL** | Upper limit |
| **UTI** | Urinary tract infection |

# 1 SUMMARY

## 1.1 Scope of the submission

The manufacturer's submission from Bristol-Myers Squibb and AstraZeneca addressed the use of dapagliflozin (10 mg once daily) in combination with other glucose-lowering therapies including insulin in adults aged 18 years and older suffering from type 2 diabetes mellitus (T2DM).

## 1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence for the clinical effectiveness of dapagliflozin came from direct (five RCTs involving dapagliflozin) and indirect evidence (51 RCTs involving other comparators). The five main RCTs included three metformin add-on trials and two insulin-add on trials. In four trials the comparator was placebo and in the fifth the comparator was the suplhonylurea, glipizide. The primary outcomes were HbA1c/glycaemic control, weight change, systolic blood pressure, and frequency of hypoglycaemic events. The evidence related to the safety profile of dapagliflozin came from a series of Phase 2 and Phase 3 clinical trials within the international dapagliflozin programme (exact number of trials was difficult to disentangle).

*Efficacy*

- Dapagliflozin 10 mg was effective in reducing Hb1Ac levels compared with placebo, either when used as add-on to metformin or to insulin;
- Dapagliflozin 10 mg demonstrated similar effects to those of DPP-4, TZD or SU with respect to Hb1Ac reduction;
- Dapagliflozin 10 mg was effective in reducing weight when added to metformin (participants on dapagliflozin lost about 2 kg more in weight than participants receiving placebo);
- Dapagliflozin 10 mg resulted in a statistically significant reduction in systolic blood pressure compared with placebo when added to metformin or insulin;
- Dapagliflozin 10 mg resulted in a lower number of hypoglycaemic events compared with SU at 52 weeks and was not associated with a greater risk of hypoglycaemic events when added to insulin. There was no evidence that dapagliflozin 10 mg added to metformin was associated with a lower incidence of hypoglycaemic events at 24 weeks.
- The evidence for dapagliflozin 10 mg in the triple therapy setting was less robust since no trials of dapagliflozin in triple oral therapy have been completed yet, but the results appeared to be broadly in line with the metformin and insulin add-on results.

*Safety*

- The incidence of genital and urinary tract infections was reported to be higher after administration of dapagliflozin 10 mg compared with placebo (but infections were not serious and of mild intensity);
- The manufacturer reported that in a meta-analysis of 14 Phase 2 and Phase 3 clinical trials, dapagliflozin was not associated with an increased risk of cardiovascular events (using a composite outcome of cardiovascular death, MI, and stroke). No further details of this meta-analysis were, however, provided;
- The overall rate of all cancers was similar between dapagliflozin and placebo/comparators but the total number of clinical trials which contributed to these rates was not given;
- The rates of bladder, prostate, and breast cancer were higher in the dapagliflozin group compared with placebo/comparators (with wide confidence intervals for the incidence rate ratios);
- There is a concern that the rates of bladder and breast cancer within the dapagliflozin programme are higher than those expected in the general T2DM population
- The potential risk of cancer required further investigations



In summary, dapagliflozin is a clinically effective drug which improves glycaemic control and provides benefits in terms of weight changes and systolic blood pressure. With the current available evidence, no firm conclusions can be drawn on the risk of cancer after dapagliflozin administration.

### 1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

While most aspects of the manufacturer's review were robust and conducted to acceptable standards there were some areas of concern:

- The main short-coming was the absence of RCTs against active comparators, and in particular against the DPP-4 inhibitors, which the ERG regards as the key comparators;
- One trial against a sulphonylurea was included, but given the very low cost of SUs and their known safety record, the ERG would expect SUs to be tried before dapaglifozin, a much more expensive drug with only short-term safety data. So, SUs would be precursors not comparators;
- Given the absence of head-to-head trials between dapagliflozin and active comparators, the submission relies on a network meta-analysis (NMA);

- The methodological details and assumptions related to the NMA were not always watertight;
- The methodology for the review of triple therapy was much less robust than that used for the main submission;
- Different inclusion criteria were adopted for the assessment of adverse events;
- No formal meta-analyses of adverse events were conducted (with the exception of hypoglycaemic events).

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

The manufacturer used the dapagliflozin cost effectiveness model (DCEM), written in software not approved by NICE, with which the ERG was not familiar. Some of the usual checks could therefore not be carried out. A report by the DSU on the model is being submitted to NICE separately.

The manufacturer compared dapagliflozin:

- In dual therapy with sulphonylurea, DPP-4 and thiazolidinedione, all in addition to metformin;
- In triple therapy with DPP-4, thiazolidinedione and GLP-1s, all in addition to metformin and sulphonylurea;
- As add-on to insulin and metformin with DPP-4.

The manufacturer used the DCEM, previously the CARDIFF model, to simulate the cost effectiveness of dapagliflozin over a 40 year time horizon. This is a patient level discrete event model that simulates the incidence of the following 7 complications of T2DM at baseline:

- Ischaemic heart disease
- Myocardial infarction
- Congestive heart failure
- Stroke
- Amputation
- Blindness
- End stage renal disease

While a slight simplification, these can be seen as being modelled as functions of the following risk factors:

- HbA1c

- SBP
- Total cholesterol to HDL cholesterol ratio (TC:HDL)
- BMI

During the incident year for any of: myocardial infarction, congestive heart failure, stroke, or renal failure, these events may be fatal. Other deaths are modelled as a function of life table entries.

Most of the risk functions are drawn from the standard UKPDS 68 reference, though these are amended within the DCEM through the application of the UKPDS 66 risks of myocardial infarction and stroke being fatal. The general mortality equation is also amended.

Given a baseline set of patient characteristics, each therapy is associated with an initial effect upon each of the risk factors. Each therapy is also associated with a range of adverse events: discontinuations in the 1st year, non-severe hypoglycaemic events, severe hypoglycaemic events, urinary tract infections, and genital infections

The DCEM has the facility to specify a threshold HbA1c value. When the modelled HbA1c of a therapy arm rises to this threshold HbA1c value or above it, the patient is modelled as moving onto the next line of therapy. This therapy is also associated with therapy specific effects upon the risk factors and rates of the adverse events. The therapy switch gives rise to a saw-tooth evolution of the risk factors. The timing of the therapy switch will be later for the treatments with the larger effect upon HbA1c. A further switch to another line of therapy can also be specified within the DCEM.

*DCEM inputs*

The impacts the initial treatments have upon the risk factors is largely drawn either from the relevant head to head study for the comparison with sulphonylurea in dual therapy, or from the manufacturer NMA. The source data for the impacts of the initial treatments upon adverse events is not clear within the submission.

Event costs and HRQoL data are drawn from a range of fairly standard references. The main exception to this is the HRQoL of weight changes. This is drawn from an unpublished manufacturer commissioned study. It appears that this study may also have considered the HRQoL impact of urinary tract infections and genital infections, but this is not mentioned or considered within the submission.

*DCEM validation*

The validation exercises presented by the manufacturer do not summarise the results of the Mt Hood challenges, which would be regarded as an obvious starting point. The Mt Hood challenge 4 suggests that the DCEM [CARDIFF] and the CORE model are similar in terms of their output, but that both tend to over predict myocardial infarction and do not predict stroke particularly well. The UKPDS outcomes model appears better in terms of prediction of myocardial infarction, but, similarly, does not seem to predict stroke particularly well.

The validation report using epidemiological data not used in construction of the DCEM achieved an $R^2$ or 0.70, which seems quite reasonable. But this validation report, prepared for the current submission, has not been peer reviewed and there is relatively little the ERG can do to examine the internals of it.

The validation report comparing the DCEM outputs with the CORE model outputs appears to report a selective set of outcomes. But there are quite large divergences between the outputs that are reported, despite the final ICERs being less divergent than the model outputs that go into their construction.

*DCEM results: dual therapy*

For the comparison with sulphonylurea the differences in modelled event rates over the time horizon of the model are relatively minor: all net impacts are a fraction of one per cent. The exceptions to this are the adverse event rates where around 20% more patients experience a urinary tract infection and 10% more a genital infection, though there are offsetting reductions in the number of hypoglycaemic events being experienced.

Around 82% of the anticipated net 0.467 QALYs from dapagliflozin arises from the direct HRQoL impacts of weight changes. The direct drug costs in the dapagliflozin arm are estimated to be £1,525 higher than those of the sulphonylurea arm, but cost offsets mainly from reduced rates of renal failure result in an overall net cost of £1,246. This results in a base case deterministic ICER of £2,671 per QALY. The central estimate of probabilistic modelling is in line with this.

For the comparison with the DPP-4 and pioglitazone, the net impacts upon event rates are smaller than those of the comparison with the sulphonylurea. Again, dapagliflozin is associated with increased rates of urinary tract infections and genital infections, but also with

offsetting reductions in hypoglycaemic events. This is surprising given that DPP-4 inhibitors and pioglitazone do not usually cause hypoglycaemia.

Around 23% of the anticipated net 0.020 QALYs from dapagliflozin compared to the DPP-4 arises from the direct HRQoL impacts of weight changes, while they actually more than offset HRQoL losses from events and survival within the overall net 0.420 QALYs of the comparison with pioglitazone. Dapagliflozin is estimated to be slightly inferior in terms of the QALY impacts derived from the impacts of the complications of diabetes. Net drug costs are £52 higher for dapagliflozin than for the DPP-4, but are broadly the same compared with pioglitazone at full proprietary drug cost (the patent has recently expired). Cost offsets, again mainly from reduced renal failure, results in dapagliflozin being estimated save £149 and £58 compared to the DPP-4 and pioglitazone respectively. This results in dapagliflozin being estimated to dominate both the DPP-4 and pioglitazone in dual therapy.

*DCEM results: triple therapy*

For all the comparisons in triple therapy, the estimated net impact from dapagliflozin upon event rates over the 40 year time horizon is miniscule: less than an absolute 0.1% reduction. As a consequence, the anticipated direct HRQoL effects of weight changes account for practically all the net QALY gains from dapagliflozin: 0.243 QALYs compared to the DPP-4 and 0.622 QALYs for the comparison with the thiazolidinedione. For the comparison with the GLP-1 due to the similarity of the weight changes the net impact from dapagliflozin is only 0.021 QALYs, with the direct HRQoL effects of weight changes accounting for 83% of this.

The direct drug costs in the dapagliflozin arm are estimated to be less than all the comparators: net savings of [redacted] compared to the DPP-4, [redacted] compared to the TZD and [redacted] compared to the GLP-1. Due to dapagliflozin being slightly less effective in preventing renal failure, the total net cost savings are estimated to be £109 compared to the DPP-4, £86 compared to the TZD and £1,380 compared to the GLP-1. As a consequence, dapagliflozin is estimated to dominate in triple therapy.

*DCEM results: add-on to insulin*

For the comparison as add-on to insulin, again the net effect of dapagliflozin compared to the DPP-4 upon event rates over the 40 year time horizon is miniscule. As would be anticipated, while dapagliflozin results in a net 0.119 QALYs this is entirely due, or almost entirely due, to the direct HRQoL impacts of weight changes. Dapagliflozin is actually estimated to be worse than the DPP-4 in terms of the HRQoL impacts from the complications of diabetes.

The net drug costs are £479 higher for dapagliflozin, which with the addition of the costs of the complications of diabetes and adverse events increases to £517. Given the net 0.119 QALYs this results in an ICER of £4,358 per QALY.

*DCEM sensitivity analyses*

The manufacturer presents a reasonable range of sensitivity analyses for the dual therapy and add-on to insulin comparisons. But the range of sensitivity analyses presented for the triple therapy comparisons is restricted to consideration of the HRQoL impact of weight changes.

A credible multivariate scenario analysis of the manufacturer that reduces the HbA1c switching threshold to be more in line with the NICE guideline, applies the CG87 HRQoL impact of weight changes and applies a literature derived baseline prevalence of complications, results in cost effectiveness estimates in the range £5,307 per QALY to £11,269 per QALY for the dual therapy comparisons and £20,579 per QALY for the add-on to insulin comparison. This multivariate scenario analysis is not presented for the triple therapy comparisons.

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

The ERG views many of the inputs and structural assumptions of the model as standard to the modelling of T2DM.

The ERG is concerned at the revisions to the UKPDS risk equations and their selective implementation, and what appears to be the unnecessary use of risk equations from outside the cohesive set presented in the UKPDS 68. This appears to reduce the role of HbA1c and increase the role of SBP. Dapagliflozin is typically estimated to have a smaller impact upon HbA1c than its comparators, but a larger effect upon SBP than its comparators.

There are some concerns with the implementation of the evolution of some of the risk factors. This is highlighted by some of the effects at baseline being estimated to be broadly maintained over the 40 time horizon of the model. Scenario analyses around the structural assumptions required for these should have been undertaken. There are also concerns with the implementation of the event risk equations.

The direct HRQoL impacts of weight changes is pivotal to this assessment. These are by far the greater part of the estimated net QALY gains from dapagliflozin. In some cases they offset, admittedly small, net QALY losses from the complications of diabetes.

There may be a number of errors in the DCEM C++ coding.

The modelling assumes that treatment changes once HbA1c rises above a user-specified threshold level. However, these thresholds vary amongst comparisons, and are not based on the NICE Clinical Guidance 87 level of 7.5%. They are all higher, and in two cases are 8.17% and 8.9%. This reduces the relevance of the modelling to standard care.

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

### *1.6.1 Strengths*

The manufacturer conducts what appears to be a good systematic review for clinical effectiveness for the dual therapy and add-on to insulin comparisons. The presentation of the results of the NMA for the main risk factors is coherent, as well as the presentation of most of the other inputs to the modelling. Many of these draw upon standard sources from the literature, the notable exceptions to this being the HRQoL impact of weight and the costs of severe hypoglycaemic events. The DCEM simulates the usual range of complications of diabetes, drawing many of its risk equations from the UKPDS which is again a strength.

### *1.6.2 Weaknesses and areas of uncertainty*

The main weakness is the lack of direct trials against relevant active comparators. All but one of the submitted trials compared dapaglifozin against placebo. All trials were sponsored by the manufacturer.

The primary outcome is reduction in HbA1c. There are as yet no trials that report effect on long-term complications, in particular cardiovascular disease.

In the absence of head-to-head trials against active comparators, the submission relied on a NMA. The ERG thought, however, that some aspects of the NMA were not transparent or reproducible - justification for some of the NMA assumptions was insufficient and it was unclear why adjustment for baseline HbA1c was undertaken for some analyses but not for others.

There is also little transparency in the submission for many of the adverse event rates used in the economic model: discontinuations, symptomatic hypoglycaemic events, severe hypoglycaemic events, urinary tract infections and genital infections.

As is common in much modelling of diabetes, pairwise comparisons are undertaken. But this may be a relatively poor guide to the optimal sequence of treatments. Even if only a proportion of patients show sufficient benefit from a cheaper drug, it may be cost effective to

trial the larger patient group on the cheaper drug and only use the more expensive drug for those who do not respond sufficiently to the cheaper drug.

There are concerns around the HbA1c therapy switching values that are applied within the base case modelling being much in excess of the 7.5% of the NICE guideline. The manufacturer does undertake scenario analyses around this. But the DCEM model structure is not suited to evaluating what proportion of patients will respond sufficiently to remain on a therapy and what proportion will not and will have to move onto the next line of therapy. The probabilistic modelling may partially address this. But since the range of baseline HbA1c values of the trials is typically quite broad, not sampling the baseline characteristics within the probabilistic modelling may again limit this[A]. A simpler analysis of subgroup effects grouped by HbA1c at baseline might have been the most appropriate means of addressing this.

The application of the UKPDS 68 risk factor evolution equations does not apply the values at diagnosis for a number of variables as specified in a literal reading of the UKPDS 68 but rather applies the value after the treatment effect of each arm has been applied. This differentiates the risk factor evolution equations such that some never converge and the anticipated initial benefit endures for the time horizon of the DCEM. Structural sensitivity analyses around these assumptions should have been undertaken.

The application of the UKPDS 68 event equations similarly does not apply the values at diagnosis for a number of variables as specified in a literal reading of the UKPDS 68 but rather the contemporaneous values as they are modelled as evolving within the model. This applies to BMI in the UKPDS 68 equation for the incidence of congestive heart failure, within BMI also being differentiated by arm. This seems to double count the impact of this given that contemporaneous SBP is specified within this equation. There are also feedback loops within the model where congestive heart failure increases the risk of myocardial infarction, stroke and diabetes related mortality.

The modelling of triple therapy has an unnecessary common first line of therapy prior to the main comparisons of interest. Taken together these use up the first two lines of the three lines of therapy permitted within the DCEM. This leaves only one further line of therapy within the model which is occupied by insulin with metformin. For this reason the triple therapy modelling does not consider the switch to intensified insulin with its higher cost and further weight gain. This is in the context of dapagliflozin having a smaller central estimate for its

[A] Manufacturer response to ERG clarification question B13.

impact upon HbA1c, and so switching to subsequent lines of therapy at an earlier date than its comparators.

Of the possible risk factors of HbA1c, SBP, TC:HDL and BMI the UKPDS 68 only models event mortality as a function of the HbA1c. Applying the equation drawn from UKPDS 66 makes the myocardial infarction mortality a function of both the HbA1c and the SBP risk factors. The stroke mortality is changed to only be a function of the SBP risk factor. This is in the context of dapagliflozin typically having a smaller central estimate for its impact upon HbA1c than its comparators, but a larger central estimate for its impact upon SBP.

Quite a lot of the clinical inputs to the DCEM appear to relate to week 24 rather than the week 52 of the DCEM, the implicit assumption being the maintenance of treatment effect between weeks 24 and 52.

It appears that the study by Lane et al (commissioned by the manufacturer and presented as abstract at the 17th International Society for Pharmacoeconomics and Outcomes Research Conference, Washington, June 2012) of weight changes and HRQoL also examined the impact of urinary tract infections and genital infections upon HRQoL. No mention of this is made within the submission. The manufacturer chooses to rely upon Lane et al for the base case HRQoL from weight changes, but to draw a value from the literature for the HRQoL from urinary tract infections and genital infections. The study by Lane et al was quite small, and produced quality of life increments that are greater than in published data used to inform previous NICE appraisals and guidelines.

For the costing of pioglitazone the manufacturer applies market share data to arrive at a weighted average dose of 28.8 mg. For the costing of the GLP-1 no market share data is presented. The manufacturer simply averages the £884 cost of exenatide b.i.d. and the £1,009 cost of liraglutide 1.2 mg to arrive at an average cost of £938. This ignores the arrival of once-weekly exenatide, which has been recommended for use by NICE and is likely to become the most-used GLP-1 analogue.

It appears that the DCEM only includes the direct drug costs and the costs of events, the latter estimated by applying the unit costs of the UKPDS 65. But the UKPDS 65 also includes inpatients and outpatient costs for those who have not yet experienced any of the complications of diabetes. These costs should be included in the DCEM.

The £390 cost per severe hypoglycaemic event may not correspond with the UK weighted average suggested within the cited reference. There is a further concern that the weights applied to calculate the weighted average may be skewed due to respondents being identified by medical practitioners, so increasing the proportion of respondents who sought medical attention for their severe hypoglycaemic event. The cost per severe hypoglycaemic episode appears to have been over-estimated.

There may be errors within the DCEM C++ coding:

- Applying ln(TC:HDL/5.23) rather than ln(TC:HDL-5.23) within the UKPDS 68 equations;
- The annual costs of incident events not being adjusted for the cycle length of 6 months;
- Double counting mortality from incident events of myocardial infarction, congestive heart failure, stroke, amputation and/or renal failure;
- Not applying equation 9 of the UKPDS 68 to estimate the annual fatality associated with events subsequent to the first year of incidence of myocardial infarction, congestive heart failure, stroke, amputation and/or renal failure.

It is currently unclear how the probabilities of the UKPDS 68 have been adjusted to arrive at the probability for the cycle length of 6 months.

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

The ERG has not undertaken any further exploratory and sensitivity analyses using the DCEM. Many of the concerns of the ERG, coupled with those of the DSU, which cross checked the C++ coding of the model, relate to the model structure, choice of risk equations and implementation of risk equations within the DCEM. Due to the inter-related nature of the Excel, Visual Basic, and C++ the ERG has not attempted to resolve these elements of the DCEM.

In terms of the main uncertainties around the input values that should be used the ERG considers the HRQoL impacts of weight changes, the HRQoL impacts of severe hypoglycaemic events and the costs of severe hypoglycaemic events as the inputs that have the most questionable values applied in the manufacturer base case. The annual cost of renal failure is also a driver of the anticipated cost offsets. Within the constraints of the structure of the DCEM the manufacturer has undertaken a wide range of sensitivity analyses, and has explored the impacts of changing the HRQoL associated with weight changes. Given the disaggregate reporting of the HRQoL impacts and costs of events of Chapter 5 below, the

impacts of changing the HRQoL impacts of severe hypoglycaemic events, the costs of severe hypoglycaemic events, the costs of renal failure and a number of other DCEM inputs are easily inferred without the DCEM having to be re-run.

### 1.8 Conclusions

The ERG concludes that dapagliflozin is clinically effective in lowering HbA1c, by about 0.5% compared to placebo. Adverse effects such as urinary tract infections occur in about 8%.

There is a lack of direct trials against the main comparators.

There are uncertainties around cost-effectiveness, arising partly from revisions to risk equations, assumptions about some costs such as of hypoglycaemic episodes, assumptions about some utilities, notably the direct effects of weight changes, and concerns about the C++ model.

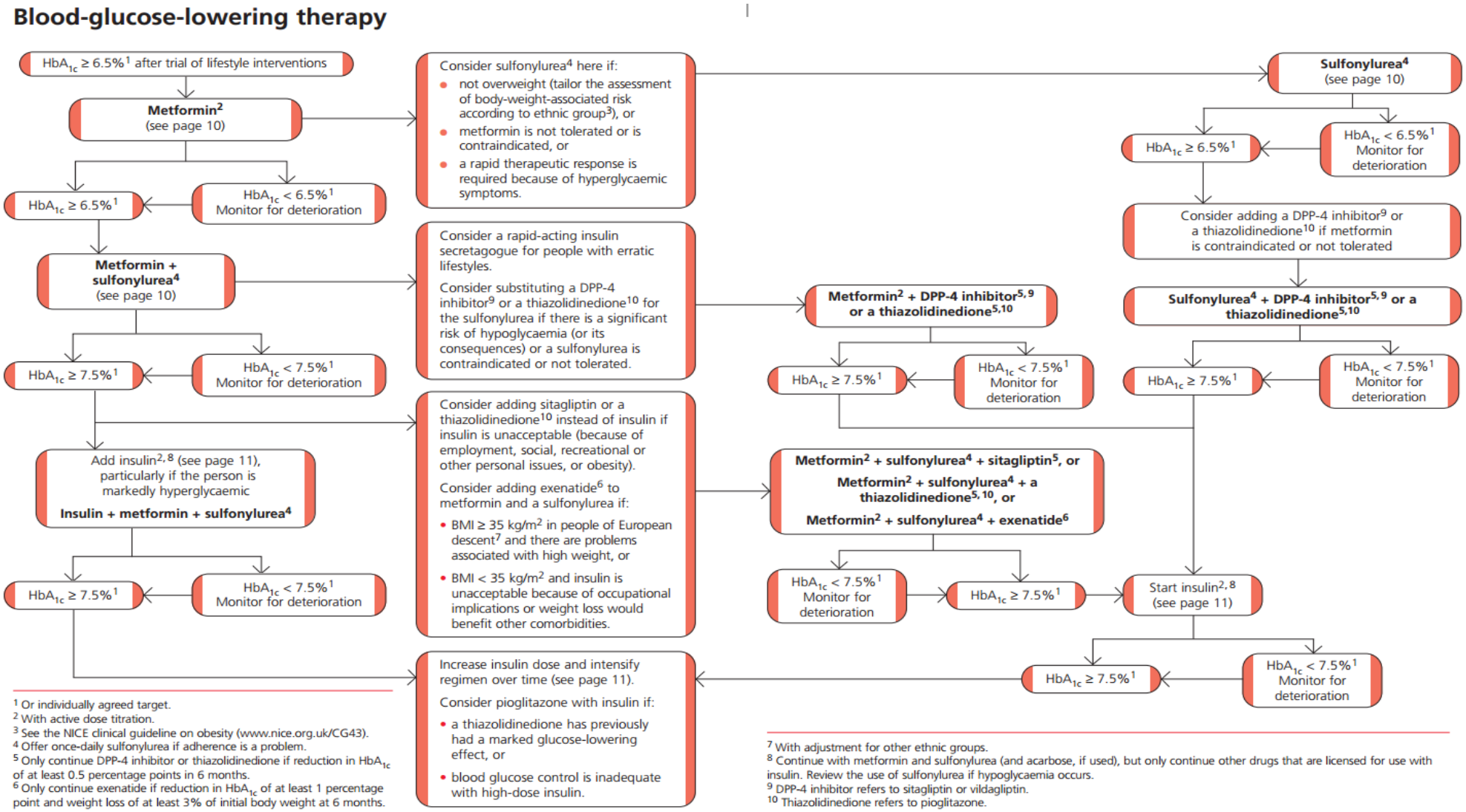
## 2 BACKGROUND

Type 2 diabetes (T2DM) is one of the most important chronic diseases today, with in excess of 2.6 million people affected in the UK in 2010, and an increasing prevalence.[1] Diabetes is increasingly costly to the NHS, with a recent study estimating that 10% of all NHS expenditure is on diabetes.[2]

The guidelines on the management of T2DM from the UK's National Institute for Health and Clinical Excellence (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing on insulin.[3] However sulphonylureas, glitazones and insulin all cause weight gain which may worsen insulin resistance. Sulphonylureas and insulin can also cause hypoglycaemia. Pioglitazone, now the only glitazone left in use, can cause oedema, heart failure and fractures, and there is increasing concern about whether its use is associated with bladder cancer. Pioglitazone has now been banned in France.[4]

The NICE Clinical Guideline 87 on T2DM contains a flowchart, reproduced in the manufacturer's submission, and included here for convenience.[3]

**Figure 1** **Flow diagram of blood-glucose-lowering treatments for the management of type 2 diabeter (source: NICE Clinical Guidleines 87)**



The number of glucose lowering drugs for T2DM has been gradually increasing. We have eight classes, though some contain only a single drug:

- Biguanides: metformin
- Sulphonylureas: gliclazide,glimeperide and gliclazide
- Thiazolidinediones: pioglitazone
- Acarbose
- Meglitinides: nateglinide and repaglinide
- The GLP-1 analogues: exenatide (now with a once a week form) and liraglutide (once daily)
- The DPP-4 inhibitors, also known as the 'gliptins'
- Insulins. In T2DM, insulin treatment starts with a once daily basal insulin (NICE recommends NPH as first choice) but if intensification is needed, short-acting insulins may be added at mealtimes, or twice daily biphasic insulin may be used.

Despite the number of medications now available there is a need for a class of medication that will lower glucose without causing hypoglycaemia or weight gain and improve cardiovascular outcomes.

We now have the first of a new class, the sodium glucose co-transporter 2 receptor inhibitors. Glucose is normally filtered in the kidney and is reabsorbed in the proximal tubules. Glycosuria occurs when the renal threshold of glucose (blood glucose of approximately 10 mmol/L (160-180 mg/dl) has been reached. At this threshold the proximal tubule cannot reabsorb all of the filtered glucose, resulting in glycosuria. 90% of the urinary glucose is transported across the membrane of the proximal tubule by sodium glucose co-transporter 2 (SGLT2).[5] The sodium/glucose cotransporter 2 (SGLT2) protein in humans is encoded by the SLC5A2 (solute carrier family 5 sodium/glucose cotransporter) gene. A naturally occurring mutation in the SLC5A2 gene, resulting in a defective SGLT2 protein, produces significant glycosuria. Individuals who have this mutation have not been seen to have significant problems related to the glycosuria, such as urinary tract infections (UTIs).[6]

Therefore a therapeutic option in T2DM is to mimic the effect of the SLC5A2 mutation and prevent the reabsorption of renal filtered glucose back into to circulation, thereby reducing hyperglycaemia, without the side-effects of weight gain or hypoglycaemia.[7]

A new class of drugs has been developed to do this, including dapagliflozin and canagliflozin. This appraisal concerns only dapagliflozin. Dapagliflozin is a highly selective inhibitor of

SGLT2. It contains a C-glucoside that increases its vivo stability, prolongs half-life and produces a consistent pharmacodynamic activity.[8]

Canagliflozin is expected to be the subject of another STA. A scoping meeting was held in November 2012.

Since there are existing drugs which are inexpensive and with a long safety record, it is unlikely that SGLT2 inhibitors would be used first line, and we therefore see their role as second or third drugs used in combination therapy in T2DM. However, they represent a paradigm shift in management of diabetes by acting through a mechanism that is not dependant on insulin secretion. Thus they have the potential to be used in combination with oral anti-diabetic agents as well as insulin to exert additive or synergistic effects on lowering blood glucose levels.

There are two main issues for this appraisal:

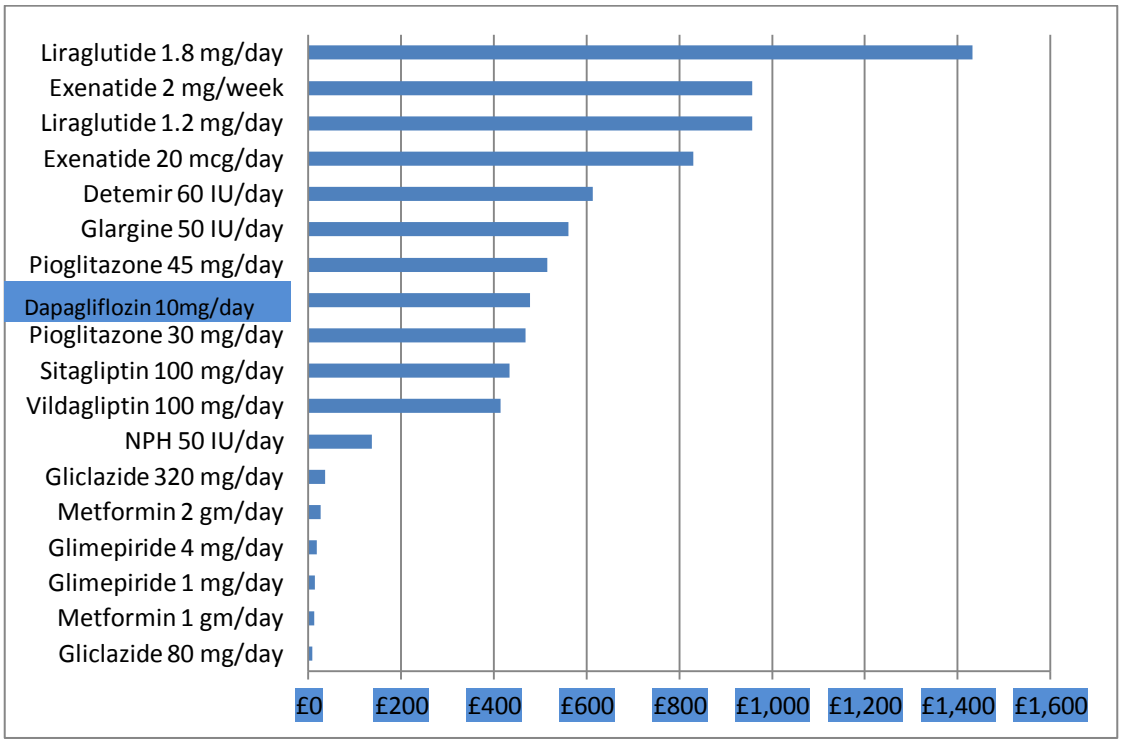
i) The first question is whether dapagliflozin is clinically effective in improving glycaemic control in T2DM, with an acceptable adverse event profile;

ii) The second question is about whether it is cost-effective, and one issue that arises is where the SGLT2 inhibitors fit into the therapeutic pathway. Factors to be considered include:

- Effect on glycaemic control as reflected in HbA1c reductions
- Effect on weight, compared to other drugs, some of which cause marked weight gain
- Adverse effects, particularly increased genital and urinary infections
- Duration of effectiveness: some other drugs exhibit decreasing efficacy as duration of diabetes increases, especially those that act mainly by stimulating insulin release; the duration of action of dapagliflozin will not be affected by remaining levels of endogenous insulin production
- Interactions with other drugs, especially in patients on treatment for co-morbidities
- Ease of use, by oral administration rather than injection
- Potential for combination therapy
- Cost

Figure 2 shows the costs of drug therapies for T2DM.

**Figure 2 Costs of different pharmacological interventions for diabetes**




*Source: British National Formulary*

### 2.1 Critique of manufacturer's description of underlying health problem

The manufacturer description of the underlying health problem (T2DM) in terms of prevalence, relevant symptoms, complications and required treatments is accurate.

### 2.2 Critique of manufacturer's overview of current service provision

The manufacturer points out the current variation in the delivery of diabetes care (including both primary and secondary care services) and suggests that there is a need to individualise patient management in T2DM taking into consideration both patient preferences and clinical needs (e.g. weight gain, risk of hypoglycaemia, compliance). The variations have been documented recently in a national audit report on diabetes care.[9]

The manufacturer argues that whilst current clinical guidelines on T2DM debate the ideal HbA1c level, there is no guide to support individualisation of patient management with respect to their appropriate HbA1c level. Moreover, current guidelines do not persuade clinicians to reach HbA1c target levels more rapidly with the consequence that the implementation and progression of patients' treatment to reach the ideal HbA1c level is slow.

The manufacturer's position is supported by evidence, documented in reports for past NICE appraisals, and summarised in the assessment report for the CG87 guidelines group.[10] In brief;

- Both patients and their doctors have been reluctant to start insulin, as documented in the DAWN study[11]
- This is partly because most patients with T2DM who are on insulin, do not achieve good control[12]
- Many patients therefore remain poorly controlled on combination oral agents for years before stating insulin[13,14]

The manufacturer's summary can be considered a reasonable description of the current T2DM service provision.

## 3 DEFINITION OF THE DECISION PROBLEM

### 3.1 Population

The manufacturer's submission states that dapagliflozin is indicated as a second or third drug treatment in adults over 18 years old with type 2 diabetes (T2DM) whose glycaemic control, with metformin or insulin, with or without a second oral agent, and together with diet and exercise, is not satisfactory.

The definition of the population is in line with the final scope of this appraisal and the license indications.



### 3.2 Intervention

The technology submitted is a highly potent, selective and reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2) - dapagliflozin - that is given at a dose of 10 mg once daily at any time during the day, with or without food. In the current submission there is no proposed dose adjustment based on renal function. Nevertheless, the manufacturer states that dapagliflozin is indicated in patients with mild renal impairment and not recommended in patients with moderate to severe renal impairment (defined as creatinine clearance <60 mL/min or estimated glomerular filtration rate <60 mL/min/1.73 $m^2$). Monitoring of renal function is recommended i) prior to initiation of dapagliflozin and at least yearly thereafter, and ii) prior to initiation of concomitant medications that may potentially reduce renal function. Due to the fact that dapagliflozin causes an increase in the urinary volume excretion, it is not recommended in patients receiving loop diuretics or those who are volume depleted.

The method of administration, monitoring and side-effects are those described in the summary of product characteristics.

There are currently no approved SGLT2 inhibitors for the management of T2DM. If approved, dapagliflozin will be a first-in-class therapy. In April 2012, the CHMP issued a recommendation that dapagliflozin should be approved.

### 3.3 Comparators

The manufacturer states that the main comparators for dapagliflozin used as a second line treatment option (add-on to metformin) are: sulphonylureas (SUs), thiazolidinediones (TZDs - now only pioglitazone) and dipeptidyl peptidase-4 inhibitors (DPP-4). The main comparators for dapagliflozin used as a third line treatment option (add-on to insulin) are: TZDs and DPP-4 inhibitors. NICE Clinical Guideline 87 recommends pioglitazone with insulin in patients

with T2DM for whom metformin is contraindicated or not tolerated. With regard to the DPP-4 inhibitors, only saxagliptin and sitagliptin are licensed to be used in combination with insulin (with or without metformin) in T2DM.[3]

Section 4, *Statement of the decision problem*, of the current submission outlines the differences between the manufacturer's decision problem and the NICE scope. It should be noted that the original NICE scope included a very broad range of comparators, not all of which were in keeping with previous NICE guidance. There are a few differences from the scope:

1. The manufacturer's submission does not include a comparison with GLP-1 analogues in dual therapy, whereas the scope does. The ERG supports the position taken by the manufacturer, though for a different reason. The manufacturer maintains that the use of GLP-1 analogues in dual therapy is not standard practice and cites prescribing data. The ERG notes that the technology appraisals of liraglutide and long-acting exenatide recommended that use in dual therapy should be very restricted.
2. The manufacturer's submission does not include an analysis of dapagliflozin in patients inadequately controlled on sulphonylurea monotherapy. The standard first line drug in T2DM is metformin, as recommended by NICE. Most patients usually tolerate metformin.
3. The main submission states that no comparison in triple therapy will be provided, but that statement has been superseded by an addendum. However, the studies used in the triple therapy addendum compare dapagliflozin with placebo rather than with active comparators.

For the management of T2DM, the NICE guideline recommends starting with diet and lifestyle, adding metformin if control is inadequate, and next adding a sulphonylurea. There is an option in the current guideline to use pioglitazone as an alternative to a sulphonylurea, but due to increasing concerns about the adverse effects of pioglitazone it is possible that this guidance will be revised in the future.

Hence in dual therapy, if sulphonylures or metformin cannot be tolerated, we would expect a gliptin as an oral alternative to be tried if patients could not tolerate either metformin or a sulphonylurea.

The gliptins therefore seem to be the key comparator for dapagliflozin in dual therapy.

In triple therapy, comparators include the gliptins, a GLP-1 analogue (liraglutide or exenatide, but probably now once-weekly exenatide) or insulin. We would expect the gliptins to be tried before long-acting exenatide on grounds of cost and the need to inject exenatide. The same reasons apply to dapagliflozin. So in triple therapy, the main comparators are again the gliptins. It could be argued that insulin with once daily NPH would cost less, but as noted in the previous chapter, there tends to be resistance to starting insulin because of its adverse effects of weight gain and hypoglycaemia, and because insulin often fails to ensure good control unless intensified. Intensive life style interventions have been shown to be as good as insulin in one small Danish study[15] but that needs to be confirmed by further research.

The combination of insulin and a GLP-1 analogue was unlicensed but widely used, as a logical combination. Twice daily exenatide has now been licensed for use in combination with insulin.[16,17]

The NICE scope did not mention acarbose, nor the meglitinide analogues, repaglinide and nateglinide. The latter are insulin secretagogues, shorter acting but less potent than the sulphonylureas.[18] None of these drugs are widely used in the UK, and their effectiveness in triple therapy is limited.[19]

In conclusions, the ERG regards the gliptins as the key comparators, and the place of dapagliflozin to be mainly in triple therapy, though it may also be used as an add-on to insulin.

Neither the NICE scope nor the manufacturer's submission considers the use of dapagliflozin in type 1 diabetes (T1DM), so that will not feature in this appraisal. The mechanism of action is such that it should also be effective in T1DM.

### 3.4 Outcomes

The main outcomes considered by the manufacturer are acceptable. They include HbA1c, weight change, systolic blood pressure, episodes of hypoglycaemia, incidence of cardiovascular events, and renal diseases. Whilst in the final scope issued by NICE 'adverse events of treatment' (including genitourinary tract infections) are clearly stated, these are overlooked in the manufacturer' statement of the decision problem. The manufacturer maintains that none of the five included dapagliflozin RCTs were primarily designed to assess safety outcomes and in section 5 *Adverse events* presents the safety profiles of a series of Phase 2 and Phase 3 randomised placebo controlled trials within the dapagliflozin international programme selected for the purpose of the submission.

# 4 CLINICAL EFFECTIVENESS

## 4.1 Critique of the methods of review(s)

### *4.1.1 Description of manufacturer's search strategies and critique*

Overall the sources searched for this submission were appropriate although the electronic searches lacked sensitivity. Furthermore, no systematic searching was undertaken after May 2011. However, four studies (including three of the five main dapagliflozin RCTs considered by the manufacturer) were published after this date and it is unclear which methods were used to identify these additional papers. There were no literature searches undertaken for additional information on adverse events from case series studies therefore the evidence-base for evaluation of adverse events might be incomplete. A detailed critique of the manufacturer's search strategies is given in Appendix 1.



A recent systematic review of SDGLT2 drugs was identified which did not identify any additional trials that met the inclusion criteria for this assessment.[20]

### *4.1.2 Inclusion criteria*



The inclusion criteria used in the systematic review of clinical effectiveness are tabulated in Table 1.

**Table 1 Inclusion criteria used in the systematic review of clinical effectiveness**

| | |
|---|---|
| **Population** | • Adults with type 2 diabetes mellitus; and<br><br>*For the metformin add-on indication:*<br>• Inadequate glycaemic control on metformin alone<br><br>*For the insulin add-on indication:*<br>• Inadequate glycaemic control on insulin with or without oral anti-diabetic agents |
| **Intervention** | Drugs from the following classes administered at their licensed dose in the United States or Europe:<br><br>*Metformin add-on (as sole agent added to metformin monotherapy):*<br>• SGLT2 inhibitors (dapagliflozin only)<br>• SUs + meglitinides<br>• DPP-4 inhibitors<br>• TZDs<br>• GLP-1 analogues<br><br>*Insulin add-on (with or without other anti-diabetic agents):*<br>• SGLT2 inhibitors (dapagliflozin only)<br>• Biguanides<br>• SUs + meglitinides<br>• DPP-4 inhibitors<br>• TZDs |
| **Comparator** | The drugs mentioned in the interventions must have been compared to each other, or to a placebo/no-intervention arm. |
| **Outcomes** | Reported at least one of the following outcomes:<br><br>*Efficacy outcomes:*<br>• HbA1c level<br>• Systolic blood pressure<br>• Weight<br>• Fasting blood glucose level<br>• HDL level<br>• LDL level<br>• Total cholesterol level<br>• Triglyceride level<br><br>*Safety outcomes:*<br>• Hypoglycaemia<br>• UTI<br>• Genital infection<br>• Gastrointestinal event<br>• Any adverse event<br>• Any serious adverse event |
| **Study design** | RCTs of at least 12 weeks duration |
| **Language restriction** | None |

### *4.1.3 Identified studies*

The manufacturer identified five RCTs which included dapagliflozin (three metformin add-on and two insulin add-on).[21-25] In addition, 50 RCTs which focused on various comparator interventions were identified.[26- 76]

The main characteristics of the five identified dapagliflozin trials are summarised in Table 2. All trials included dapagliflozin at a 10mg dose as the intervention.

**Table 2 Summary of identified dapagliflozin RCTs**

| Study | Population | Intervention | Comparator | Primary outcome | Duration |
|---|---|---|---|---|---|
| ***Metformin add-on*** | | | | | |
| Study 4[23] | Type 2 diabetics inadequately controlled on metformin alone | Dapagliflozin 2.5mg up titrated to ≤10mg | Glipizide 5mg up titrated to ≤20mg | Change in HbA1c | 52 weeks |
| Study 12[22] | Type 2 diabetics inadequately controlled on metformin alone | Dapagliflozin 10mg | Placebo | Weight loss | 24 weeks |
| Study 14[21] | Type 2 diabetics inadequately controlled on metformin alone | Dapagliflozin 10mg | Placebo | Change in HbA1c | 24 weeks |
| ***Insulin add-on*** | | | | | |
| Study 6[25] | Type 2 diabetics inadequately controlled on insulin with or without other agents | Dapagliflozin 10mg | Placebo | Change in HbA1c | 24 weeks |
| Study 9[24] | Type 2 diabetics inadequately controlled on insulin with or without other agents | Dapagliflozin 10mg | Placebo | Change in HbA1c | 12 weeks |

### *4.1.4 Quality assessment*

The manufacturer assessed the quality of all included RCTs (both dapagliflozin and comparator RCTs). The quality assessment strategy is considered adequate by the ERG.

The quality of the five dapagliflozin RCTs was good. Methods to achieve randomisation were adequate and allocation was concealed using computerised schedules or interactive voice response systems. Analysis was on a modified intention-to-treat basis. The full analysis sets for the trials included all randomised patients who had received at least one dose of the investigational product, had a baseline measurement, and at least one post-baseline assessment. The ERG considers this strategy an acceptable alternative to a strict intention-to-treat analysis.

The quality of the comparator RCTs was generally good. However, the reporting of some of the comparator trials was not always adequate, particularly with respect to randomisation sequence generation and allocation concealment.

The ERG assessed the methodological quality of the manufacturer's systematic review of clinical effectiveness using the CRD criteria (Table 3). In general, the quality of the systematic review was good. The ERG did, however, have concerns about the sensitivity of the literature search and the fact that it appeared that the search had not been updated since May 2011.

**Table 3 Quality assessment of the manufacturer's review**

| CRD quality item | Score |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? | **Yes** |
| 2. Is there evidence of a substantial effort to search for all of the relevant research? | **Partial** |
| 3. Is the validity of included studies adequately assessed? | **Yes** |
| 4. Are sufficient details of the individual studies presented? | **Yes** |
| 5. Are the primary studies summarised appropriately? | **Yes** |

## 4.2 Summary of submitted evidence

### *4.2.1 Introduction and overview*

The manufacturer presented separate analyses for two distinct treatment stages: dapagliflozin as an add-on to metformin and as an add-on to insulin. Analyses for dapagliflozin as triple

therapy were also presented in an addendum. Dapagliflozin as monotherapy (first-line therapy) was not considered in this submission.

The manufacturer included five relevant randomised controlled trials (RCTs) of dapagliflozin (Table 4). Dapagliflozin was used as an add-on to metformin in three of these RCTs; the other two RCTs compared dapagliflozin as an add-on to insulin. Studies were labelled according to the final digits of their BMS/AZ trial number.

Analyses were presented for four main outcomes: change in HbA1c, weight change, systolic blood pressure (SBP) and hypoglycaemia. Separate results were presented for two time points (around 24 weeks and around 52 weeks). Information on safety and adverse events was also presented.

The manufacturer also identified randomised trials which compared other relevant treatments as add-ons to either metformin or insulin and included these in network meta-analyses (NMA). The treatments included differed for the 24 and 52 week networks (see Table 7).

**Table 4 Summary of the five main dapagliflozin trials considered by the manufacturer (Tables 18-22 in the submission)**

| | Study (primary reference) | Intervention and comparator | Time point used for primary analysis | Baseline HAb1c (mean (SD) (%)) | HbA1c (mean change from baseline (95% CI) (%)) | Weight (mean change from baseline (95% CI) (kg)) | SBP (mean change from baseline (95% CI) (mmHg)) | Hypoglycaemia (n/N (%)) |
|---|---|---|---|---|---|---|---|---|
| Metformin add-on studies | | | | | | | | |
| | Study 14[21] | Dapagliflozin (n=135) | 24 weeks | 7.92 (0.82) | -0.84 (-0.98, -0.70) | -2.86 (-3.33, -2.39) | -5.1 (-7.7, -2.5 ) | 5/135 (3.7) |
| | | Placebo (n=137) | | 8.11 (0.96) | -0.30 (-0.44, -0.16) | -0.89 (-1.35, -0.42) | -0.2 (-2.6, 2.2) | 4/137 (2.9) |
| | Study 12 [22] | Dapagliflozin (n=91) | 24 weeks | 7.19 (0.44) | -0.39 (-0.48, -0.29) | -2.96 (-3.51, -2.41) | -2.70 (-4.90, -0.60) | 2/91 (2.2) |
| | | Placebo (n=91) | | 7.16 (0.53) | -0.10 (-0.20, -0.01) | -0.88 (-1.43, -0.34) | 0.10 (-2.00, 2.20) | 3/91 (3.3) |
| | Study 4[23] | Dapagliflozin (n=406) | 52 weeks | 7.69 (0.86) | -0.52 (-0.60, -0.44) | -3.22 (-3.56, -2.87) | -4.3 (-5.4, -3.2) | 14/400 (3.5) |
| | | Glipizide (SU) (n=408) | | 7.74 (0.89) | -0.52 (-0.60, -0.44) | 1.44 (1.09, 1.78) | 0.8 (-0.3, 1.9) | 162/401 (40.8) |

| | Study (primary reference) | Intervention and comparator | Time point used for primary analysis | Baseline HAb1c (mean (SD) (%)) | HbA1c (mean change from baseline (95% CI) (%)) | Weight (mean change from baseline (95% CI) (kg)) | SBP (mean change from baseline (95% CI) (mmHg)) | Hypoglycaemia (n/N (%)) |
|---|---|---|---|---|---|---|---|---|
| Insulin add-on studies | | | | | | | | |
| | Study 6 [25] | Dapagliflozin (n=194) | 24 weeks | 8.57 (0.82) | -0.96 (NR) | -1.67 (-2.02, -1.31) | -6.9 (-8.7, -5.1) | 83/196 (42.3) |
| | | Placebo (n=193) | | 8.47 (0.77) | -0.39 (NR) | 0.02 (-0.34, 0.38) | -3.9 (-5.7, -2.1) | 69/197 (35.0) |
| | Study 9 [24] | Dapagliflozin (n=24) | 12 weeks | 8.4 (0.7) | -0.61 (-0.87, -0.36) | -4.51 (-5.48, -3.53) | -7.2 (-12.1, -2.3) | 7/24 (29.2) |
| | | Placebo (n=23) | | 8.4 (0.9) | 0.09 (-0.19, 0.37) | -1.88 (-2.89, -0.88) | 2.8 (-4.9, 10.5) | 3/23 (13.0) |

### *4.2.2 Dapagliflozin as an add-on to metformin*

Three RCTs involved dapagliflozin as an add-on to metformin: two comparing dapagliflozin with placebo (Studies 12 and 14) and one comparing dapagliflozin with an SU (glipizide) (Study 4). Although both Studies 12 and 14 had the same indication, comparator, and length of follow-up (24 weeks), the manufacturer did not perform a meta-analysis because baseline levels of HbA1c differed and it proved unfeasible to adjust for this imbalance by means of standard statistical techniques. For Study 12 the inclusion criteria specified levels of HbA1c of 6.5% and 8.5%, for study 14 the HbA1 level was 7% to 10%. Originally these studies had also different primary outcomes: change in HbA1c for Study 14 and change in bodyweight for Study 12. Pairwise comparisons of dapagliflozin with placebo were therefore only made graphically in the main text of the submission. The results of a meta-analysis using a random effects model were presented, however, in Tables 38-41.

**Table 5 Comparison of metformin add on RCTs**

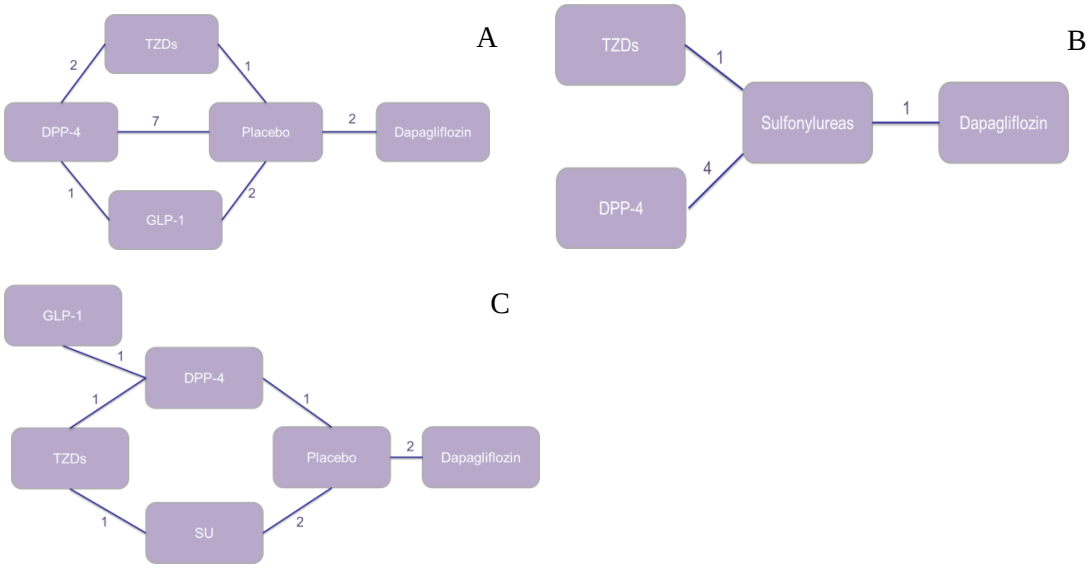
| | Study 14 | Study 12 | Study 4 |
|---|---|---|---|
| **Main inclusion criteria** | • Aged 18-77 years<br>• Diagnosis of T2DM<br>• HbA1c between 7-10%<br>• BMI <45<br>• Taking a stable dose of metformin (≥1500mg per day) for at least 8 weeks | • Males aged 30-75 years<br>• Females aged 55-75 years, who had been postmenopausal for at least 5 years<br>• Diagnosis of T2DM<br>• HbA1c between 6.5 -8.5%<br>• BMI ≥25<br>• Body weight ≤120kg<br>• Taking a stable dose of metformin (≥1500mg per day) for at least 12 weeks | • Aged ≥ 18 years<br>• Diagnosis of T2DM<br>• HbA1c between 6.5 - 10%<br>• Treatment with an oral antidiabetic drug including metformin for at least 8 weeks prior to enrolment |
| **Main exclusion criteria** | • Serum creatinine >133µmol/L for men and >124µmol/L for women<br>• Urine albumin/creatinine ratio >203.4mg/mmol<br>• AST or ALT > 3 times upper limit of normal<br>• Symptoms of poorly controlled diabetes<br>• Clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease<br>• Cardiovascular event within 6 months | • Diagnosis of T1DM<br>• Body weight change >5% within 3 months of enrolment<br>• Use of weight loss medication within 30 days of enrolment<br>• Renal failure or dysfunction | • Diagnosis of T1DM<br>• Treatment with insulin within one year of enrolment<br>• BMI>45<br>• Renal failure or dysfunction |

| | | | |
|---|---|---|---|
| | • New York Heart Association class III or IV congestive heart failure<br>• Systolic blood pressure ≥180mmHg<br>• Diastolic blood pressure ≥110mmHg | | |
| **Mean baseline HbA1c level (%)**<br>Dapagliflozin<br>Comparator | <br>7.92<br>8.11 | <br>7.19<br>7.16 | <br>7.69<br>7.74 |
| **Mean baseline systolic blood pressure (mmHg)**<br>Dapagliflozin<br>Comparator | <br>126.0<br>127.7 | <br>135.9<br>133.3 | <br>132.8<br>133.8 |
| **Mean baseline body weight (kg)**<br>Dapagliflozin<br>Comparator | <br>83.6<br>87.7 | <br>92.06<br>90.91 | <br>88.44<br>87.6 |
| **Primary efficacy outcome** | Change from baseline HbA1c level | Change from baseline body weight | Change from baseline HbA1c level |
| **Duration** | 24 weeks | 24 weeks | 52 weeks |
| **Number of patients randomised** | Dapagliflozin 2.5mg - 137<br>Dapagliflozin 5mg - 137<br>Dapagliflozin 10mg - 135<br>Placebo - 137 | Dapagliflozin 10mg - 91<br>Placebo - 91 | Dapagliflozin 2.5-10mg - 406<br>Glipizide 5-20mg - 408 |

The manufacturer then presented a network meta-analysis (NMA) incorporating RCTs of other comparators used as add-ons to metformin or insulin. Fifty reports of 37 RCTs, of which three involved dapagliflozin, were initially identified. The manufacturer analysed the four main outcomes separately at 24 weeks (+/- 6 weeks) and at 52 weeks (+/- 6 weeks) and studies reporting at other time points were not included. Additional exclusion criteria were introduced: GLP-1 analogues were excluded and SUs were excluded from the 24 week NMA for all outcomes except SBP. SUs were, however, included in the NMA analysis at 52 weeks.

Different networks of comparators were available for each time point: for 24 weeks the network diagram involved five classes of treatment (dapagliflozin DPP-4, GLP-1, TZD and placebo) and 15 studies. For 52 weeks the network diagram involved four treatments (dapaliflozin, DPP-4, TZD and SU) and six studies, but it was not possible to include placebo as one of the comparators. A third network was set up for the SBP outcome at 24 weeks, which involved six treatments (Dapagliflozin, DPP-4, GLP-1, SU, TZD and placebo) and eight studies. The network diagrams from the manufacturer's submission for each of these situations are shown in Figure 3 below (Figure 17 of the manufacturer's submission).

**Figure 3 Network for randomised clinical trials reporting any of HbA1c, weight, or hypoglycaemia (metformin add-on indication)**




Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptiodase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylurea; TZD, Thiazolidinediones;

A) 24 week network; B) 52 week network; C) 24 week metformin add-on network for systolic blood pressure.

The results of a NMA may be presented as a relative effect between each pair of treatments in the network – for HbA1c, weight and SBP this is expressed as mean differences in the change from baseline levels, for hypoglycaemia it is expressed as an odds ratio (OR). The

manufacturer presented the results of each NMA in two ways: first with the results of all comparators with respect to placebo (or SU in the case of the 52 week results) and then with respect to dapagliflozin. This appraisal focuses on the treatment effects relative to dapagliflozin.

*Change in HbA1c*

At 24 weeks dapagliflozin was associated with greater reductions in HbA1c relative to placebo [redacted]. Although all other active comparators in the NMA (DPP-4, TZD and GLP-1) had larger point estimate reductions in HbA1c when compared with placebo, there was no evidence that these effects differed to that of dapagliflozin. Relative to DPP-4, TZD and GLP-1, dapagliflozin was associated with mean differences in the change in HbA1c of [redacted] and [redacted] respectively. These 24 week results were all adjusted for baseline HbA1c.

There was also no evidence that the effect of dapagliflozin differed to that of DPP-4, TZD or SU at 52 weeks: mean differences in the change in HbA1c were [redacted] respectively. The 52 week results were not adjusted for baseline HbA1c and placebo was not included in the network as a comparator.

*Weight change*

At 24 weeks, dapagliflozin was associated with mean weight loss of over 2kg compared with placebo [redacted]. There was also evidence that this relative weight loss was greater than for DPP-4 [redacted] and for TZD [redacted]. There was no evidence that dapagliflozin had greater weight loss than GLP-1 [redacted].

At 52 weeks there was evidence that dapagliflozin was associated with greater relative weight loss than both DPP-4 [redacted] and SU [redacted].

*Systolic blood pressure (SBP)*

The main difference in the NMA for this outcome is that the manufacturer included SU in the network for 24 weeks. No analyses were conducted at 52 weeks.

Dapagliflozin was associated with a statistically significant reduction in SBP compared with placebo [redacted]. Dapagliflozin was also associated with greater relative reductions in SBP compared with the other comparators in the network, but this was only statistically significant when compared with SU [redacted].

*Hypoglycaemia*

As rates of major hypoglycaemia were low and there was wide variation in the definitions of hypoglycaemia reported in the available studies, the manufacturer included all types of hypoglycaemia (whether major or minor) in the main NMA analyses.

At 24 weeks, when considering all types of hypoglycaemia there was no evidence that dapagliflozin had greater odds of hypoglycaemia than placebo [redacted], DPP-4 [redacted], TZD [redacted] or GLP-1 [redacted]. Although the point estimates suggested greater risk of hypoglycaemia for dapagliflozin and some of the odds ratios might be considered clinically important these were generally based on a very small number of hypoglycaemic events (see Table 130 of the manufacturer's submission).

At 52 weeks, dapagliflozin had similar rates to DPP-4 and TZD but hypoglycaemia was less frequent than for SU [redacted].

### *4.2.3 Dapagliflozin as an add-on to insulin*

For the insulin add-on, two studies comparing dapagliflozin with placebo were identified, one with 12 week (Study 9) and one with 24 week (Study 6) follow-up. The manufacturer decided not to present standard meta-analysis because of this difference in time points. Study 9 was small compared with Study 6.

A maximum of four RCTs (involving dapagliflozin, DPP-4, TZD and placebo) contributed to the NMA for the add-on to insulin analysis. Only one dapagliflozin trial (Study 6) was included; Study 9 was excluded because its duration was only 12 weeks. Three further studies comparing TZD with placebo were also excluded because they allow up-titration of insulin. Analyses were only possible at 24 weeks – the follow-up times criteria in the protocol were amended from 24 weeks +/- 6 weeks to +/- 8 weeks in order to allow studies with measurements at 16 weeks to be included.

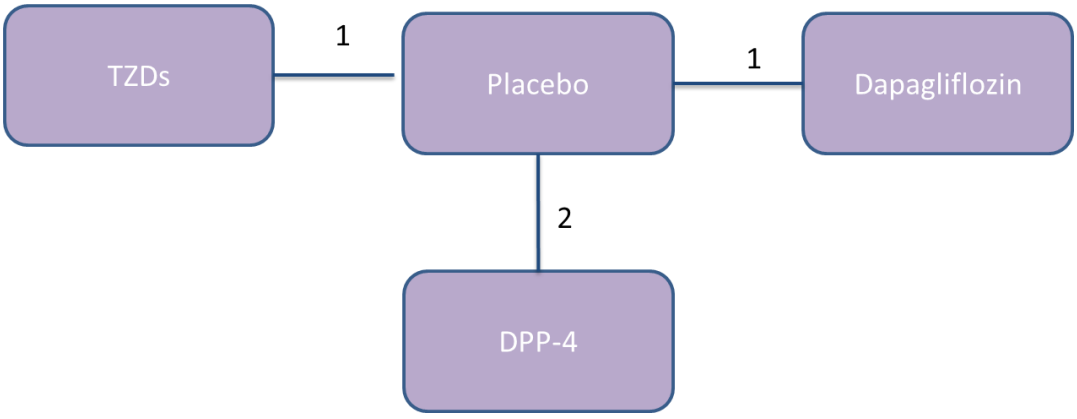
**Table 6 Comparison of insulin add on RCTs**

| | Study 6 | Study 9 |
|---|---|---|
| **Main inclusion criteria** | • Aged 18-80 years<br>• Diagnosis of T2DM<br>• BMI ≤45<br>• HbA1c ≥7.5 and ≤10.5<br>• On a stable insulin regimen of at least 30 IU daily for at least eight weeks without any other oral antidiabetic drugs or with a stable dose of antidiabetic drugs | • Aged 18-75 years<br>• Diagnosis of T2DM<br>• HbA1c ≥7.5 and ≤10.5<br>• Treated with subcutaneous insulin for at least 12 weeks before enrolment<br>• Insulin treatment stable for at least six weeks at enrolment |
| **Main exclusion criteria** | • Diagnosis of T1DM<br>• Symptoms of poorly controlled diabetes<br>• Calculated creatinine clearance <50mL/min per 1.73$m^2$<br>• If not receiving metformin, serum creatinine >177µmol/L<br>• If receiving metformin, serum creatinine >133 µmol/L for men or 124 µmol/L for women<br>• Treatment with >2 additional oral antidiabetic drugs<br>• Moderate or severe renal failure or dysfunction | • Diagnosis of T1DM<br>• AST and/or ALT >2.5 times upper limit of normal<br>• Creatinine kinase ≥3 times upper limit of normal<br>• Symptoms of severly uncontrolled diabetes<br>• History of severe hypoglycaemia<br>• Unstable condition<br>• Series cardiovascular, renal or hepatic disease |

| | Study 6 | Study 9 |
|---|---|---|
| **Mean baseline HbA1c level (%)** | | |
| Dapagliflozin | 8.58 | 8.39 |
| Placebo | 8.46 | 8.32 |
| **Mean baseline systolic blood pressure (mmHg)** | | |
| Dapagliflozin | 140.6 | 124.7 |
| Placebo | 136.1 | 134.6 |
| **Mean baseline body weight (kg)** | | |
| Dapagliflozin | 94.63 | 102.78 |
| Placebo | 94.21 | 101.29 |
| **Primary efficacy outcome** | Change in HbA1c | Change in HbA1c |
| **Duration** | 24 weeks | 12 weeks |
| **Number of patients randomised** | Dapagliflozin 2.5mg - 196<br>Dapagliflozin 5mg - 212<br>Dapagliflozin 10mg - 202<br>Placebo - 197 | Dapagliflozin 10mg - 24<br>Dapagliflozin 20mg - 24<br>Placebo - 23 |

The network diagram for the insulin add-on NMA is reproduced in Figure 4 (Figure 18 of the manufacturer's submission).

**Figure 4 Network for randomised clinical trials reporting any of HbA1c, weight, or hypoglycaemia (insulin add-on indication)**




Abbreviations: DPP-4, Dipeptidyl peptidase-4 inhibitors; TZD, Thiazolidinediones;
*Note*: three additional trials involving TZDs were excluded based on not requiring that the insulin dose remain stable throughout the study period

*Change in HbA1c*

For the main analysis presented by the manufacturer, only three RCTs were included as the TZD study which reported results at 16 weeks[65] had higher baseline values of HbA1c. Relative to placebo, dapagliflozin was associated with greater reduction in HbA1c [redacted]. *Although results are also provided for DPP4 and after including the TZD trial, the ERG considers the reporting of this section of the manufacturer's submission (p.132) rather unclear.*

*Weight change*

Dapagliflozin was associated with greater weight loss compared with placebo [redacted] and with DPP-4 [redacted]. The results of dapagliflozin versus TZD were reported to be similar but numerical results were not given.

*Systolic blood pressure (SBP)*

Only one study[25] (Study 6) met the inclusion criteria for the NMA - the other RCTs either did not report the change in SBP or they involved up-titration of insulin. In this study there was a

statistically significant reduction in SBP compared with placebo (mean difference: -2.99mmHg, 95% CrI: -5.50 to -0.45).

*Hypoglycaemia*

There was no evidence that the odds of a hypoglycaemic event differed for dapagliflozin compared with placebo (OR: 1.37, 95% CrI: 0.91 to 2.06) or with DPP-4 (OR: 0.96, 95% CrI: 0.56 to 1.65). Dapagliflozin was, however, associated with statistically significantly lower odds of hypoglycaemia compared with TZD (OR: 0.36, 95% CrI: 0.15 to 0.87).

*Total daily dose of insulin*

Study 6 also measured changes in insulin requirements over time. While the mean total daily dose of insulin did not increase in participants receiving dapagliflozin, continued to increase progressively in those receiving placebo.

### *4.2.4 Adverse events after dapagliflozin*

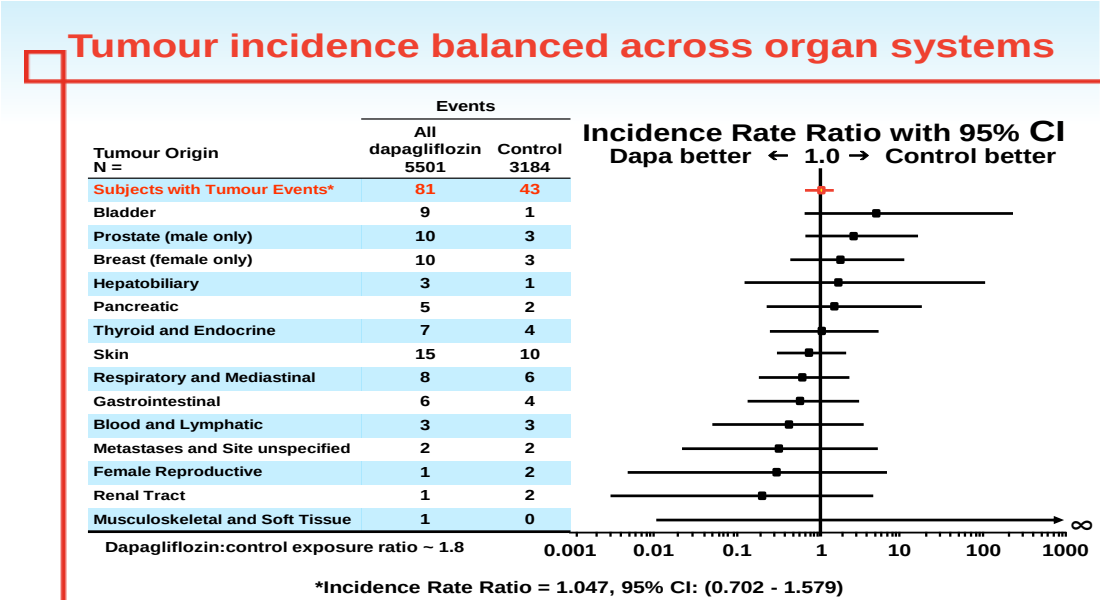
The manufacturer presented information about the risk of adverse events following dapagliflozin using pooled results from a variety of placebo-controlled randomised studies – this included monotherapy studies, add-on studies following other antidiabetic medication and studies of initial combination therapy with metformin (manufacturer's response to clarification question A5). Most analyses involved three Phase 2b and twelve Phase 3 randomised studies and included only 10mg dapagliflozin and placebo arms, even where other doses of dapagliflozin had also been administered. Most results are based on short term (up to 24 weeks) results. For rare outcomes, such as cancers, longer term results including more recent trials were considered.

Rates of genital and urinary tract infections were similar but were slightly higher after dapagliflozin than after placebo. There were few events of renal impairment or failure with no difference between the groups. Events of depletion (hypotension/hypovolaemia/dehydration) were slightly more common after dapagliflozin but no numerical results appear to be given.

The overall proportion of patients with cancer was similar between those who received dapaglaflozin and those who received placebo: all cancers (81/5501; 1.47% vs 43/3184; 1.35%). However, the rates of bladder cancer (9/5501; 0.16% vs 1/3516; 0.03%), prostate cancer (10/5501; 0.34% vs 3/3184; 0.16%), and breast cancer (10/2531; 0.40% vs 3/1359; 0.22%) were higher after dapagliflozin than after placebo (see also Figure 5, which replicates Figure 23 in the manufacturer's submission). Given the small number of events and the wide

confidence intervals for the incidence rate ratios it is not possible to establish the relative risk of cancer for these organ systems with certainty. The FDA briefing document on the safety profile of dapagliflozin drew attention to the fact that the incidence rates of bladder and breast cancer were higher than those commonly expected in an age-matched reference diabetic population.[77]

**Figure 5 Incidence of cancer across organ systems**




The manufacturer did not present new analyses of cardiovascular safety, but in a section on the interpretation of the results (page 187 of the manufacturer's submission) they refer to the FDA submission. Based on a meta-analysis of 14 studies (involving over 6,000 participants), they conclude that there is no evidence that dapagliflozin is associated with an increased cardiovascular risk (HR 0.67; 95% CI 0.32 to 1.10) for a composite endpoint of cardiovascular death, MI, and stroke. The ERG was not able to assess this properly as no details of this analysis were presented.

### *4.2.5 Dapagliflozin in triple therapy*

The manufacturer's analyses for the effect of dapagliflozin as a triple therapy were submitted as an addendum to the main submission. The data come from a subset of patients from two Phase 3 clinical studies (Studies 18 and 19) which were designed to assess the efficacy and safety of dapagliflozin in patients at high risk of cardiovascular events. These may not be representative of the overall population of those with T2DM since all patients in these studies had documented cardiovascular disease, had an average age of 63-64 years and [redacted] had moderate or severe renal impairment.

[redacted]

The manufacturer did not conduct a NMA of triple therapy but referred to a good quality review produced by the Canadian Agency for Drugs and Technologies in Health (CADTH) instead[19] In this review, literature searches for identified relevant studies were conducted in 2009. The manufacturer acknowledges the limitations of using this report and suggests that there is at present insufficient evidence to evaluate the comparative efficacy of the various antidiabetic drugs in the triple therapy setting.

## 4.3 Critique of submitted evidence

### *4.3.1 Methodology of the review*

The manufacturer performed separate analyses for dapagliflozin as an add-on to metformin and as an add-on to insulin. The ERG considers this approach correct.

The manufacturer chose to conduct separate analyses by time point. Analyses were only considered for outcomes at 24 weeks (+/- 6 weeks) and at 52 weeks (+/- 6 weeks). They made no attempt to perform recently-published methods that allow for modelling of data at multiple follow-up times within a network meta-analysis[78] because they reckoned the model results would have been less intuitive and because they required a time effect to be modelled explicitly.

This meant that studies reporting outcomes at less than 18 weeks, between 30 and 46 weeks or greater than 58 weeks were excluded from the review. According to Tables 7 and 8 of the manufacturer's submission,16 of the 55 studies identified for inclusion in the review had, however, a duration of less than 18 weeks. It is not clear whether studies with a duration between 30 and 46 weeks or greater than 58 weeks were also identified. For the insulin add-on NMA, analyses were only performed for 24 weeks and an amendment was made to the protocol to include studies in the range 24 weeks +/- 8 weeks, instead of +/- 6 weeks. The manufacturer later acknowledged that this was done to allow studies with a duration of 16 weeks to be included in the NMA. While accepting that this approach increased the evidence base for the insulin add-on analysis and was decided in accordance with clinical advice, the ERG considers this a *post hoc* amendment to the protocol.

No standard meta-analyses comparing dapagliflozin against placebo or against another comparator were presented in the main text, either for the metformin add-on or for the insulin add-on, although some of these results are given in later tables (Tables 38-41). The manufacturer stated that this was because there were insufficient numbers of studies and because of the inability to adjust for baseline HbA1c. Only one comparison (dapagliflozin versus placebo at 24 weeks for the metformin add-on) had more than a single study but these two studies had different baseline HbA1c levels and it was not possible to adjust for baseline HbA1c imbalance using standard meta-analysis techniques. Instead a NMA was conducted which allowed the inclusion of evidence from non-dapagliflozin studies. The ERG considers this approach acceptable in the absence of head-to-head trials of dapagliflozn against its key comparators.

The manufacturer initially intended to create networks for each indication (metformin add-on and insulin add-on) at both 24 and 52 weeks. Since sulphonylureas were not included for the 24 week metformin add-on network for HbA1c, body weight and incident hypoglycaemia, but were considered suitable for the assessment of systolic blood pressure, the manufacturer created two 24 week metformin add-on networks (one for HbA1c, body weight and hypoglycaemia; and one for systolic blood pressure). For the insulin add-on indication, the manufacturer was only able to create a network at the 24 week time point as there were no data available for dapagliflozin at 52 weeks (± eight weeks). The interventions and outcomes used for each of these networks are summarised in Table 7.

**Table 7 Summary of network meta-analyses**

| Time point | Intervention | Outcomes |
|---|---|---|
| *Metformin add-on indication* | | |
| 24 weeks | Dapagliflozin, TZDs, DPP-4s, GLP-1s, placebo | HbA1c, body weight, hypoglycaemia |
| 24 weeks (SBP only) | Dapagliflozin, TZDs, DPP-4s, GLP-1s, sulphonylureas placebo | systolic blood pressure |
| 52 weeks | Dapagliflozin, TZDs, DPP-4s, GLP-1s, sulphonylureas placebo | HbA1c, body weight, hypoglycaemia, systolic blood pressure |
| *Insulin add-on indication* | | |
| 24 weeks | Dapagliflozin, TZDs, DPP-4s, placebo | HbA1c, body weight, hypoglycaemia, systolic blood pressure |

The manufacturer adjusted some of the NMAs for baseline HbA1c, but made no attempt to adjust the analyses for any other variables. Although both fixed and random effect models and adjusted and unadjusted models are all reported in Tables 38-39 (along with results from classical meta-analysis), certain results are highlighted in the main text and tables. In the main text they presented a mixture of adjusted and unadjusted results and explained that the decision was based on the *a priori* choice of model (i.e. a random effects model adjusted for baseline HbA1c), statistical and clinical significance of the model coefficient, the model fit and assessment of the posterior distribution of the between studies variance. In the footnote to Tables 25 and 26 of the manufacturer's submission, it is also stated that a model whose deviance information criterion (DIC) is at least three points lower than that of another model is deemed to have better fit, but it is difficult to reconcile this with the DIC values given in these tables. An adjusted random effects model is presented only for the HbA1c outcome for the metformin add-on analysis at 24 weeks; at 52 weeks an unadjusted random effects model is presented as the main result. Analyses for all other outcomes appear to be unadjusted for baseline HbA1c with no adjusted results presented in the corresponding tables (Tables 39-41).

The ERG considers that the manufacturer's approach to model selection lacks transparency and that they do not provide sufficient justification as to whether or not adjusted results were presented on an analysis-by-analysis basis. The information provided does not allow the analyses to be replicated. It should be noted, however, that the magnitude of the adjusted and unadjusted results was reasonable similar (Tables 38-39).

#### *4.3.2 Assumptions of the network meta-analyses*

There were many assumptions in the manufacturer's NMA. Various additional eligibility criteria were introduced (pages 114-115, manufacturer's submission).

Although only dapagliflozin studies with a dose of 10mg were included, other comparators in the NMA comprised a variety of agents and doses (Tables 124-126 of the manufacturer's submission). For the data extracted for the metformin add-on NMA, the DPP-4 class incorporated siptagliptin, saxagliptin, vildagliptin and linagliptin at various doses, the GLP-1 class incorporated exenatide and liraglutide at various doses, and the TZD class incorporated pioglitazone at various doses. The SU class at 52 weeks incorporated glipizide, gliclazide, glimepiride and glibenclamide; at 24 weeks (used only for the SBP NMA) this class included other drug options (Table 117, manufacturer's submission). The drugs and doses for the insulin add-on NMA do not seem to be given explicitly. Despite the differences in drugs and doses, all treatments within a drug class were considered to be equivalent for the purposes of

the NMA. Although the ERG considers the manufacturer's NMA approach to be reasonable, it is worth pointing out that many details were lacking.

Due to the wide variation in the definitions of hypoglycaemia, the manufacturer considered both major and minor hypoglycaemic events within the NMA, even though the rates varied considerably. The ERG considers this approach acceptable in view of the limited data available, though we note that the greatest impact on quality of life comes from severe hypoglycaemic episodes.

Two RCTs[39,67] involving both GLP-1 analogues and intensive diet regimes were excluded. The rationale for these exclusions was that the intervention resulted in a much greater weight loss than it would be expected with the use of a GLP-1 analogue alone, and so the addition of an intensive dietary component to the drug intervention rendered these trials not comparable to other studies in the network. The ERG agrees with this.

SUs were excluded from the 24 week metformin add-on NMA, except for the analysis of SBP, due to an unstable effect size at the duration of follow-up (attributed by the manufacturer to a possible J-curve effect of the drug over time and due to the fact that it may take up to 18 weeks for titration of SUs*)*. The ERG thought that it was uncommon to exclude just one class of drug from the meta-analyses for the above reasons and would have liked to have seen greater justification for this exclusion. However, in practice, SUs would not be a comparator to dapagliflozin, but a precursor.

In the insulin add-on NMA, RCTs were deemed suitable for inclusion if they reported outcomes at 24 weeks (± eight weeks). The time window around 24 weeks was widened *ad hoc* from six to eight weeks to allow for the inclusion of a TZD trial.[65] Three RCTs[27,54,76] which compared TZDs to placebo were excluded on the basis that they allowed up-titration of insulin in order to maintain glycaemic control. In response to an ERG query, the manufacturer explained that they thought that this was the best strategy to maintain the consistency assumption in the MTC model, as up-titration of insulin was considered to modify the treatment effect. Even though exclusion of these trials meant that insulin was not being used to its best clinical effect in the remaining trial, the ERG considers this revised eligibility criterion to be acceptable as the decision to exclude trials which consent to up-titration of insulin appears to have been a pragmatic choice to allow a comparison to be made between dapagliflozin and TZDs.

RCTs involving metformin as a comparator in the insulin add-on NMA were also excluded at this stage. The manufacturer maintained that as metformin is not a comparator of interest in the UK for the insulin add-on indication since it would usually be used in combination with insulin, before dapagliflozin.

### *4.3.3 Triple therapy*

This part of the submission was presented as an addendum. The data come from a subset of patients from two RCTs which included participants who were at high risk of cardiovascular events. The report was conducted in a shorter time frame than for the original submission. Therefore, the manufacturer recommends caution in interpreting the results of dapagliflozin in triple therapy.



Four studies were selected by the manufacturer. One was an ongoing trial of dapagliflozin used in combination with metformin and SU, which is not expected to report results until late 2013. Of the remaining three studies, one (Study 10) focused on patients who had failed to reach glycaemic control following metformin and DPP-4, and was not considered further; the remaining two studies (Studies 18 and 19) enrolled patients who were being treated with metformin and SU at baseline. It is worth noting that all patients suffered from prior cardiovascular disease and therefore could differ from those recruited in other dapagliflozin studies.

The manufacturer's results appear to come mainly from simple pooling of the results of the triple therapy patients from Studies 18 and 19, but the methods of the presented analyses are not particularly clear.

Instead of conducting a new NMA including all evidence from all appropriate comparators, the manufacturer referred to a Canadian report.[19] The literature search for this report only included studies up to 2009.

Overall, the ERG considers the methodology of the triple therapy review as less robust as that of the main submission. It is worth noting, however, that this was submitted as an addendum to the main submission following a request by NICE. The manufacturer did not initially intend to provide findings of the use of dapagliflozin in the triple therapy setting as an important triple therapy RCT is currently ongoing. No up-to-date searches were performed and only studies involving some kinds of triple therapy were included. The two dapagliflozin studies that were included were subsets of larger studies and only included patients with cardiovascular disease that were older and might be expected to have poorer outcome than

other patient groups taking dapaglifozin. The results presented appear to be derived from simple pooling of these subgroups.

### *4.3.4 Adverse events*

Except for hypoglycaemia, no formal meta-analyses of adverse event data were conducted. The manufacturer explained that this was a methodologically contentious area. Simple pooling of adverse events in dapagliflozin and placebo groups of various RCTs was conducted for some adverse events. The inclusion criteria for the studies in these analyses varied by type of adverse event and were not particularly clear, even after further clarifications from the manufacturer. Results from the main five dapagliflozin studies are given separately but do not appear to be included in the overall pooled analyses. The ERG highlights the lack of clarity about the studies' inclusion criteria, which renders the interpretation of the results difficult. In particular, the justification for having different inclusion criteria for cancer and other types of adverse events is not straightforward.

It is difficult to draw firm conclusions about the risk of cancer after administration of dapagliflozin (in particular bladder, prostate and breast cancer). The ERG was concerned that there was a lack of transparency as to how studies had been selected for this analysis and that simple pooling had been used instead of formal meta-analysis techniques. Furthermore, i) the trials were not originally designed to assess the relationship between dapagliflozin and risk of cancer; ii) the manufacturer's submission does not provide information on how many studies actually contributed to the reported cancer rates; iii) the reported incidence rate ratios show wide confidence intervals. The 2011 FDA advisory committee meeting briefing document pointed out that the age-specific incidence rates of bladder and breast cancer were higher than those reported in the literature.[77] The manufacturer's response to the ERG clarification letter on this point states that the relative risk associated with dapagliflozin is above 1 for bladder, prostate and breast cancer and below 1 for other types of cancer and maintains that a causal relationship is unlikely. The ERG believes that the manufacturer was unable to rule out completely a possible association between dapagliflozin and an increased risk of cancer and that the current available data are insufficient to draw firm conclusions on the risk of cancer after dapagliflozin therapy. The ERG's position is in line with that of the
CHMP from the EMA:

*"Overall there was no imbalance of malignancies between dapagliflozin-treated patients and those on control. The unexpected finding of more bladder (0.16% as compared to 0.03% in the controls) and breast cancers (0.40% as compared to 0.22% in the controls) in dapagliflozin-treated patients is of concern especially in the light of potentially long treatment*

*periods and a possible widespread use. Even though data from carcinogenicity studies in animals did not indicate a genotoxic or carcinogenic effect of dapagliflozin, the CHMP considered it necessary to keep this potential risk under close observation and requested the applicant to conduct an epidemiological study with dapagliflozin. The potential risk of cancer will also be looked at in the planned cardiovascular outcome study further investigating potential cardiovascular risks of dapagliflozin. Following the review of all available data, the Committee concluded during its April 2012 meeting that the benefits of dapagliflozin outweigh its risks, and recommended that a marketing authorisation be granted."*

### 4.4 Additional work carried out by the ERG

None.

### 4.5 Conclusions of the clinical effectiveness section

Dapagliflozin at a dose of 10 mg appears to be effective compared to placebo at reducing blood glucose levels, weight, and systolic blood pressure. Rates of genital and urinary tract infections are increased after dapagliflozin, compared to most other glucose-lowering agents, though not compared to the gliptins.[10] The incidence of bladder, prostate and breast cancers appear to be higher after dapagliflozin administration, but the significance of this is uncertain, and the incidence of some other cancer is lower.

The main short-coming of the clinical effectiveness evidence is the lack of head-to-head trials against the main comparators, the DPP-4 inhibitors. There are two trials (one not used in the submission but included in the review by Clar et al[20]) but since the SUs are old and cheap drugs with a known safety record, one would expect them to be tried before dapagliflozin. So the ERG regards them as a stage before dapagliflozin, rather than as comparators.

In triple therapy, there is no comparison with the GLP-1 analogues such as long-acting, once-weekly exenatide. This may be a reasonable approach, on the basis that the much lower cost, and the oral administration, means that dapagliflozin should be tried before a GLP-1 analogue.

### 4.6 Findings of a recent independent review

A systematic review[20] of the SGLT2 inhibitors was published recently.[B] It included 7 RCTs of dapagliflozin, six comparing it to placebo, and one to glipizide. This review reaches similar

[B] One of the authors of this ERG report (NW) was a co-author of the Clar et al systematic review.

conclusions to those of the current BMS/AZ submission, namely that dapagliflozin, in T2DM patients with inadequate glycaemic control:

- Reduced HbA1c (by around 0.5%)
- Led to weight loss
- Lowered systolic blood pressure

The meta-analyses of HbA1c and weight, for dapagliflozin compared to placebo, are shown in Figures 6 and 7 below.

**Figure 6 Meta-analysis for HbA1c change from baseline, 10 mg dapagliflozin versus placebo**

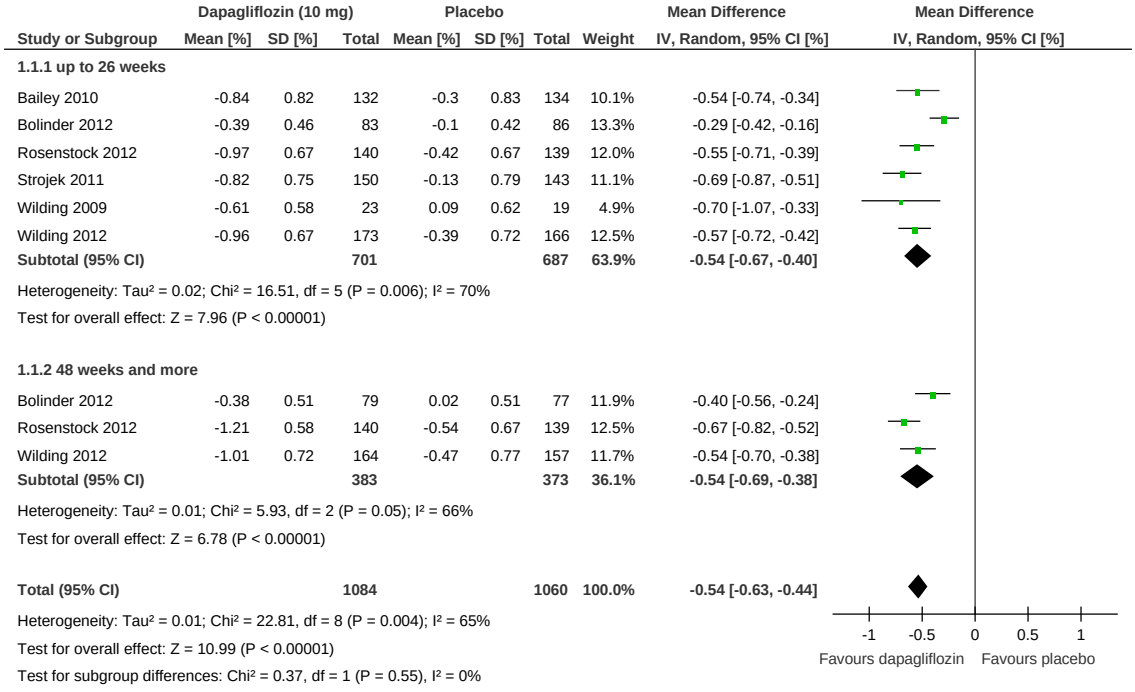
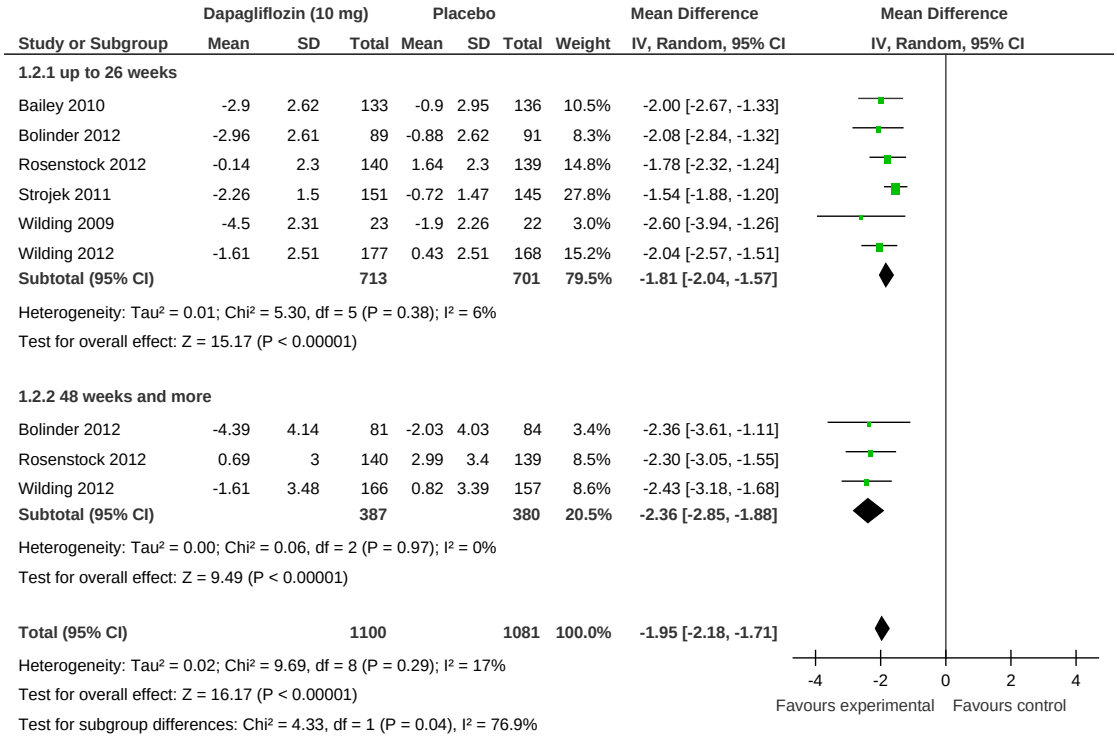


**Figure 7** **Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus placebo**



# 5 COST EFFECTIVENESS

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

### *5.1.1 Description of manufacturer's search strategy and critique*

The searches for economic evaluations are reproduced in Appendix 10 of the manufacturer's submission. A search was designed for each database to retrieve relevant cost-effectiveness, utilities and resource utilisation studies. Ten databases were searched, including the major relevant ones; MEDLINE, EMBASE, NHS EED, and HTA Database. The ERG is unclear, however, on why databases of clinical effectiveness reviews (CDSR and DARE) and of trials (CENTRAL) were also searched. The searches were conducted in October 2011.

The MEDLINE and EMBASE searches were structured by combining a fairly focused clinical search using diabetes and relevant drug terms with an appropriate range of controlled vocabulary and free text economic terms. The strategies were considered fit-for-purpose.

NHS EED and HTA database (as well as CDSR, DARE and CENTRAL) were searched using the Cochrane Library interface. The search strategy was focused using the appropriate MeSH diabetes term combined (using AND) with any of the included drugs and a range of economic terms. Since the former is a database of economic evaluations and the latter of health technology assessments is seems unnecessary to use any economic or cost terms in the search strategy and potentially comprising sensitivity.

These searches were supplemented by consulting recent HTA and ERG reports on T2DM drugs and clinical guidelines produced for NICE for any additional relevant studies.

### *5.1.2 Inclusion and exclusion criteria*

Inclusion criteria for the search for economic evaluation covered:

- Any full economic evaluation: cost-utility, cost-effectiveness, cost-benefit, cost-minimisation conducted in a UK specific setting.
- The search included the following indications within the dapagliflozin licence in order to match the patient populations covered by the dapagliflozin economic model presented in this submission:
    - Dual therapy, with any of the following used as an add-on to metformin (or background therapy): dapagliflozin, SUs, pioglitazone (a TZD), DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin), GLP-1 (liraglutide, exenatide), insulin and insulin analogues, in adults with T2DM.

- Add-on therapy to insulin with one of: dapagliflozin, pioglitazone, a DPP-4 inhibitor or a GLP-1 analogue.

### *5.1.3 Results and conclusion*

The manufacturer did not identify any economic evaluation on dapagliflozin for T2DM (either for the UK or any other country). Four economic evaluations that reported cost per QALY outcomes in a UK context for therapy as an add-on to metformin (dual therapy) were identified (Table 54 of the manufacturer's submission). No relevant UK economic evaluations for add-on to insulin therapy were identified.

As no relevant economic evaluations for dapagliflozin were identified a de novo economic evaluation was performed using a different model than that used previously in economic evaluations of dual therapy for T2DM.

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

### *5.2.1 Comparison of economic submission with NICE reference case*

**Table 8 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 stipulates:<br>For dual therapy: sulphonylureas, pioglitazone, DPP-4 and GLP-1<br>For triple therapy: pioglitazone, DPP-4, GLP-1, insulin<br>For add-on to insulin: insulin | Not entirely.<br><br>For dual therapy despite the GLP-1s being included in the NMA they are not considered in the economic evaluation.<br><br>For triple therapy insulin is not considered.<br><br>For add-on to insulin the DPP-4s are considered as a comparator. The GLP-1s are not considered. The option of only using insulin is not considered.<br><br>Within the manufacturer NMA |

| | | |
|---|---|---|
| | | clinical effectiveness estimates for the TZD are limited to studies of pioglitazone, while those for the DPP-4 encompass studies of sitagliptin, saxagliptin, vildagliptin, and linagliptin. |
| **Patient group** | As per NICE scope.<br><br>The scope specifies that for a given line of therapy the patient population should have been inadequately controlled on the previous line of therapy. | The range of HbA1c values within some of the patient groups may be quite broad. This also gives rise to assumptions about the appropriate values for the threshold HbA1c therapy switching values which are well above the 7.5% of the NICE T2DM guideline.<br><br>There is no consideration of cost effectiveness by HbA1c subgroup. This might have helped address the above concern about threshold values. |
| **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. 40 years. |
| **Synthesis of evidence on outcomes** | Systematic review | Yes. |
| **Outcome measure** | Quality adjusted life years | Yes. |
| **Health states for QALY** | Described using a standardised and validated instrument | For the complications of diabetes the manufacturer mainly uses the UKPDS 62 which estimates decrements through EQ-5D using the UK social tariff.<br><br>A key HRQoL value relates to the direct impact of weight changes. The manufacturer has commissioned a study for the |

| | | |
|---|---|---|
| | | current submission among 110 Canadian patients with T2DM.[79] |
| **Benefit valuation** | Time-trade off or standard gamble | TTO for the UK social tariff.<br><br>TTO for the HRQoL impacts of weight changes. |
| **Source of preference data for valuation of changes in HRQL** | Representative sample of the public | Yes for the UKPDS 62 and the complications of diabetes decrements.<br><br>Not for the HRQoL impacts of weight changes. These were estimated directly through TTO from 110 Canadian patients with T2DM. These estimates are used for the base case in preference to values from published studies, some of which have been used in previous NICE appraisals. |
| **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 | Yes. Probabilistic modelling and results are presented alongside the base case deterministic estimates. |
| **Sensitivity analysis** | | A range of univariate sensitivity analyses are undertaken. |

Three groups of comparisons are made, under the headings:

- Dapagliflozin as an add-on to metformin in dual therapy
- Dapagliflozin in triple therapy[C]
- Dapagliflozin as an add-on to insulin

Note that there appear to be some inconsistencies in the marking up of AIC and CIC material in the triple therapy indication. The ERG has attempted to follow the manufacturer approach.

[C] Submitted as an addendum to the HTA submission dapagliflozin for the treatment of T2DM.

### *5.2.2 Model structure*

The Dapagliflozin Cost Effectiveness Model [DCEM] is a variant of the CARDIFF model that has been presented at a number of the Mt. Hood challenges. But as noted in response to ERG clarification question B19 the CARDIFF model has been amended since the 4th Mt. Hood challenge, which is the only Mt. Hood challenge to which the CARDIFF model has been submitted to have its results published. The performance of the CARDIFF model in the 4th Mt. Hood challenge is reviewed in the model validation section 5.2.11 below.

The DCEM is a discrete event simulation model with an Excel front end and an intermediary visual basic coding, but with the main calculations being performed by compiled C++ programming. As submitted for this assessment, patients are assumed to have none of the following 7 complications of T2DM at baseline:

- Ischaemic heart disease
- Myocardial infarction
- Congestive heart failure
- Stroke
- Amputation
- Blindness
- End stage renal disease

This reduces the applicability of the model to routine care, since many patients will have had prior events. Indeed, some will only have T2DM diagnosed as a result of these events. But also note that angina and age over 65were exclusion criteria for entry to the UKPDS, so the UKPDS recruits did not reflects the totality of people with T2DM.

The DCEM simulates the possibility of a first event of each of the above complications of T2DM as a function of the evolution of the following risk factors:

- HbA1c
- SBP
- Total cholesterol to HDL cholesterol ratio (TC:HDL)
- BMI

During the incident year for any of: myocardial infarction, congestive heart failure, stroke, amputation or renal failure, these events may be fatal. Other deaths are modelled as a function of life table entries.

The probabilities of the events as functions of the risk factors and many of the probabilities of a diabetes event related death are based upon the UKPDS 68. The evolutions of HbA1c, SBP and the total cholesterol to HDL cholesterol ratio through time are also based upon the UKPDS 68. The evolution of weight is based upon the UKPDS 33.

The model permits two therapies to be compared. Given a baseline set of patient characteristics, including the baseline prevalence of the complications of T2DM, each therapy is associated with an initial effect upon each of the risk factors coupled with the duration of the effect after which the UKPDS 68 risk factor evolution equations are applied. The duration of effect prior to the UKPDS 68 risk factor evolution equations being applied is assumed to be one year for the base case, with the exception of BMI.

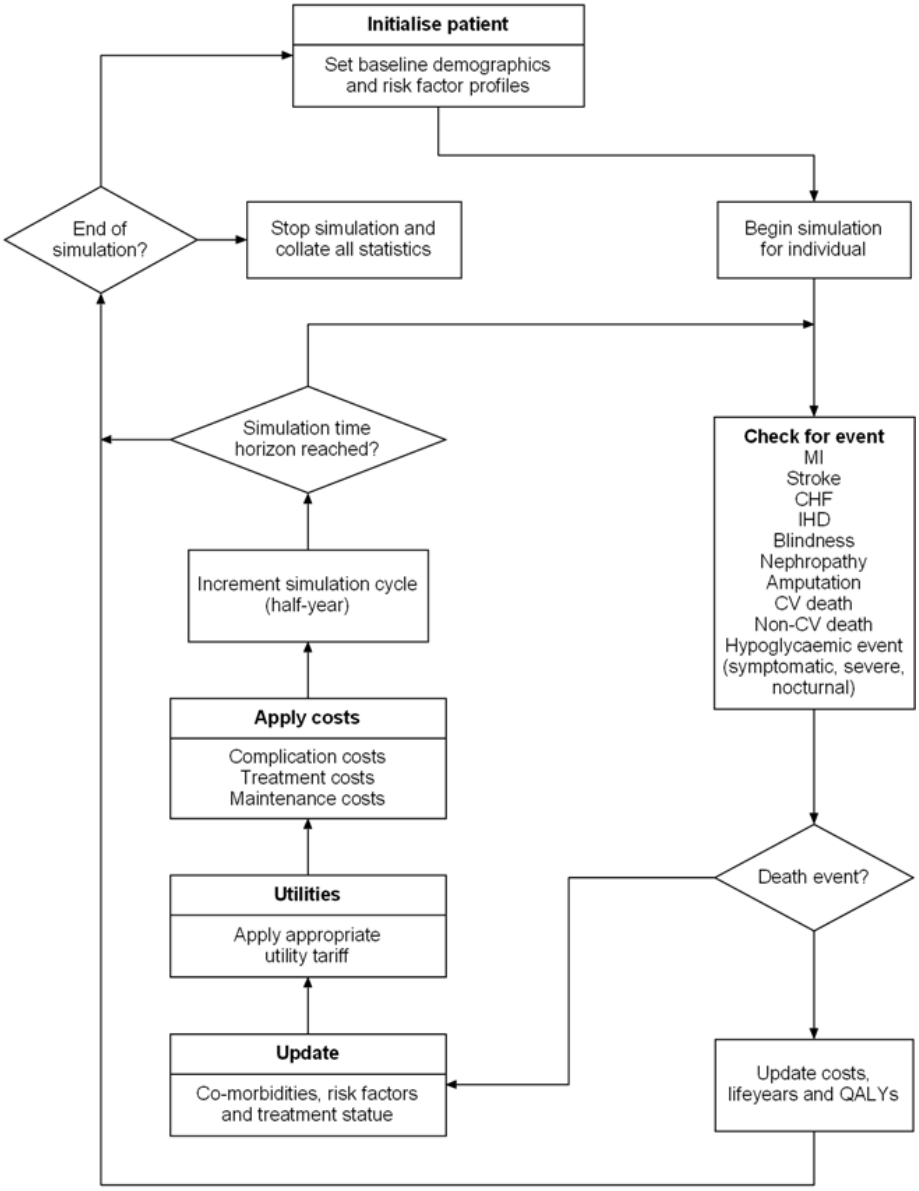
Each therapy is also associated with a range of adverse events: discontinuations in the 1st year, non-severe hypoglycaemic events, severe hypoglycaemic events, urinary tract infections and genital infections.

The DCEM has the facility to specify a threshold HbA1c value. When the modelled HbA1c of a therapy arm rises to this threshold HbA1c value or above it, the patient is modelling as moving onto a 2nd line therapy. This 2nd line of therapy is similarly associated with therapy specific effects upon the risk factors and rate of the adverse events. The therapy switch gives rise to a saw-tooth evolution of the risk factors. The timing of the therapy switch from 1st line to 2nd line will be delayed for the 1st line treatments which have a larger effect upon HbA1c.

All the submitted models have a therapy switch from 1st line to 2nd line. A further switch to a 3rd line therapy can also be specified.

The model structure is as below:

**Figure 8 DCEM model structure**



### *5.2.3 Population*

The patient populations apparently reflect those of:

- The dual therapy head to head trial comparison of dapagliflozin with sulphonylurea, both additional to metformin
- The dual therapy NMA comparison of dapagliflozin with DPP-4 inhibitors and thiazolidinediones, all additional to metformin
- The add on to insulin NMA comparison of dapagliflozin with DPP-4 inhibitors

Note that the manufacturer's own NMA of thiazolidinediones only considers pioglitazone, but that for the triple therapy comparisons relies upon a review from the literature which may not have only considered pioglitazone.

For the triple therapy comparison of dapagliflozin with DPP-4 inhibitors, all additional to sulphonylurea plus metformin, the patient population is assumed to be the same as that of the comparison of the first dual therapy bullet.

The baseline prevalence of the complications of T2DM among the patient populations being modelled is assumed to be zero.

### *5.2.4 Interventions and comparators*

*Dapagliflozin as an add-on to metformin*

Dapagliflozin [DAPA] plus metformin [MET] is compared with:

- Sulphonylurea [SU] plus MET, with evidence drawn from Study 4
- DPP-4 inhibitor [DPP-4] plus MET, with evidence drawn from the NMA
- Thiazolidinedione [TZD] plus MET, with evidence drawn from the NMA

Note that the GLP-1 plus MET is not considered as a comparator despite it being within the NMA. Table 28 of the submission suggests that the manufacturer estimates GLP-1 to have the largest impact upon HbA1c and 0.38% greater than that of dapagliflozin, though tables 30 and 32 suggest GLP-1 having a smaller net impact upon weight and SBP. The ERG agrees that, due to cost, the GLP-1s are not a direct comparator for this comparison. The cheaper drugs would be tried first for a sufficient response.

*Dapagliflozin in triple therapy*

Dapagliflozin plus SU+MET is compared with:

- DPP-4 plus SU+MET

- TZD plus SU+MET
- GLP-1 plus SU+MET

Using both evidence drawn from studies 18 and 19 and evidence drawn from the review of triple therapy by the Canadian Agency for Drugs and Technologies in Health (CADTH) for the comparators.[19]

*Dapagliflozin as an add-on to insulin*

Dapagliflozin as an add-on to insulin [INS] is compared with:

- DPP-4 plus INS, with evidence drawn from the NMA

### *5.2.5 Perspective, time horizon and discounting*

The perspective is as per the NICE guidelines: the patient perspective for benefits and the NHS/PSS for costs. The time horizon is 40 years, with costs and benefits being discounted at an annual rate of 3.5%.

### *5.2.6 Treatment effectiveness and extrapolation*

*Treatment effectiveness: Dapagliflozin as an add-on to metformin*

For the comparison with the sulphonylurea, given the availability of a head-to-head RCT the effectiveness estimates are drawn directly from study 4. For the remaining comparisons the effectiveness estimates are drawn from the NMA. The baseline characteristics and clinical effectiveness central estimates are as below.

For the impact upon weight, two additional parameters are included. The duration of any *plateauing* of weight after the initial weight effect, coupled with the subsequent duration of the loss of effect and return to the baseline value. These apply to treatments estimated to have an initial weight loss. Once these are worked through, an annual 0.10kg increase is assumed. Those treatments not associated with an initial weight loss experience the weight gain of the treatment with this being maintained for the first year, and thereafter the annual 0.10kg increase.

**Table 9 Dapagliflozin as an add-on to metformin: Baseline characteristics and effects**

| Study | Study 4 | | | NMA | | | |
|---|---|---|---|---|---|---|---|
| | **Baseline** | **Dapa** | **SU** | **Baseline** | **Dapa** | **DPP-4** | **TZD** |
| Baseline characteristics | | | | | | | |
| Age | 58.4 | .. | .. | 55.16 | .. | .. | .. |
| Female | 44.9% | .. | .. | 44.2% | .. | .. | .. |
| Diabetes duration | 6.32 | .. | .. | 5.03 | .. | .. | .. |
| Height (m) | 1.67 | .. | .. | 1.7 | .. | .. | .. |
| Afro-Caribbean | 6.2% | .. | .. | 6.2% | .. | .. | .. |
| Smokers | 17.6% | .. | .. | 55.0% | .. | .. | .. |
| Risk factors | | | | | | | |
| HbA1c | 7.72% | -0.52% | -0.52% | 8.17% | -0.58% | -0.74% | -0.90 % |
| Cholesterol (mg/dL) | 182.54 | 0.071 | -0.028 | 185 | n.a. | n.a. | n.a. |
| HDL (mg/dL) | 45.87 | 0.070 | -0.002 | 45.53 | n.a. | n.a. | n.a. |
| SBP (mmHg) | 133.3 | -4.3 | 0.8 | 133.83 | -4.5 | -1.37 | -2.87 |
| Weight (kg) | 88.02 | -3.22 | 1.44 | 90.14 | -2.79 | -0.51 | 1.72 |
| Weight plateau (yrs) | .. | 2 | 1 | .. | 2 | 2 | 1 |
| Loss of effect (yrs) | .. | 1 | .. | .. | 2 | 3 | .. |
| Adverse Events | | | | | | | |
| Discontinuation | .. | 9.10% | 5.90% | .. | 2.20% | 3.10% | 6.00 % |
| Hypoglycaemia | .. | 3.50% | 40.80% | .. | 7.50% | 4.90% | 2.30 % |
| Severe hypoglycaemia | .. | 0.00% | 0.74% | .. | 0.01% | 0.01% | 0.00 % |
| UTI | .. | 10.80% | 6.40% | .. | 6.70% | 5.20% | n.a. |
| GI | .. | 12.30% | 2.70% | .. | 8.90% | 0.50% | n.a. |

n.a.: not available so assumed to be zero

The rate of severe hypoglycaemia is rounded to the nearest 2 decimal points of the percentage, so may not be zero

The reason for the shorter duration of the loss of weight effect for dapagliflozin in the NMA comparison with sulphonylurea is not immediately clear, as is the longer duration for the DPP-4. It may be linked to the HbA1c effects and HbA1c baseline values and so onto the modelled durations of 1st line therapies as summarised below.

*Treatment effectiveness: dapagliflozin in triple therapy*

The baseline characteristics and clinical effectiveness central estimates are shown in Table 10.

**Table 10 Dapagliflozin in triple therapy: Baseline characteristics and effects**

| **Study** | **Triple therapy review** | | | | |
|---|---|---|---|---|---|
| | **Baseline** | **Dapa** | **DPP-4** | **TZD** | **GLP1** |
| Baseline characteristics | | | | | |
| Age | 58.4 | .. | .. | .. | .. |
| Female | 44.9% | .. | .. | .. | .. |
| Diabetes duration | 6.32 | .. | .. | .. | .. |
| Height (m) | 1.67 | .. | .. | .. | .. |
| Afro-Caribbean | 6.2% | .. | .. | .. | .. |
| Smokers | 17.6% | .. | .. | .. | .. |
| Baseline risk factors | | | | | |
| HbA1c | 7.72% | [redacted] | -0.89% | -0.96% | -1.06% |
| Cholesterol (mg/dL) | 182.54 | [redacted] | n.a. | n.a. | n.a. |
| HDL (mg/dL) | 45.87 | [redacted] | n.a. | n.a. | n.a. |
| SBP (mmHg) | 133.3 | [redacted] | n.a. | n.a. | n.a. |
| Weight (kg) | 88.02 | [redacted] | 1.11 | 3.10 | -1.59 |
| Weight plateau (yrs) | .. | 1 | 1 | 1 | 1 |
| Loss of effect (yrs) | .. | .. | .. | .. | .. |
| Adverse Events | | | | | |
| Discontinuation | .. | [redacted] | 1.70% | 3.70% | 7.30% |
| Hypoglycaemia | .. | [redacted] | 16.40% | 23.00% | 25.00% |
| Severe hypoglycaemia | .. | [redacted] | 0.00% | 0.00% | 0.88% |
| UTI | .. | [redacted] | 0.00% | 0.00% | 0.00% |
| GI | .. | [redacted] | 0.00% | 0.00% | 0.00% |

Despite the anticipate weight losses, in contrast to the modelling of dual therapy these are assumed to plateau for only one year within the triple therapy comparison.

*Treatment effectiveness: dapagliflozin as an add-on to insulin*

For the comparison undertaken the effectiveness estimates are drawn from the NMA. The baseline characteristics and clinical effectiveness central estimates are shown in Table 11.

**Table 11 Dapagliflozin as an add-on to insulin: Baseline characteristics and effects**

| **Study** | **NMA** | | |
|---|---|---|---|
| | **Baseline** | **Dapa** | **DPP-4** |
| Baseline characteristics | | | |
| Age | 57.8 | .. | .. |
| Female | 53.0% | .. | .. |
| Diabetes duration | 12.8 | .. | .. |
| Height (m) | 1.675 | .. | .. |
| Afro-Caribbean | 6.2% | .. | .. |
| Smokers | 17.6% | .. | .. |
| Risk factors | | | |
| HbA1c | 8.90% | -0.82% | -0.69% |
| Cholesterol (mg/dL) | 195.04 | n.a. | n.a. |
| HDL (mg/dL) | 45.07 | n.a. | n.a. |
| SBP (mmHg) | 134.5 | n.a. | n.a. |
| Weight (kg) | 91.4 | -1.63 | 0.19 |
| Weight plateau (yrs) | .. | 2 | 1 |
| Loss of effect (yrs) | .. | 5 | .. |
| Adverse Events | | | |
| Discontinuation | .. | n.a. | n.a. |
| Hypoglycaemia | .. | 140.00% | 144.00% |
| Severe hypoglycaemia | .. | 0.68% | 0.70% |
| UTI | .. | 5.60% | 6.30% |
| GI | .. | 9.20% | 0.30% |

*Extrapolation: therapy switch*

The model contains the facility for patients to switch therapy once their HbA1c rises above a user specified threshold level. This threshold level is not drawn from the NICE guideline but is rather assumed to be the same the baseline HbA1c of the various 1st line therapies as outlined below. When the modelling HbA1c reaches the threshold values the patient being simulated is assumed to move onto the next line of therapy, with the associated clinical effect. Note that threshold value also applies to the switch from insulin plus metformin to intensified insulin, and so differs between the comparisons being undertaken.

**Table 12 Therapy switch HbA1c thresholds and therapy sequences**

| Comparisons | HbA1c Threshold | Next in line | Next in line |
|---|---|---|---|
| **Dual therapy add on to metformin** | | | |
| DAPA+MET with:<br>SU+MET | 7.72% | INS+MET | Intensified INS |
| Dapagliflozin + metformin with:<br>DPP-4+MET<br>TZD+MET | 8.17% | INS+MET | Intensified INS |
| Triple therapy add on to metformin and sulphonylurea | | | |
| DAPA+MET with:<br>DPP-4+MET<br>TZD+MET<br>GLP-1+MET | 7.72% | INS+MET | .. |
| Add on to insulin | | | |
| DAPA+INS with:<br>DPP-4+INS | 8.90% | Intensified INS | .. |

While possible liable to misinterpretation, within what follows the initial treatment in the above sequences will be referred to as the initial or 1st line treatment, the next in line will be referred to as 2nd line and the last will be referred to as 3rd line. As a consequence, 1st, 2nd and 3rd line refer to their place in the pairwise comparison under consideration, and so may change between comparisons. For instance, when considering the comparisons of dual therapies as add-on to metformin treatment with intensified insulin is the 3rd line of therapy, but when considering the comparison therapies as add-on to insulin treatment with intensified insulin is the 2nd line of therapy. The comparisons remain distinct in the presentation which follows.

The implementation of therapy switching for the triple therapy comparisons is unusual. The model only permits three lines of therapy to be considered. The triple therapy combinations are all assumed to be preceded by SU+MET; i.e. they are in effect 2nd line to a common 1st line treatment of dual therapy, hence the HbA1c threshold of 7.72%. Note that the SU+MET treatment will net out between the two arms and so in itself appears to have no impact upon the modelling results. But it does serve to use up one of the three available lines of therapy, and thereby prevents the modelling of patients moving on to intensified insulin within this comparison.

The evidence for the triple therapy comparison for dapagliflozin is drawn from Studies 18 and 19, which had a pooled baseline HbA1c of [redacted], SBP of [redacted] and average weight of [redacted]. The manufacturer justifies the 1st line SU+MET in the triple therapy comparisons in response to ERG clarification question B23. The rationale is apparently that Studies 18 and 19 are sub-populations of the triple therapy patient populations. As a consequence, their baseline characteristics are not representative of the triple therapy patient population hence the application of the Study 4 patient population baseline characteristics. This may be a reasonable justification for the application of the Study 4 patient population baseline characteristics within this modelling, though to the ERG the pooled baseline characteristics of Studies 18 and 19 do not seem particularly out of line with those of the other comparisons. It does not explain the modelling of 1st line SU+MET in the triple therapy comparisons.

It should also be noted that in the triple therapy comparison, dapagliflozin is estimated to have noticeably smaller impact upon HbA1c than the other comparators. This means that it has the shortest delay to the use of insulin: 2.74 years compared to 3.71 years for the DPP-4, 3.64 years for the TZD and 3.51 years for the GLP-1. Using up the 3 lines of therapy within the DCEM model with SU+MET 1st line, triple therapy 2nd line and INS+MET 3rd line prevents the modelling of further progression to intensified INS within this comparison. Whether the Study 4 baseline characteristics should be applied is a moot point, though one which appears likely to have limited impact upon the modelling. But the obvious treatment sequence that should be modelled is triple therapy 1st line, INS+MET 2nd line and intensified INS 3rd line. The ERG can think of no justification for not doing so.

At therapy switch the following clinical effectiveness estimates apply.

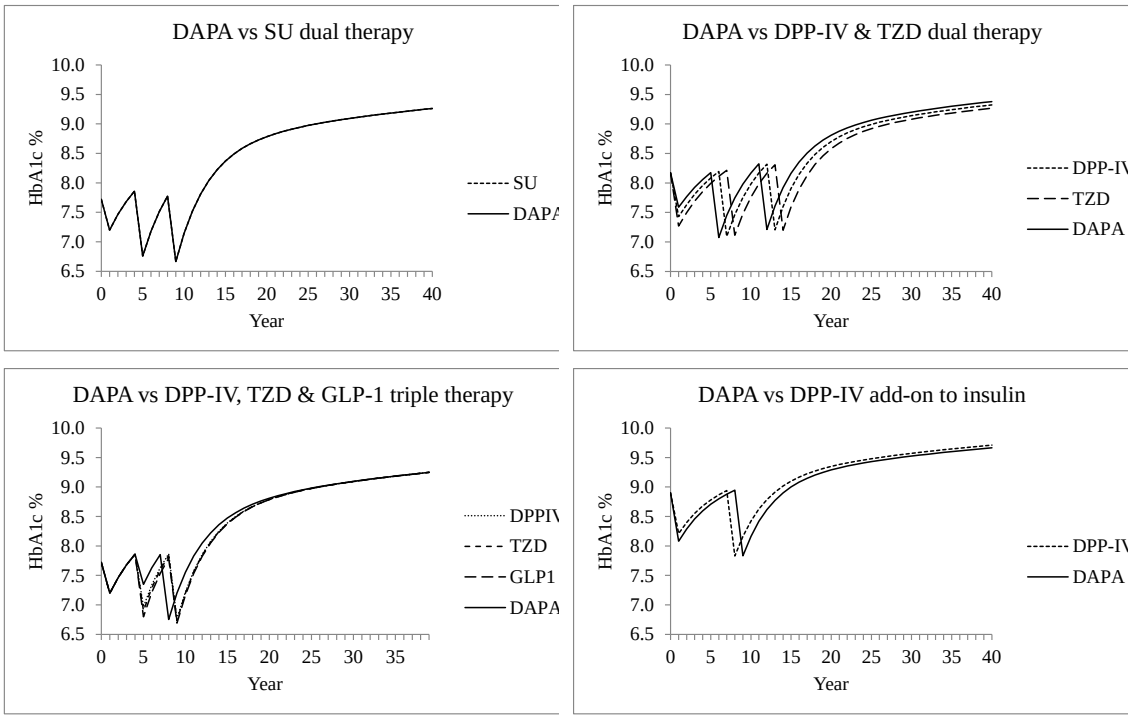
**Table 13 Therapy switch: Insulin plus metformin and intensified insulin effects**

| | Ins. + Met | Intense Ins. |
|---|---|---|
| Baseline risk factors | | |
| HbA1c | -1.10% | -1.11% |
| Cholesterol (mg/dL) | n.a. | n.a. |
| HDL (mg/dL) | n.a. | n.a. |
| SBP (mmHg) | n.a. | n.a. |
| Weight (kg) | +1.08 | +1.90 |
| Adverse Events | | |
| Discontinuation | n.a. | n.a. |
| Hypoglycaemia | 1.08% | 61.60% |
| Severe hypoglycaemia | 3.70% | 2.20% |
| UTI | n.a. | n.a. |
| GI | n.a. | n.a. |

*Extrapolation: HbA1c*

The response to the ERG clarification question B9 in effect states that HbA1c is modelled using equation 11 of the UKPDS 68.

**Figure 9 DCEM model evolutions of HbA1c**

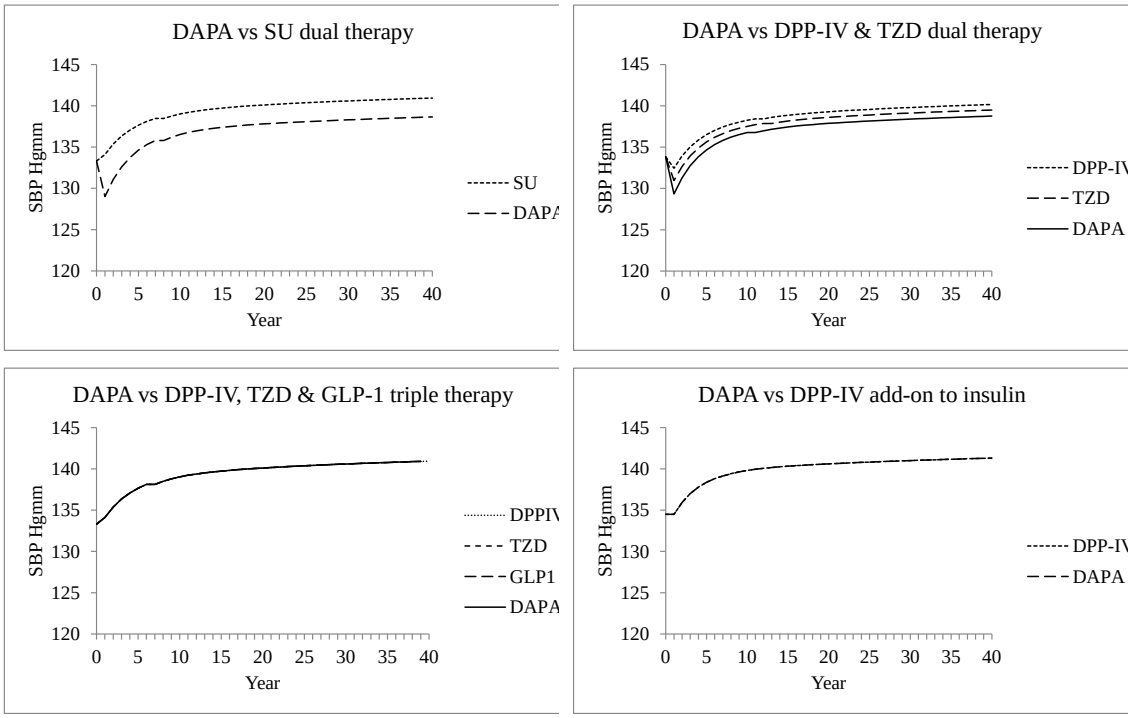


The unusual evolution of HbA1c for the triple therapy comparisons is due to the unnecessary modelling of a prior line of metformin plus sulphonylurea. The above gives a graphical presentation of the extent to which the modelling permits the HbA1c to rise above the NICE guideline of 7.5% without a move to intensification of therapy. This applies with particular force to the comparison of dapagliflozin with the DPP-4 as add-on to insulin.

*Extrapolation: SBP*

The response to the ERG clarification question B9 in effect states that SBP is modelled using equation 12 of the UKPDS 68. The evolutions of SBP only differ between the arms for the dual therapy comparison of dapagliflozin with sulphonylurea and the NMA dual therapy comparison of dapagliflozin with the DPP-4 and the TZD.

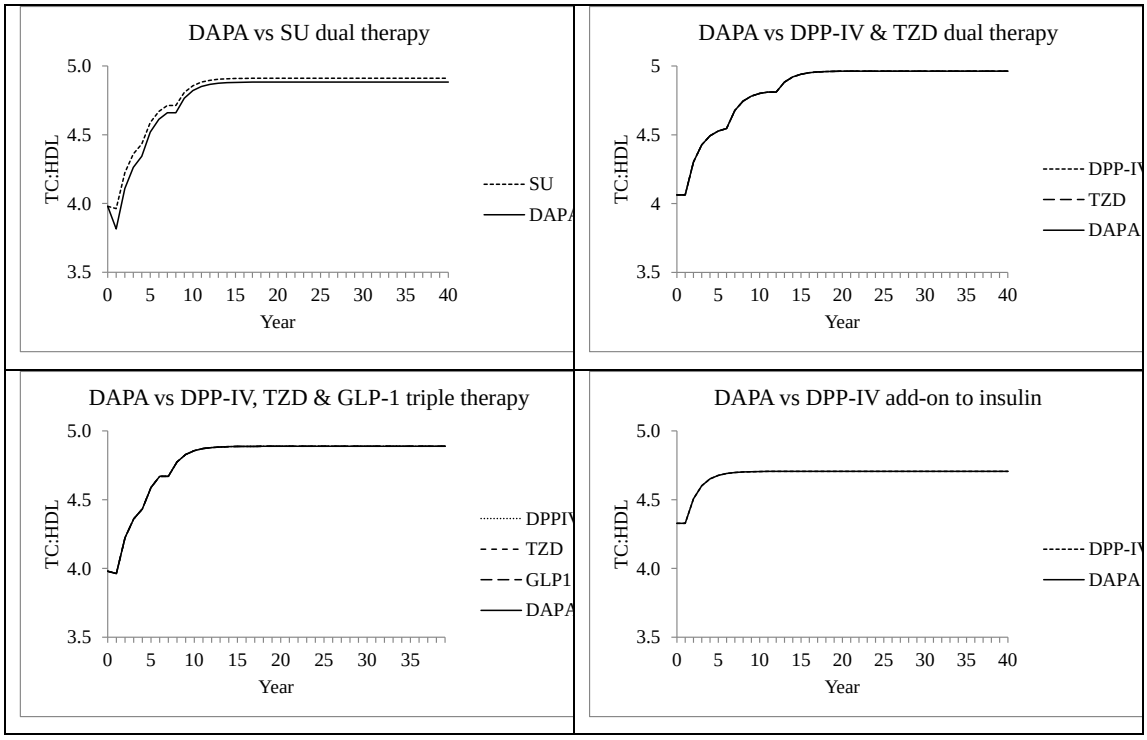
**Figure 10 DCEM model evolutions of SBP**




*Extrapolation: TC:HDL*

The response to the ERG clarification question B9 in effect states that TC:HDL is modelled using equation 13 of the UKPDS 68. The evolutions of TC:HDL only differ between arms for the dual therapy comparison of dapagliflozin with sulphonylurea.

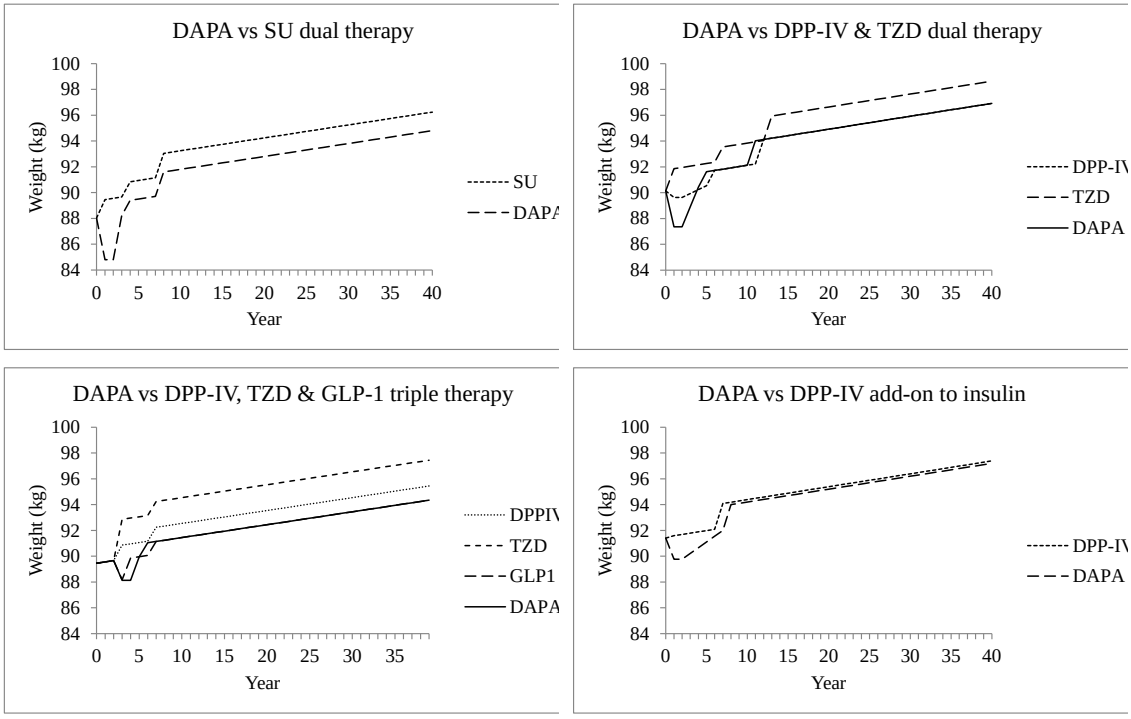
**Figure 11 DCEM model evolutions of TC:HDL**




*Extrapolation: Weight*

The model applies the initial treatment effect. As already noted, in general there is a plateau followed by a loss of effect for those treatments that reduce weight while for those treatments that increase weight this is maintained for one year. Thereafter a 0.10kg annual weight increase drawn from UKPDS 33 is assumed. Given the centrality of weight within the cost-effectiveness, the resulting weight extrapolations are graphed below for the four main groups of comparisons.

**Figure 12 Evolution of patient weights**




*Extrapolation: Effectiveness*

The incidence of events and mortality is mainly drawn from the event equations of UKPDS 68. The manufacturer response to ERG clarification B10 question suggested that all were drawn from the UKPDS 68. But subsequent to initial clarification the manufacturer has further clarified that not all the UKPDS 68 event equations are applied within the model. The UKPDS 68 equation 8 for mortality from events during their year of incidence covers myocardial infarction, CHF, stroke, amputation and renal failure. This is only applied in the DCEM to incident events of CHF, amputation and renal failure. The DCEM drawn the mortality associated with incident events of myocardial infarction and stroke from the UKPDS 66.

The UKPDS 68 also includes equation 9, which estimates the probability of mortality associated with myocardial infarction, CHF, stroke, amputation and renal failure for the years subsequent to the incident year of any of these. There is some confusion as to whether the UKPDS 68 equation 9 is applied within the DCEM. The manufacturer response to Q5 of the ERG additional set of clarification questions states that "*The event fatality [ERG: UKPDS equation 8] and diabetes mortality [ERG: UKPDS equation 9] equations from UKPDS68 are used in the model to calculate non-MI and non-stroke event related mortality and subsequent diabetes related mortality*". But during the cross checking of the DCEM C++ as far as the

DSU can determine the UKPDS equation 9 is not applied within the DCEM. This would be quite a serious omission.

The UKPDS equation 10 for general mortality is also not applied, with the DCEM model instead using a weighted average of UK life tables. This may be less contentious as it is common to both arms.

### *5.2.7 Health related quality of life*

*Baseline HRQoL*

An age dependent baseline utility function was derived from EQ-5D data from the DoH Health Survey for England (2003) of patients with no major complications.[80] This results in a baseline utility estimate for those aged between 55 and 58 of 0.882 to 0.878. The baseline HRQoL remains constant over the period of the modelling, only being affected by weight changes, hypoglycaemia and the complications of diabetes.

*HRQoL impact of the complications of diabetes*

The HRQoL impacts for the complications of diabetes are mainly drawn from the UKPDS 62. Since UKPDS 62 does not estimate a value for end stage renal disease, the value for this is drawn from Currie et al.[81]

**Table 14 HRQoL impacts of the complications of diabetes**

| | UKPDS 62 | Currie et al |
|---|---|---|
| Ischaemic heart disease | -0.090 | .. |
| Myocardial infarction | -0.055 | .. |
| Congestive heart failure | -0.108 | .. |
| Stroke | -0.164 | .. |
| Amputation | -0.280 | .. |
| Blindness in one eye | -0.074 | .. |
| End stage renal disease | .. | -0.263 |

*HRQoL impact of weight gains and losses*

The manufacturer undertook a systematic review of the literature for studies of HRQoL and weight in T2DM. But the values chosen are those of Lane et al.[79] This is a poster presentation of a manufacturer commissioned TTO exercise among 100 Canadian patients with T2DM, though four respondents were excluded from the analysis for having illogical responses.

Lane et al[79] found no statistically significant relationship between patient's actual weight and their HRQoL when grouped into the three bands of BMI 18 to 25, BMI 25 to 30 and BMI greater than or equal to 30. The HRQoL for the BMI 18 to 25 group and the BMI greater than or equal to 30 were broadly similar, the estimates for no weight change both being about 0.90. But the HRQoL for the BMI 25 to 30 group lay above these, the estimate for no weight change being about 0.96. Lane et al[79]did stratify by age, region, current BMI, sex and weight preference[D] but did not stratify by the comorbidities of diabetes despite collecting this data.

Lane et al[79] explored changes in BMI of ±3%, ±5% and ±7% from baseline and found that the impact of weight gains was greater than that of losses.

**Table 15 HRQoL and weight: Lane et al 2012**

| | Weight loss | | Weight gain | |
|---|---|---|---|---|
| **BMI group** | **Coef** | **95% C.I.** | **Coef** | **95% C.I.** |
| 18.0-24.9 | 0.0077 | (-0.0108, 0.0262) | -0.0684 | (-0.0972, -0.0397) |
| 25-0-29.9 | 0.0134 | (0.0007, 0.0261) | -0.0473 | (-0.0661, -0.0285) |
| 30+ | 0.0212 | (0.0122, 0.0301) | -0.0434 | (-0.0557, -0.0311) |
| Pooled | 0.0171 | (0.0103, 0.0238) | -0.0472 | (-0.0569, -0.0375) |

The coefficients of 0.0171 per BMI point of weight loss and -0.0472 per BMI point of weight gain are applied within the DCEM. Note that given the baseline patient weights, the manufacturer could have argued for applying the BMI30+ subgroup coefficients of 0.0212 per BMI point of weight loss and -0.0434 per BMI point of weight gain. But given the DCEM coefficients, a patient is willing to trade a little more than 5% of their remaining survival to avoid a 3% weight increase of around 3kg.

*HRQoL impact of hypoglycaemic events*

The manufacturer reviewed the literature for studies of HRQoL and hypoglycaemia. The values chosen for the model are drawn from the study by Currie et al[81] which applies decrements of 0.0420[E] for a symptomatic event and 0.047 for a severe event. The latter approximately equates to being willing to trade 19 days survival per severe event avoided.

[D] Whether the patient reported wanting to lose weight, wanting to remain the same weight or wanting to gain weight.

[E] This appears to be a typo in the submission which does not carry over to the model.

*HRQoL impact of adverse events*

The manufacturer applies a disutility per UTI of 0.00282, drawn from the study of UTI in ambulatory women by Barry et al.[82] In the apparent absence of other data, the same disutility was applied to GIs.

### *5.2.8 Resources and costs*

*Direct treatment costs*

Unfortunately, there is limited information upon the drug costs applied within the modelling in the written submission and the following values are taken from the electronic copies of the model and so presumably include metformin, sulphonylurea and insulin where appropriate.

**Table 16 DCEM direct drug costs**

| Comparison | DAPA | SU | DPP-4 | TZD | GLP-1 |
|---|---|---|---|---|---|
| Dual therapy | £500.38 | £51.36 | £457.03 | £437.53 | .. |
| Triple therapy | £528.28 | .. | £484.93 | £465.43 | £938.26 |
| Add-on to insulin | £808.92 | .. | £765.57 | .. | .. |

Insulin plus metformin alone as next in line therapy is costed at £217.19 while intensified insulin is costed at £412.06, though this may vary slightly by baseline patient characteristics and weight.

*Costs of diabetic complications*

The UKPDS 65 estimated the annual mean inpatient costs and annual mean non-inpatient costs during the year of incidence and subsequent years of six of the seven events of the UKPDS, with renal failure not being included. These costs are presented in 1999 prices. The model applies the sum of the mean inpatient costs and non-inpatient costs, appropriately increased by 53% to 2011 prices by using the PSSRU Hospital and Community Services Pay and Prices Index (HCSPPI).

An annual dialysis cost of £34,806 is drawn from Baboolal et al.[83] Note that the UKPDS 68 models renal failure. It is unclear to the ERG economic reviewer whether this is synonymous with dialysis. But in the absence of other information, it seems reasonable to apply the costs derived from Baboolal et al.[83]

**Table 17 Annual costs of diabetic complications**

| Event | Fatal | Non-fatal | Maintenance |
|---|---|---|---|
| Ischaemic Heart Disease | | £3,479 | £1,149 |
| Myocardial Infarction | £2,244 | £6,709 | £1,105 |
| Congestive Heart Failure | £3,880 | £3,880 | £1,360 |
| Stroke | £5,658 | £4,103 | £776 |
| Amputation | £13,359 | £13,359 | £771 |
| Blindness | | £1,752 | £742 |
| ESRD | | £34,806 | £34,806 |

*Costs of adverse events*

A cost per severe event of hypoglycaemia of £390 is drawn from Hammer et al,[84] inflated from 2007 prices to 2011 prices by 10.48% using the HCSPPI.

UTIs and GIs are assumed to require one GP consultation at a cost of £36 as drawn from the PSSRU 2011 Unit Costs of Health and Social Care.

*Costs of renal monitoring*

The model contains a £39 cost for renal monitoring during the first cycle for those receiving dapagliflozin. The DSU report confirms that this is applied, though not to those modelled as discontinuing dapagliflozin.

### *5.2.9 Cost effectiveness results*

The following results report the total modelled events, QALYs and costs over the 40 year time horizon of the modelling. Note that by the end of the 40 year time horizon very few patients are modelled as surviving.

*Cost effectiveness: Dapagliflozin as an add-on to metformin: vs SU+MET*

For the comparison with SU+MET the event rates in the DAPA+MET arm and the net impact compared to the SU+MET arm are as below.[F]

[F] Due to apparent reporting errors in the submission for the proportion of patients experiencing fatal CHF events, the macro-vascular and micro-vascular event rates reported here are drawn from the *Results* worksheet cells F6:J28 divided by the number of patients simulated.

**Table 18 Dapagliflozin as an add-on to metformin: vs SU+MET: Events**

| | DAPA | | Net vs SU | |
|---|---|---|---|---|
| | **N-F** | **Fatal** | **N-F** | **Fatal** |
| Macro-vascular | | | | |
| IHD | 12.93% | | -0.29% | |
| MI | 20.19% | 11.57% | -0.27% | -0.49% |
| CHF | 5.77% | 3.91% | -0.11% | -0.05% |
| Stroke | 8.72% | 1.47% | -0.44% | -0.19% |
| Micro-vascular | | | | |
| Blindness | 7.80% | | 0.02% | |
| Nephropathy | 1.38% | 1.46% | -0.10% | -0.15% |
| Amputation | 2.63% | 2.65% | -0.08% | -0.12% |
| Adverse events | | | | |
| UTI | 38.60% | | 14.90% | |
| GI | 44.00% | | 34.00% | |
| Hypo (sympt) | 880% | | -126% | |
| Hypo (severe) | 44.80% | | -2.10% | |
| N-F: Non-Fatal | | | | |

The net impacts on most events are relatively minor. Note that the reporting of severe hypoglycaemia events implies 8.8 events per patient in the dapagliflozin and over the period of the modelling and 1.3 more events per patient in the sulphonylurea arm.

**Table 19 Dapagliflozin as an add-on to metformin: vs SU+MET: QALYs**

| | **DAPA** | **SU** | **net** |
|---|---|---|---|
| Total QALY decrements due to[G]: | | | |
| Weight | -0.639 | -1.024 | 0.385 |
| Hypos | -0.020 | -0.025 | 0.005 |
| Events | -0.027 | -0.027 | 0.000 |
| Total QALYs | 11.745 | 11.278 | 0.467 |

Note that the total QALYs are not directly estimable from the total QALY decrements due to weight, hypos and events. Also note that the sum of the net QALY decrements will not in general equal the overall net QALYs, as the latter will also incorporate survival effects. This presentation arises due to the reporting within the model and the submission.

[G] Taken from the *T2_Events* worksheet sum of rows 66:68 and rows 71:73 of columns AZ:BB

In the above, 82% of the anticipated gain from dapagliflozin arises from the direct HRQoL of weight changes.

**Table 20 Dapagliflozin as an add-on to metformin: vs SU+MET: Costs**

| | DAPA | SU | net |
|---|---|---|---|
| **1st line drugs** | £1,707 | £183 | £1,524 |
| 2nd line drugs | £622 | £626 | -£4 |
| 3rd line drugs | £2,176 | £2,170 | £6 |
| Drug treatment | £4,502 | £2,977 | £1,525 |
| Hypoglycaemia | £115 | £123 | -£8 |
| Other AE | £67 | £14 | £53 |
| Events | | | |
| IHD | £1,168 | £1,194 | -£26 |
| MI | £2,311 | £2,355 | -£43 |
| Stroke | £583 | £616 | -£33 |
| CHF | £582 | £590 | -£8 |
| Blindness | £399 | £396 | £3 |
| Nephropathy | £2,682 | £2,878 | -£196 |
| Amputation | £497 | £516 | -£19 |
| Total | £12,904 | £11,658 | £1,246 |

Note that the sum of the three lines of therapies may not exactly equal the total as these have been drawn directly from the model[H], while the totals are drawn from the written submission. The additional drug costs of £1,525 are partially offset by lower nephropathy costs of £196 to give a net cost of £1,246.

The average time spent on the 1st line therapy before the switch to insulin is 3.59 years for dapagliflozin and 3.71 years for the sulphonylurea.

This results in the following cost effectiveness estimates.

[H] Taken from the *T2_Events* worksheet rows 66:68 and rows 71:73 of column AU

**Table 21 Dapagliflozin as an add-on to metformin: vs SU+MET: Cost effectiveness**

| | DAPA | SU | net |
|---|---|---|---|
| QALYs | 11.740 | 11.280 | 0.467 |
| Costs | £12,904 | £11,658 | £1,246 |
| ICER | | | £2,671 |

Probabilistic modelling as reported in table 90 of the submission estimates exactly the same net QALYs, net costs and ICER as reported above for the deterministic modelling. The probability of dapagliflozin being cost saving is estimated to be 0%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated as effectively 100%.

*Cost effectiveness: Dapagliflozin as an add-on to metformin: vs DPP-4+MET and TZD+MET*

For the comparison with DPP-4+MET and TZD+MET the event rates, costs and QALYs in the DAPA+MET arm and the net impact compared to the DPP-4+MET arm and the TZD+MET arm are as below.

**Table 22 Dapagliflozin and metformin: vs DPP-4+MET and TZD+MET: Events**

| | DAPA | | Net vs DPP-4 | | Net vs TZD | |
|---|---|---|---|---|---|---|
| | N-F | Fatal | N-F | Fatal | N-F | Fatal |
| Macro-vascular | | | | | | |
| IHD | 13.89% | | -0.14% | | -0.06% | |
| MI | 23.85% | 12.86% | -0.17% | -0.19% | -0.13% | 0.04% |
| CHF | 5.58% | 3.56% | -0.07% | 0.03% | -0.04% | 0.04% |
| Stroke | 9.82% | 1.67% | -0.24% | -0.10% | -0.09% | -0.06% |
| Micro-vascular | | | | | | |
| Blindness | 7.95% | | 0.03% | | 0.01% | |
| Nephropathy | 1.63% | 1.70% | -0.08% | -0.07% | -0.06% | -0.04% |
| Amputation | 3.28% | 3.20% | -0.06% | -0.02% | 0.02% | 0.06% |
| Adverse events | | | | | | |
| UTI | 32.20% | | 2.70% | | 38.90% | |
| GI | 42.80% | | 40.00% | | 42.80% | |
| Hypo (sympt) | 846% | | 60% | | 109% | |
| Hypo (severe) | 49.30% | | 2.30% | | 3.80% | |
| N-F: Non-Fatal | | | | | | |

As before for the comparison with the sulphonylurea, the net impacts on most events are relatively minor.

**Table 23 Dapagliflozin and metformin: vs DPP-4+MET and TZD+MET: QALYs**

| | DAPA | DPP-4 | net | TZD | net |
|---|---|---|---|---|---|
| Total QALY decrements due to: | | | | | |
| Weight | -0.595 | -0.599 | 0.005 | -1.038 | 0.443 |
| Hypos | -0.020 | -0.019 | -0.002 | -0.017 | -0.003 |
| Events | -0.029 | -0.028 | -0.001 | -0.027 | -0.002 |
| Total QALYs | 12.623 | 12.603 | 0.020 | 12.204 | 0.420 |

For the comparison with the DPP-4 23% of the anticipated gain arises from the direct HRQoL impacts of weight changes. The percentage for the comparison with the TZD is 106%.

**Table 24 Dapagliflozin and metformin: vs DPP-4+MET and TZD+MET: Costs**

| | DAPA | DPP-4 | net | TZD | net |
|---|---|---|---|---|---|
| **1st line drugs** | £2,250 | £2,392 | -£141 | £2,538 | -£288 |
| 2nd line drugs | £866 | £827 | £39 | £809 | £57 |
| 3rd line drugs | £1,868 | £1,715 | £154 | £1,639 | £229 |
| Drug treatment | £4,984 | £4,932 | £52 | £4,985 | -£1 |
| Hypoglycaemia | £120 | £112 | £8 | £107 | £13 |
| Other AE | £64 | £12 | £52 | £2 | £64 |
| Events | | | | | |
| IHD | £1,287 | £1,297 | -£10 | £1,289 | -£1 |
| MI | £2,771 | £2,783 | -£13 | £2,771 | £0 |
| Stroke | £662 | £680 | -£18 | £669 | -£7 |
| CHF | £566 | £573 | -£7 | £570 | -£4 |
| Blindness | £414 | £411 | £3 | £412 | £3 |
| Nephropathy | £3,263 | £3,469 | -£207 | £3,394 | -£132 |
| Amputation | £602 | £612 | -£9 | £594 | £8 |
| Total | £14,733 | £14,882 | -£149 | £14,793 | -£58 |

Despite the slightly higher drug costs for dapagliflozin compared to the DPP-4 of £52, an overall cost offset of £149 is estimated mainly due to lower nephropathy costs. Overall, drug costs are estimated to be the same for dapagliflozin and the TZD, but again lower nephropathy costs results in a small overall cost saving of £58.

The average time spent on the 1st line therapy before the switch to insulin is 4.82 years for dapagliflozin, 5.70 years for the DPP-4 and 6.42 years for the TZD.

This results in the following cost effectiveness estimates.

**Table 25 Dapagliflozin and metformin: vs DPP-4+MET and TZD+MET: Cost effectiveness**

| | DAPA | DPP-4 | net | TZD | net |
|---|---|---|---|---|---|
| QALYs | 12.620 | 12.600 | 0.020 | 12.200 | 0.420 |
| Costs | £14,733 | £14,882 | -£149 | £14,793 | -£60 |
| ICER | | | Dominant | | Dominant |

Probabilistic modelling as reported in table 92 of the submission estimates exactly the same net QALYs and costs for the comparison with the DPP-4. The probability of dapagliflozin being cost saving compared to the DPP-4 is estimated to be 57%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated to be between 60% and 70%.

Probabilistic modelling as reported in table 94 of the submission estimates almost exactly the same net QALYs, 0.419, and costs, -£58, for the comparison with the TZD. The probability of dapagliflozin being cost saving compared to the TZD is estimated to be 49%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated as effectively 100%.

*Cost effectiveness: Dapagliflozin in triple therapy*

For the triple therapy comparisons the event rates, costs and QALYs in the DAPA+SU+MET arm and the net impact versus the comparators is as below.

**Table 26 Dapagliflozin in triple therapy: Events**

| | DAPA | | Net vs DPP-4 | | Net vs TZD | | Net vs GLP-1 | |
|---|---|---|---|---|---|---|---|---|
| | N-F | Fatal | N-F | Fatal | N-F | Fatal | N-F | Fatal |
| Macro-vascular | | | | | | | | |
| IHD | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| MI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CHF | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Stroke | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Micro-vascular | | | | | | | | |
| Blindness | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| Nephropathy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Amputation | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adverse events | | | | | | | | |
| UTI | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| GI | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| Hypo (sympt) | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| Hypo (severe) | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| N-F: Non-Fatal | | | | | | | | |

As in the dual therapy analyses, the net impacts on events are relatively minor.

**Table 27 Dapagliflozin in triple therapy: QALYs**

| | DAPA | DPP-4 | net | TZD | net | GLP-1 | net |
|---|---|---|---|---|---|---|---|
| Total QALY decrements due to: | | | | | | | |
| Weight | -0.677 | -0.919 | 0.242 | -1.296 | 0.619 | -0.694 | 0.017 |
| Hypos | -0.022 | -0.020 | -0.001 | -0.021 | -0.001 | -0.022 | 0.000 |
| Events | -0.027 | -0.027 | 0.000 | -0.027 | 0.000 | -0.027 | 0.000 |
| Total QALYs | 11.711 | 11.468 | 0.243 | 11.088 | 0.622 | 11.689 | 0.021 |

For the comparison with the DPP-4 and with the TZD virtually 100% of the anticipated gain arises from the direct HRQoL impacts of weight changes. The percentage for the comparison with the GLP-1 is 83%.

**Table 28 Dapagliflozin in triple therapy: Costs**

| | DAPA | DPP-4 | net | TZD | net | GLP-1 | net |
|---|---|---|---|---|---|---|---|
| 1st line drugs | [redacted] | £183 | [redacted] | £183 | [redacted] | £183 | [redacted] |
| **2nd line drugs** | [redacted] | **£1,498** | [redacted] | **£1,412** | [redacted] | **£2,749** | [redacted] |
| 3rd line drugs | [redacted] | £1,619 | [redacted] | £1,663 | [redacted] | £1,636 | [redacted] |
| Drug treatment | [redacted] | £3,298 | [redacted] | £3,255 | [redacted] | £4,563 | [redacted] |
| Hypoglycaemia | [redacted] | £125 | [redacted] | £126 | [redacted] | £137 | [redacted] |
| Other AE | [redacted] | £14 | [redacted] | £15 | [redacted] | £16 | [redacted] |
| Events | | | | | | | |
| IHD | [redacted] | £1,195 | [redacted] | £1,194 | [redacted] | £1,195 | [redacted] |
| MI | [redacted] | £2,349 | [redacted] | £2,355 | [redacted] | £2,352 | [redacted] |
| Stroke | [redacted] | £617 | [redacted] | £617 | [redacted] | £617 | [redacted] |
| CHF | [redacted] | £589 | [redacted] | £590 | [redacted] | £589 | [redacted] |
| Blindness | [redacted] | £395 | [redacted] | £395 | [redacted] | £395 | [redacted] |
| Nephropathy | [redacted] | £2,876 | [redacted] | £2,890 | [redacted] | £2,864 | [redacted] |
| Amputation | [redacted] | £515 | [redacted] | £515 | [redacted] | £516 | [redacted] |
| Total | [redacted] | £11,974 | [redacted] | £11,951 | [redacted] | £13,244 | [redacted] |

In the above, the net costs are driven by the net drug costs. All other costs net effects are that dapagliflozin is more expensive by only [redacted] for the comparison with the DPP-4, [redacted] for the comparison with the TZD and [redacted] for the comparison with the GLP-1.

The average time spent on the 2nd line therapy before the switch to insulin is 2.74 years for dapagliflozin, 3.71 years for the DPP-4, 3.64 years for the TZD and 3.51 years for the GLP-1. The durations for the comparators may initially seem peculiar, given that they vary inversely to their impact upon HbA1c: -0.89%, -0.96% and -1.06% respectively. But these durations are driven more by the differences in discontinuation rates: 2%, 4% and 7% respectively.

This results in the following cost effectiveness estimates.

**Table 29 Dapagliflozin in triple therapy: Cost effectiveness - Deterministic**

| | DAPA | DPP-4 | net | TZD | net | GLP-1 | net |
|---|---|---|---|---|---|---|---|
| QALYs | 11.710 | 11.468 | 0.242 | 11.088 | 0.622 | 11.689 | 0.021 |
| Costs | £11,865 | £11,974 | -£109 | £11,951 | -£86 | £13,244 | -£1,380 |
| ICER | | | Dominant | | Dominant | | Dominant |

Despite having the smallest estimate for its impact upon HbA1c, dapagliflozin is estimated to dominate DPP-4, TZD and GLP-1.

The submission does not report the central estimates of the probabilistic modelling in triple therapy, only presenting the scatterplots and the lower and upper confidence limits of the probabilistic modelling. Running the submitted models over 1,000 iterations results in the following pairwise central cost effectiveness estimates.

**Table 30 Dapagliflozin in triple therapy: Cost effectiveness - Probabilistic**

| | DAPA | DPP-4 | net | TZD | net | GLP-1 | net |
|---|---|---|---|---|---|---|---|
| Survival | 14.670 | 14.669 | 0.001 | 14.658 | 0.012 | 14.676 | -0.006 |
| QALYs | 11.688 | 11.440 | 0.248 | 11.050 | 0.638 | 11.665 | 0.024 |
| Costs | £11,897 | £12,053 | -£156 | £12,039 | -£143 | £13,319 | -£1,422 |
| ICER | | | Dominant | | Dominant | | Dominant |

For the comparison with the DPP-4 the probability of dapagliflozin being cost saving compared to the DPP-4 is estimated to be 57%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated to be between 60% and 70%.

For the comparison with the TZD the probability of dapagliflozin being cost saving compared to the DPP-4 is estimated to be 57%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated to be between 60% and 70%.

For the comparison with the GLP-1 the probability of dapagliflozin being cost saving compared to the DPP-4 is estimated to be 57%. The probability of dapagliflozin being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated to be between 60% and 70%.

*Cost effectiveness: Dapagliflozin as an add-on to insulin*

For the comparison of add-on to insulin the event rates, costs and QALYs in the DAPA+INS arm and the net impact compared to the DPP-4+INS arm are as below.

**Table 31 Dapagliflozin as an add-on to insulin: Events**

| | DAPA | | Net vs DPP-4 | |
|---|---|---|---|---|
| | N-F | Fatal | N-F | Fatal |
| Macro-vascular | | | | |
| IHD | 12.32% | | -0.03% | |
| MI | 16.46% | 8.02% | 0.01% | -0.06% |
| CHF | 4.85% | 2.07% | -0.03% | -0.03% |
| Stroke | 5.77% | 1.05% | -0.03% | 0.00% |
| Micro-vascular | | | | |
| Blindness | 5.82% | | 0.00% | |
| Nephropathy | 1.94% | 1.19% | 0.00% | 0.00% |
| Amputation | 4.34% | 2.43% | -0.07% | -0.03% |
| Adverse events | | | | |
| UTI | 41.90% | | -0.10% | |
| GI | 68.90% | | 66.90% | |
| Hypo (sympt) | 1987% | | 38% | |
| Hypo (severe) | 38.60% | | -1.40% | |
| N-F: Non-Fatal | | | | |

As before, the net impacts on most events are relatively minor.

**Table 32 Dapagliflozin as an add-on to insulin: QALYs**

| | DAPA | DPP-4 | net |
|---|---|---|---|
| Total QALY decrements due to: | | | |
| Weight | -0.475 | -0.592 | 0.117 |
| Hypos | -0.024 | -0.025 | 0.001 |
| Events | -0.024 | -0.023 | -0.002 |
| Total QALYs | 12.329 | 12.210 | 0.119 |

The direct HRQoL effects of weight changes contribute 98% of the anticipated gains from dapagliflozin.

**Table 33 Dapagliflozin as an add-on to insulin: Costs**

| | DAPA | DPP-4 | net |
|---|---|---|---|
| **1st line drugs** | **£5,304** | **£4,558** | **£746** |
| 2nd line drugs | £3,578 | £3,845 | -£267 |
| 3rd line drugs | £0 | £0 | £0 |
| Drug treatment | £8,881 | £8,402 | £479 |
| Hypoglycaemia | £92 | £96 | -£4 |
| Other AE | £74 | £15 | £59 |
| Events | | | |
| IHD | £1,164 | £1,169 | -£5 |
| MI | £1,838 | £1,842 | -£4 |
| Stroke | £394 | £396 | -£1 |
| CHF | £484 | £488 | -£4 |
| Blindness | £314 | £314 | £0 |
| Nephropathy | £3,875 | £3,867 | £7 |
| Amputation | £699 | £709 | -£10 |
| Total | £17,815 | £17,298 | £517 |

The £479 higher drug cost for dapagliflozin sees further additional costs from adverse events, resulting in an overall net cost of £517.

The average time spent on add-on to insulin before the switch to intensified insulin is 7.51 years for dapagliflozin and 6.68 years for the DPP-4.

This results in the following cost effectiveness estimates.

**Table 34 Dapagliflozin as an add-on to insulin: Cost effectiveness**

| | DAPA | DPP-4 | net |
|---|---|---|---|
| QALYs | 12.329 | 12.210 | 0.119 |
| Costs | £17,815 | £17,298 | £517 |
| ICER | | | £4,358 |

Probabilistic modelling as reported in table 96 estimates exactly the same net QALYs, net costs and ICER as reported above for the deterministic modelling. The probability of dapagliflozin being cost saving is estimated to be 50.8%. The probability of dapagliflozin

being cost effective for a willingness to pay of anything more than £10,000 per QALY is estimated as effectively 100%.

### *5.2.10 Sensitivity analyses*

*Sensitivity analyses: dapagliflozin as an add-on to metformin*

A range of univariate sensitivity analyses are presented for the upper and lower confidence limits for the individual treatments' effect upon HbA1c, weight and SBP. The impact of the upper and lower confidence limits for the BMI HRQoL impacts of weight increase and weight decreases are also considered, as is varying the HRQoL impacts of the events by ±10% and the costs of events by ±25%.

When interpreting the following table note that the lower limit (LL) and the upper limit (UL) for te effectiveness estimates are typically referring to negative values: e.g. declines in HbA1c from baseline. As a consequence, the lower limit for these variables represents the biggest impact while the upper limit represents the smallest impact.

**Table 35 Univariate sensitivity analyses: Dapagliflozin as an add-on to metformin**

| | Study 4: DAPA vs SU | | | NMA: DAPA vs DPP-4 | | | NMA : DAPA vs TZD | | |
|---|---|---|---|---|---|---|---|---|---|
| | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** |
| Base case | £1,246 | 0.467 | £2,671 | -£149 | 0.020 | Dom. | -£ 58 | 0.419 | Dom. |
| HbA1c LL DAPA | £1,222 | 0.472 | £2,589 | £231 | 0.133 | £1,739 | £323 | 0.532 | £ 607 |
| HbA1c UL DAPA | £1,014 | 0.457 | £2,218 | -£284 | -0.076 | £3,764 | -£193 | 0.324 | Dom. |
| HbA1c LL Comp. | £1,253 | 0.462 | £2,714 | -£342 | -0.008 | £40,354 | -£178 | 0.368 | Dom. |
| HbA1c UL Comp. | £1,104 | 0.477 | £2,312 | -£177 | 0.051 | Dom. | £21 | 0.490 | £ 43 |
| Weight LL DAPA | £1,246 | 0.471 | £2,647 | -£149 | 0.034 | Dom. | -£58 | 0.433 | Dom. |
| Weight UL DAPA | £1,246 | 0.462 | £2,695 | -£149 | 0.006 | Dom. | -£58 | 0.406 | Dom. |
| Weight LL Comp. | £1,256 | 0.382 | £3,290 | -£149 | 0.010 | Dom. | -£35 | 0.183 | Dom. |
| Weight UL Comp. | £1,236 | 0.552 | £2,241 | -£150 | 0.041 | Dom. | -£81 | 0.656 | Dom. |
| SBP LL DAPA | £1,152 | 0.480 | £2,400 | -£331 | 0.052 | Dom. | -£239 | 0.451 | Dom. |
| SBP UL DAPA | £1,329 | 0.457 | £2,907 | £61 | -0.009 | S.E. | £152 | 0.391 | £ 390 |
| SBP LL Comp. | £1,314 | 0.457 | £2,875 | £54 | -0.016 | S.E. | £242 | 0.374 | £ 647 |
| SBP UL Comp. | £1,164 | 0.479 | £2,433 | -£354 | 0.051 | Dom. | -£414 | 0.466 | Dom. |
| Util. BMI inc. LL | £1,246 | 0.399 | £3,122 | -£149 | 0.026 | Dom. | -£58 | 0.341 | Dom. |
| Util. BMI inc. UL | £1,246 | 0.541 | £2,303 | -£149 | 0.014 | Dom. | -£58 | 0.506 | Dom. |
| Util. BMI dec. LL | £1,246 | 0.453 | £2,753 | -£149 | 0.008 | Dom. | -£58 | 0.405 | Dom. |
| Util. BMI dec. UL | £1,246 | 0.484 | £2,577 | -£149 | 0.035 | Dom. | -£58 | 0.437 | Dom. |
| Util. events +10% | £1,246 | 0.468 | £2,666 | -£149 | 0.020 | Dom. | -£58 | 0.420 | Dom. |
| Util. events -10% | £1,246 | 0.466 | £2,676 | -£149 | 0.019 | Dom. | -£58 | 0.419 | Dom. |
| Cost. events +25% | £1,177 | 0.467 | £2,521 | -£199 | 0.020 | Dom. | -£72 | 0.419 | Dom. |
| Cost. events -25% | £1,316 | 0.467 | £2,820 | -£99 | 0.020 | Dom. | -£43 | 0.419 | Dom. |

Just as Dom. represents points in the NW quadrant where dapagliflozin is both more effective and cost saving and so is dominant, points in the SE quadrant are where dapagliflozin is both less effective and more costly and so is dominated. This applies in the comparison with the DPP-4 to the upper limit for the effect of dapagliflozin upon SBP and to the lower limit

Note that within the comparison with the DPP-4 the upper limit of dapagliflozin and the lower limit of the DPP-4 upon HbA1c result in points in the SW quadrant, and as a consequence the £3,764 per QALY and the £40,354 per QALY cost effectiveness estimates are most easily interpreted as the cost effectiveness of moving from treatment with dapagliflozin to treatment with the DPP-4. If the upper limit of the HbA1c effectiveness estimate for dapagliflozin applies, dapagliflozin is not cost effective.

A range of scenario analyses are presented:

- HbA1c threshold switch values for S01 of 7.5% and for S02 of 8.5% (S03, S04 and S05 values of 8.0%, 9.0% and 9.5% are used for the add-on to insulin analyses)
- BMI related utilities from Baghust et al[85] of 0.0061 per BMI point for S06 and an adjusted value of 0.0038 per BMI point for S07
- Removing the disutility related to hypoglycaemia for S08
- Varying the evolution of weight changes with S09 assuming that any weight loss only endures for two years and S10 assuming that the weights converge after the 2nd therapy switch.
- Rather than applying the 24 week estimates applying the 52 week estimates for S11
- Assuming no discontinuations for S12
- Applying the baseline clinical history of a study of patients who have failed on metformin from the Alvarez Guisasola et al[86] UK patient subset, coupled with baseline prevalences of myocardial infarction, stroke and congestive heart failure of 8.2%, 4.9% and 3.7% from Rubino et al,[13] for S13
- A multivariate scenario of an 8.0% HbA1c threshold, the 0.0061 BMI HRQoL impact, applying the 52 week estimates and the population characteristics as per the previous bullet for S14.

**Table 36 Scenario analyses: Dapagliflozin as an add-on to metformin**

| | Study 4: DAPA vs SU | | | NMA: DAPA vs DPP-4 | | | NMA : DAPA vs TZD | | |
|---|---|---|---|---|---|---|---|---|---|
| | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** |
| Base case | £1,246 | 0.467 | £2,671 | -£149 | 0.020 | Dom. | -£ 58 | 0.419 | Dom. |
| S01 HbA1c 7.5% | £863 | 0.471 | £1,830 | -£ 399 | 0.464 | Dom. | -£554 | 0.982 | Dom. |
| S02 HbA1c 8.5% | £3,282 | 0.583 | £5,633 | £ 27 | 0.049 | £ 558 | £320 | 0.458 | £698 |
| S06 0.0061 BMI | £1,246 | 0.141 | £,8,863 | -£ 149 | 0.024 | Dom. | -£60 | 0.043 | Dom. |
| S07 0.0038 BMI | £1,246 | 0.119 | £10,514 | -£149 | 0.021 | Dom. | -£60 | 0.018 | Dom. |
| S08 No hypo util. | £1,246 | 0.436 | £2,859 | -£149 | 0.031 | Dom. | -£60 | 0.444 | Dom. |
| S09 Weight 2 yr | £1,469 | 0.270 | £5,441 | -£ 149 | 0.017 | Dom. | -£58 | 0.410 | Dom. |
| S10 Weight 2nd | £2,589 | 0.540 | £4,793 | £ 412 | 0.076 | £ 5,455 | £135 | 0.230 | £586 |
| S11 52 week effect | £1,371 | 0.487 | £2,814 | -£ 143 | 0.018 | Dom. | £531 | 0.075 | £7,071 |
| S12 No discs. | £2,309 | 0.497 | £4,646 | £ 148 | 0.054 | £ 2,758 | -£80 | 0.401 | Dom. |
| S13 Med history | £1,246 | 0.141 | £,8,863 | -£ 149 | 0.024 | Dom. | £370 | 0.427 | £865 |
| S14 Multivariate | £1,506 | 0.134 | £11,269 | £295 | 0.056 | £5,307 | £344 | 0.056 | £6,187 |

*Sensitivity analyses: dapagliflozin in triple therapy*

A much reduced set of sensitivity analyses are presented for the triple therapy analyses. These are limited to reducing the BMI utility decrements by 10%, 50% and 100% and to applying the utility decrement of -0.0061 per BMI point as drawn from Baghust et al.[85] This results in the following deterministic net costs and QALYs.

**Table 37 Sensitivity analyses in triple therapy: BMI utility decrements**

| | DAPA vs DPP-4 | | | DAPA vs TZD | | | DAPA vs GLP-1 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** | **ΔCost** | **ΔQALY** | **ICER** |
| Base case | -£109 | 0.242 | Dom. | -£86 | 0.622 | Dom. | -£1,380 | 0.021 | Dom. |
| 10% less | -£109 | 0.218 | Dom. | -£86 | 0.560 | Dom. | -£1,380 | 0.019 | Dom. |
| 50% less | -£109 | 0.121 | Dom. | -£86 | 0.312 | Dom. | -£1,380 | 0.012 | Dom. |
| 100% less | -£109 | 0.000 | £2.35m | -£86 | 0.003 | Dom. | -£1,380 | 0.004 | Dom. |
| Baghust | -£109 | 0.031 | Dom. | -£86 | 0.083 | Dom. | -£1,380 | 0.006 | Dom. |

Note that the one sensitivity analysis for which dapagliflozin is not estimated to dominate the DPP-4 suggests a very small QALY loss from dapagliflozin but with an associated cost saving of £109 and so a point in the SW quadrant. As a consequence, the £2.35mn per QALY is most simply interpreted as the cost effectiveness estimate for moving from treatment with dapagliflozin to treatment with the DPP-4.

No scenario analyses are presented for triple therapy.

*Sensitivity analyses: Dapagliflozin as an add-on to insulin*

The same range of sensitivity analyses are presented for the add-on to insulin comparison as for the add-on to metformin comparison, with the exception of SBP for which no effects are estimated. The same set of scenario analyses are presented for the add-on to insulin comparison as for the add-on to metformin comparison, with the exception of the HbA1c threshold switch values which are for S03 8.0%, for S04 9.0% and for S05 of 9.5% and for the multivariate scenario S14 is 8.5%. There are also no 52 week estimates, so no scenario S11. The details of these are summarised in more detail in the presentation of the sensitivity analyses for add-on to metformin above.

**Table 38 Univariate sensitivity and scenario analyses: Dapagliflozin as an add-on to insulin**

| Sensitivities | NMA: DAPA vs DPP-4 | | |
|---|---|---|---|
| | ΔCost | ΔQALY | ICER |
| Base case | £517 | 0.119 | £ 4,358 |
| HbA1c LL DAPA | £731 | 0.148 | £4,948 |
| HbA1c UL DAPA | £244 | 0.090 | £2,716 |
| HbA1c LL Comp. | £313 | 0.098 | £3,206 |
| HbA1c UL Comp. | £766 | 0.139 | £5,499 |
| Weight LL DAPA | £510 | 0.131 | £3,901 |
| Weight UL DAPA | £524 | 0.106 | £4,936 |
| Weight LL Comp. | £531 | 0.063 | £8,370 |
| Weight UL Comp. | £494 | 0.214 | £2,312 |
| Util. BMI inc. LL | £517 | 0.102 | £5,060 |
| Util. BMI inc. UL | £517 | 0.137 | £3,780 |
| Util. BMI dec. LL | £517 | 0.107 | £4,831 |
| Util. BMI dec. UL | £517 | 0.133 | £3,895 |
| Util. events +10% | £517 | 0.119 | £4,352 |
| Util. events -10% | £517 | 0.118 | £4,365 |
| Cost. events +25% | £527 | 0.119 | £4,439 |
| Cost. events -25% | £507 | 0.119 | £4,277 |

| Scenarios | NMA: DAPA vs DPP-4 | | |
|---|---|---|---|
| | ΔCost | ΔQALY | ICER |
| Base case | £517 | 0.119 | £ 4,358 |
| S03 HbA1c 8.0% | £445 | 0.098 | £4,539 |
| S04 HbA1c 9.0% | £545 | 0.125 | £4,360 |
| S05 HbA1c 9.5% | £631 | 0.237 | £2,667 |
| S06 0.0061 BMI | £517 | 0.024 | £21,171 |
| S07 0.0038 BMI | £517 | 0.016 | £32,409 |
| S08 No hypo util. | £517 | 0.123 | £4,216 |
| S09 Weight 2 yr | £527 | 0.090 | £5,849 |
| S10 Weight 2nd | £625 | 0.091 | £6,864 |
| S12 No discs. | £538 | 0.126 | £4,268 |
| S13 Med history | £336 | 0.114 | £2,947 |
| S14 Multivariate | £533 | 0.026 | £20,579 |

### *5.2.11 Model validation and face validity check*

The manufacturer presents two validation reports within appendix 19 of the submission. The first compares the outputs of the DCEM modelling with the end points of a number of epidemiological studies. The second compares the outputs of the DCEM with a similar modelling exercise using the CORE model. Both appear to have been conducted for the current submission, and neither are published.

Section 1.1 of the validation report comparing the DCEM against epidemiological studies notes that the DCEM has participated in the Mt Hood challenges 3, 4, 5 and 6. The ERG incorrectly interpreted this as implying that some of the modelling results presented in table 1 of the report related to the Mt Hood challenges. In response to the ERG clarification question B18 the manufacturer notes that the validation exercise was independent of the Mt Hood challenges.

The Mt Hood 4 has been published. The manufacturer notes that the DCEM [CARDIFF] model has changed since the Mt Hood 4 challenge. The Mt Hood challenge 4 required models to simulate the outcomes of the CARDS study, which investigated the impacts of lipid lowering therapy to prevent

cardio-vascular disease in patients with T2DM. Modellers were ignorant of the trial outcomes. The following three CARDS trial outcomes were considered: acute coronary events (ACS); stroke; and, any acute coronary vascular event (CVD). Within the models' outputs, fatal and non-fatal myocardial infarctions were taken to parallel acute coronary events. The results for the trial and the modelling of DCEM [CARDIFF], CORE and the UKPDS Outcomes Model are reported below.

**Table 39 Mt Hood challenge 4**

| | ACS | | Stroke | | Acute CVD | |
|---|---|---|---|---|---|---|
| | **Control** | **Therapy** | **Control** | **Therapy** | **Control** | **Therapy** |
| CARDS 4 year cumulative | 5.1 | 3.2 | 3.2 | 1.4 | 4.9 | 9.6 |
| DCEM [CARDIFF] | 6.7 | 4.5 | 2.5 | 2.2 | 9.2 | 6.7 |
| CORE | 6.4 | 4.5 | 2.0 | 1.7 | .. | .. |
| UKPDS Outcomes Model | 5.3 | 3.6 | 2.3 | 2.0 | .. | .. |

Both the DCEM and CORE appeared to somewhat overestimate the rates of ACS, though the UKPDS Outcomes Model manages a much closer alignment with the CARDS study. All three models performance in predicting stroke rates appears relatively poor.

Turning back to the validation report of the manufacturer, the detail can be found in table 1 of the report but this is usefully summarised in Figure 3 [page 9] of the report. Unfortunately, the report was submitted as a pdf and the ERG has not been able to reproduce this figure, but the $R^2$ of the scatterplot is reported as 0.70.

The validation report comparing the outputs of the DCEM and the CORE model mainly appears to concentrate upon varying assumptions around BMI HRQoL impacts and mortality in deterministic and probabilistic modelling. As a consequence, the individual scenarios are of limited interest but the ranges of the discrepancies between the DCEM estimates and CORE estimates can be reported. Total costs are reported for the dapagliflozin arm and the sulphonylurea arm with the discrepancies between the two models being in the range -6% to +6%. But using the data from the manufacturer response to the ERG clarification B19 the discrepancies between the two models' net costs range from 78% to 89% with CORE always estimating a higher net cost. For reasons that are unclear, only the net QALYs are reported. The net QALY discrepancies range between +9% and +62% but excluding the two extremes the remainder fall into the range 27% to 48%. CORE consistently estimates a larger net

QALY. The discrepancies among the ICERs range between 6% and 22%, and again the CORE estimate is always the more favourable for dapagliflozin.

As already noted in the summary of the Mt Hood challenge 4, the DCEM and the CORE models' predictions were reasonably aligned with one another, but their predictions for acute coronary events were somewhat higher than those observed in the CARDS study. It also appears that both the DCEM and the CORE model the progression of the various risk factors in a similar manner. If the concerns of the ERG about the modelling of the progression of the risk factors, as outlined later, are valid they may apply equally to the DCEM and to CORE.

## 5.3 ERG cross check and critique

### *5.3.1 Base case results*

The deterministic and probabilistic base case results cross check with those of the submission.

### *5.3.2 Data Inputs: Correspondence between written submission and sources cited*

*Dapagliflozin as add-on to metformin: clinical effectiveness*

Within the comparison of dapagliflozin with the SU the values from table 58 for their impacts upon the risk factors cross check with the results at 52 weeks of Nauck.[23] Note that Nauck Figure A also outlines a significantly greater reduction in HbA1c reduction for the SU at 6 months, but that this has been reduced at 52 weeks due to loss of effect in the SU arm. The Nauck supplementary data[l] Figure B agrees with the SBP and cholesterol changes of table 58, though note that the cholesterol figures of Table 58 are in mmol/L and not mg/dL. The annual event rates of discontinuations due to AEs, symptomatic hypoglycaemia, severe hypoglycaemia, UTIs and GIs also cross check between Nauck[23] and Table 58.

Within the comparison of dapagliflozin with the DPP-4 and with the TZD the values from table 58 for their impacts upon the risk factors broadly cross check with the results of the manufacturer network meta-analysis when the results given for placebo in the text are combined with the 24 week adjusted central estimates of table 28: HbA1c and table 30: weight. There may be an error in table 58 for SBP, though this may arise due to rounding. The text of section 5.7.6.3 and table 32: SBP suggests that placebo reduces SBP by 0.64mmHg with an additional impact from dapagliflozin of 3.75mmHg: a total effect of 4.39mmHg. Table 58 of the submission gives this as a reduction of 4.50mmHg. The other comparators net effects versus dapagliflozin cross check with those of table 32, but the slightly exaggerated placebo effect is carried over to these comparators as well.

[l] http://care.diabetesjournals.org/content/suppl/2011/07/27/dc11-0606.DC1/DC110606SupplementaryData.pdf

Within a second set of ERG clarification questions, Q1 asked for more detail as to the sources of the discontinuation rates and safety data within table 58 of the submission, noting that table references would be particularly helpful. The manufacturer response outlined that adverse event rate data on "*discontinuation rates, hypoglycaemia, and the incidence of urinary tract infection (UTI) and genital infection (GI) were extracted within the scope of the systematic literature review and network meta-analyses (NMA) of randomized controlled trials presenting efficacy and safety of anti-diabetic agents in adults with T2DM*". The manufacturer summarised that for add-on to metformin discontinuation rates were listed in appendix 9 of the NMA report, while the other safety data was in appendix 8 of the NMA report. Unfortunately no table references were supplied. Due to the extent of the evidence presented, the nature of it and time constraints, the ERG economic reviewer has not been able to cross check the discontinuation and safety data for the dual therapy NMA.

*Dapagliflozin in triple therapy: clinical effectiveness*

The main clinical effectiveness estimates for HbA1c and weight changes for the DPP-4, the TZD and the GLP-1 cross check with the CADTH report. The ERG has not managed to source the corresponding estimates for discontinuations, hypoglycaemia, severe hypoglycaemia, UTIs and GIs.

*Dapagliflozin as add-on to insulin: clinical effectiveness*

The clinical effectiveness estimates for HbA1c and weight changes for dapagliflozin and the DPP-4 cross check with the values reported on page 132 of the submission.

The manufacturer response to the second set of ERG clarification questions outlines that for add-on to insulin 24 week UTI and GI rates were sourced from Study 6 for dapagliflozin and from the Barnett et al.[82] study of saxagliptin for the DPP-4. The sources of the hypoglycaemia rates are not given.

For the add-on to insulin, for dapagliflozin the 104 week results for study 6 are reported in tables 50 and 51 of the submission: 60.7% hypoglycaemia, "major episodes of hypoglycaemia were few", 5.1% UTI, 6.7% GI[J]. Events suggestive of UTI and GI were 13.8% and 14.3% respectively. There is no immediate read across from this to the stated DCEM 24 week rates of 140.0%, 0.7%, 5.6% and 9.20%.

Within Barnett et al[29] the 24 week rates of hypoglycaemia, severe hypoglycaemia and UTI were 18.4% 1.0% and 5.9%, compared to the 144.0%, 0.70% and 6.30% of the DCEM. The ERG was not able to source the DCEM estimate of 0.30% for GI within Barnett et al.[29]

[J] Taken to be the sum of vulvovaginal mycotic infection and genital infection fungal

*2nd line insulin with metformin and 3rd line intensified insulin effectiveness estimates*

The ERG has not been able to source the cited HbA1c changes and weight changes from the manufacturer supplied Monami et al study[87] Also note that this is a meta-analysis for T1DM. Note that the CADTH meta-analysis suggests for insulin added to metformin and sulphonylurea an HbA1c effect of -1.17%, an increase in weight of 1.8kg and which is broadly in line with table 58.

The HbA1c change of -1.11% drawn from Waugh et al[10] cross checks for intensified insulin.

*Extrapolation: weight gain*

The ERG has not been able to locate the annual 0.10kg weight increase within the UKPDS 33. Figure 3 of the UKPDS 33 suggests that the estimate of 0.10kg may be conservative.

*HRQoL*

Most of the HRQoL values cross check with the sources cited, with the possible exception of Currie et al[81] for hypoglycaemia.

Currie et al[81] was a study funded by Sanofi Aventis and Novo Nordisk. It used pooled data from postal questionnaires, these including the hypoglycaemia fear survey (HFS) and the EQ-5D. Hypoglycaemia events were self-reported for the three months prior to completing the survey. 1,500 questionnaires were sent in a first round in 2000 with another 3,200 being sent in 2004. There was a total of 1,305 responses, giving a response rate of 31.4%. While speculation on the part of the ERG, given the response rate there may be a concern that those responding may have tended to be patients whose HRQoL tended to be more affected by hypoglycaemic events. Across all patients the mean EQ-5D index score was 0.660, though it is not clear from the paper whether this applied the UK social tariff. Exploratory analyses that included the complications of diabetes as covariates found that the HFS was the most important predictor of the EQ-5D HRQoL index, with a 1 point change in the HFS causing a 0.008 change in the EQ-5D HRQoL. A relationship was also derived which mapped the frequency of hypoglycaemic events onto the HFS. This yielded a two stage process to estimate the impact of hypoglycaemic events upon the EQ-5D HRQoL.

Currie et al[81]summarise this as "*this can be interpreted as one severe event in the past 3 months causing a loss of utility equating to 4.7% of full potential utility*". This corresponds with the recall period of the survey undertaken and suggests that the values only apply to a 3 month period. Given this, it appears that the overall annualised HRQoL impact; i.e. the QALY decrement, from avoiding one event is only 25% of the value given in Currie et al.[81] This 25% has been calculated in the final column by the ERG.

**Table 40 Currie et al (2004) fear of hypoglycaemia, the HFS and the EQ-5D index**

| | 3 month data | | Annual |
|---|---|---|---|
| Severity of event | HFS per event | EQ-5D per event | QALY decrement |
| Nocturnal | +1.054 | -0.008 | -0.002 |
| Symptomatic | +1.773 | -0.014 | -0.004 |
| Severe | +5.881 | -0.047 | -0.012 |

In the opinion of the ERG the QALY decrements for hypoglycaemia derived from Currie et al[81] and summarised within Table 60 of the submission are fourfold what they should be, on the assumption that all the decrements listed are in effect annual QALY decrements. Also note that table 60 suggests -0.042 rather than -0.014 per symptomatic event, though this does not appear to carry over to the electronic model.

But the manufacturer response to ERG clarification question B28 introduces some further uncertainty in terms of the duration of the decrement that is applied, suggesting that it is applied within the 6 month cycle the hypoglycaemic event occurs in. This raises the possibility that the decrements are only twice what appears to be implied by Currie et al.[81] This appears to be confirmed by the DSU report section 2.5.6.

*Direct drug costs*

Many of the annual costs of the manufacturer cross check with the BNF accessed on line on November 14 2012 to within a few pence, though note that the manufacturer used the NHS drug tariff for England and Wales.

The sulphonylurea, gliclazide, is available as 80mg in packs of 60 for £1.49. Given a 160mg dose per day and resulting annual requirement for 12.17 packs this translates into an annual cost of £18.13 which coupled with the annual metformin cost of £35.59 results in an annual cost of £53.72 compared to the manufacturer costing of £51.36.[K] The differences between the BNF and the tariff for metformin and sulphonylurea broadly cancel out.

For dual therapy, averaging the BNF costs for pioglitazone 15mg, 30mg and 45mg including at the manufacturer (PACT data) average dose of 28.8mg results in an annual cost of £471, which is higher than the £437.53 of the manufacturer. But it appears that the November 2012 tariff suggests costs somewhat lower than both of these figures, and an annual average of as little as £139.16 compared to the £437.53 of the manufacturer drawn from the July 2012 tariff.

[K] From the *Effectiveness_and_AE* worksheet cell E59

Note that sitagliptin in combination with a metformin total daily dose of 1g is available at an annual cost of £450.51 which is slightly cheaper than the £457.03 of the manufacturer costing.

For triple therapy the GLP-1 cost, including metformin and sulphonyurea, exenatide 10µg twice daily has an annual cost of £883.97 while the prolonged release version has an annual cost of £1010.02. Liraglutide 1.2mg is available at an annual cost of £1008.56. All three of these treatments have been approved by NICE. The manufacturer appears to have average the exenatide 10µg and liraglutide 1.2mg costs. This suggests an average of £946.26 compared to the manufacturer average of £938.26. But note that no PACT data supporting this assumption of equal market share was presented, despite similar data being presented for the sulphonylurea, the DPP-4s and the doses of pioglitazone.

The ERG costings of dapagliflozin and the DPP-4 as add-on to insulin are marginally lower by around £3 for each of the comparators, in all probability due to slightly different dosing with NPH being assumed.

Given a patient weight of around 90kg the ERG costing of insulin plus metformin broadly cross checks, though intensified insulin appears to cost out at around £398 compared to the £412 of the manufacturer. But since these treatments are common to all comparators albeit with slight differences in timings these discrepancies are unlikely to have a material impact upon results.

*Costs of diabetic complications*

The costs drawn from UKPDS 65 cross check with those given within the submission. But UKPDS also includes annual inpatient and non-inpatient costs for those not experiencing a complication of £157 and £159 respectively in 1999 prices. These should be applied to those modelled as being free of complications. Within the DCEM model structure an approximation to this would be to subtract these amounts from the costs of the complications to give the additional net cost of the complications.

Baboolal et al[83] report the following costs of dialysis: £21,655 for automated peritoneal dialysis (APD); £15,570 for continuous ambulatory peritoneal dialysis (CAPD); £35,023 for hospital-based haemodialysis (HD); £32,669 satellite unit-based HD; and £20,764 for home-based HD. The paper does not appear to give the year of prices. The study was conducted in 2005 with it being published in 2008 which would suggest uplifts of either 19% or 7%. Rebasing the £34,806 in 2011 prices to 2005 prices results in £29,295, while rebasing in 2008 prices results in £32,410. The 20:80 split between the £15,570 CAPD and the higher £35,023 HD results in an average of £31,132. The £34,806 in 2011 prices applied within the DCEM seems reasonable, provided that there has not been a pronounced shift to home based haemodialysis and the 20:80 split is broadly correct.

*Costs of adverse events*

Hammer et al[84] was a 2007 Novo-Nordisk sponsored questionnaire survey of the costs of severe hypoglycaemic events among a sample of 214 German, 224 Spanish and 201 British patients with diabetes who were using insulin. Respondents were mainly recruited by health care professionals. The details of this are not given in the paper, but there is the possibility that this might tend to bias the sample towards patients who had sought medical attention for a severe hypoglycaemic event. The costs estimates for the UK T2DM patient population subset was based upon 50 events being managed by family members, 25 events requiring external medical assistance but no hospital treatment and 25 events requiring hospital treatment. The total direct costs for these as reported in table 5 of Hammer et al were £33, £231 and £862 respectively. Weighted by the events studied this gives a weighted average of £290, which when uplifted by 10.48% to give 2011 prices suggests an average of £320. This is less than the £390 applied within the DCEM model.

The £36 unit cost per GP consultation cross checks with the 11.7 minute GP consultation in the PSSRU 2011 Unit Costs of Health and Social Care.

### *5.3.3 Data Inputs: Correspondence between written submission and electronic model*

The clinical effectiveness estimates and adverse event estimates of table 58 of the submission as presented above cross check with the electronic model.

The event rates of table 58 are inputted in the *Effectiveness_and_AE* worksheet of the model: e.g. for dapagliflozin as an add-on to metformin for the comparison with the SU the SU rate of symptomatic hypoglycaemia is 40.8% while for the comparison with the DPP-4 the DPP-4 rate is 4.9%. Since the event rates drawn from Nauck[23] are annual rates, this would appear to imply that all the stated event rates in table 58 are annual rates. But it should be noted that many of the values of table 58 relate to the NMA 24 week adjusted values.

The HRQoL input values cross check.

The costs of diabetic complications, severe hypoglycaemic events, UTIs and GIs cross check with the values presented above. There is also a £39 cost for renal monitoring in the first year of dapagliflozin,

### *5.3.4 ERG commentary on model structure, assumptions and data inputs*

*Choice of comparators*

For the add-on to metformin the GLP-1s have not been considered within the cost effectiveness, despite the manufacturer NMA considering them in the clinical effectiveness.

For the add-on to insulin the comparator of no add-on to insulin has not been considered and only the DPP-4 plus insulin is considered as a comparator. The implicit assumption may be that the DPP-4 plus insulin is cost effective within the patient group under consideration. While this does not appear to be in line with the scope, ERG expert opinion suggests it may be the more reasonable comparison for dapagliflozin plus insulin.

There may also be some concerns around the treatment sequences which have been modelled. The assumption that once having started dapagliflozin in, say, triple therapy, patients will be willing to discontinue treatment with dapagliflozin when they go onto insulin therapy should perhaps have been explored as a scenario analysis.

*Cycle length and probability of events*

Section 3.1 of the DSU report confirms that the cycle length is 6 months. But the DSU has not been able to identify any adjustment to the probabilities of events derived from the UKPDS 65 to take this into account[L]. The ERG interpretation of the UKPDS 65 is that it gives estimates of the annual probabilities of events.

*Implementation of UKPDS 68 risk factor evolution equations*

Firstly, note that the UKPDS requires some values to be transformed prior to being used in equations, where $MA_2(.)$ is shorthand for the 2 year moving average:

- Age = Age – 52.59
- BMI = BMI – 27.77
- $MA_2$(HbA1c) = $MA_2$(HbA1c) – 7.09 with this applying to all HbA1c variables
- $MA_2$(SBP ) = ($MA_2$(SBP) – 135.09) / 10 with this applying to all SBP variables
- $MA_2$(TC:HDL) = $MA_2$(TC:HDL) – 5.23 with this applying to all TC:HDL variables

The constants subtracted within the above correspond very closely with the baseline patient characteristics reported in table 1 of the UKPDS 33 for all patients: 53.3 years of age, 27.5 BMI, 7.08 HbA1c, 135 SBP and 5.05 TC:HDL. These might be reasonable estimates to use for the values at diagnosis.

[L] The DSU has asked for clarification on this point, but none has been received to date.

**Table 41 Risk factor evolution equations from UKPDS for HbA1c, SBP and TC: HDL**

| | $MA_2$(HbA1c) | $MA_2$(SBP) | $MA_2$(TC:HDL) |
|---|---|---|---|
| α | -0.024 | 0.030 | -0.021 |
| Ln(Duration of diabetes) | 0.144 | 0.039 | |
| Duration of diabetes if 2nd year after diagnosis | -0.333 | | |
| HbA1c of previous period | 0.759 | | |
| HbA1c at diagnosis | 0.085 | | |
| SBP of previous period | | 0.717 | |
| SBP at diagnosis | | 0.127 | |
| TC:HDL of previous period | | | 0.526 |
| TC:HDL at diagnosis | | | 0.252 |

In the above, the dependent variable $MA_2$(HbA1c) is shorthand for the two year moving average of HbA1c. This is as per the definition of variables in table 1 of the UKPDS 68. But within the DCEM implementation of these equations, the dependent variable is taken to be the level of HbA1c rather than the moving average.

Assuming that the dependent variable in equation 11 is the HbA1c level, transformed by subtracting 7.09, and using $H_t$ as shorthand for HbA1c equation 11 of UKPDS 68 is:

This rearranges to:

which parallels that of table 3 of the manufacturer response to ERG clarification questions.

But as already noted table 1 of UKPDS 68 defines HBA1c as the two year moving average of yearly values. If the dependent variable in equation 11 is a two year moving average, equation 11 would seem to be:

Which rearranges to:

The implementation of equation 11 within the DCEM adopts the levels approach.

But there may be another more serious possible problem, in that table 1 of the UKPDS 68 defines $H_0$ as "*HbA1c (%), after diagnosis of diabetes*". The UKPDS has confirmed that BMI is the BMI at diagnosis of diabetes. UKPDS 68 describes the patient population as patients with newly diagnosed T2DM with the base value risk factor being described as "*the risk factor at the time a decision was made regarding randomisation in the UKPDS (which took place after a 3-month dietary run-in)*". It seems reasonable to also describe these are being the values at or close to diagnosis. In the light of this, unless the average duration of diabetes is particularly short within a trial it may not be sensible to try to approximate these values by anything within the trial. Rather, it may be more sensible to try to estimate the probable values at diagnosis. As a consequence, $H_0$, the HbA1c value at or close to diagnosis, should be the same value for both arms of the modelling.

It appears that within the Visual Basic of the DCEM $H_0$ is taken to be the trial baseline value minus the arm specific treatment effect.[M] As a result, $H_0$ differs between the arms. A higher value of $H_0$ results in a more aggressive evolution of HbA1c.

Similar considerations appear to apply to the DCEM implementation of the evolutions of SBP and TC:HDL.

Note that differentiating the base values by arm results in the risk factor curves not converging over time, as depicted previously in Figures 9-11. If the base values are equalised between the arms, there are the initial treatment effects but the risk factor curves converge over time. This pattern is very similar to that drawn attention to in the ERG report for TA248[N] of exenatide (prolonged release): *Appendix 5: Risk factor evolution: CORE versus the UKPDS Outcomes Model*. The risk factor evolutions in CORE did not converge between the arms, while those of the UKPDS Outcomes Model did. This may have a bearing upon the validation report for the current submission that compares the outputs of the DCEM model with those of CORE.

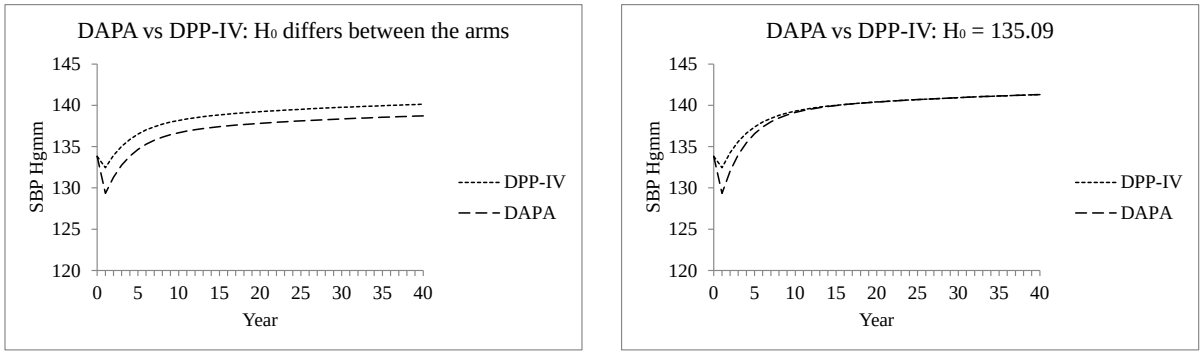
The impact upon the events modelled may not be insignificant, though it should be borne in mind that the differences between the arms are quite small and for all practical purposes appear to mainly yield only cost offsets. Choosing perhaps the most dramatic example, the evolution of the SBP within the dual therapy modelling of dapagliflozin compared to the DPP-4 can be considered. Implementing the risk factor evolution in excel as per the DCEM approach can then be compared with an approach

[M] For instance, slightly abbreviated, within the generateNonLinearProfile() subroutine and the references to the *HbA1c_profile* worksheet the control baseLine = C7, reduction = E7, values(1) = baseLine+reduction and baseValue=values(1). This is subsequently updated for the treatment baseLine = C7, reduction = G7, values(1) = baseLine+reduction and baseValue=values(1).

[N] http://www.nice.org.uk/nicemedia/live/12966/56742/56742.pdf

which sets $H_0$ = 135.09 for both of the arms[O]. Note that this has not been drawn from the DCEM, but has been modelled in excel by the ERG without any therapy switch. One effect of setting $H_0$ = 135.09 for both of the arms is that the value to which the curves converge to at year 40 is slightly higher. But the main effect is that the curves converge quite quickly, compared to a lifetime impact upon SBP adopting the DCEM approach.

**Figure 13 Base value effects on modelled evolutions of SBP**




The implementation of the risk factors' evolution within the DCEM may be incorrect due to:

- Not basing them upon a moving average;
- Not applying the value at diagnosis, but rather a base value based upon the trial data;
- Differentiating the base value by arm;

In the opinion of the ERG the last two bullet points should at least been explored through a scenario analysis that equalises the base values to an approximation of their values at diagnosis.

*Implementation of UKPDS 68 event equations*

The DCEM implements all seven event equations of the UKPDS 68: IHD, myocardial infarction, congestive heart failure, stroke, amputation, blindness in one eye and renal failure. A subset of these is presented below, with the stroke event equation being included in order to illustrate the impact that congestive heart failure has upon the incidence of stroke.

[O] The alternative of setting the dapagliflozin arm $H_0$ equal to the DCEM control arm $H_0$ results in much the same graph, only with the year 40 values converging to 140.13Hgmm rather than 141.31Hgmm. Similarly, setting the control arm $H_0$ equal to the DCEM dapagliflozin arm $H_0$ results in convergence to 138.73Hgmm.

**Table 42 Weibull event parameters from UKPDS 68 for IHD, MI, CHF and stroke**

| | IHD | MI | CHF | Stroke |
|---|---|---|---|---|
| λ | -5.310 | -4.977 | -8.018 | -7.163 |
| ρ | 1.150 | 1.257 | 1.711 | 1.497 |
| Age | 0.031 | 0.055 | 0.093 | 0.085 |
| Sex | -0.471 | -0.826 | | -0.516 |
| Race | | -1.312 | | |
| Smoking | | 0.346 | | 0.355 |
| BMI at diagnosis | | | 0.066 | |
| HbA1c | 0.125 | 0.118 | 0.157 | 0.128 |
| SBP | 0.098 | 0.101 | 0.114 | 0.276 |
| TC:HDL | 1.498 | 1.190 | | 0.113 |
| Ln(TC:HDL) | 1.498 | 1.190 | | |
| Atrial fibrillation | | 0.914 | | 1.428 |
| IHD | | 0.914 | | |
| CHF | | 1.558 | | 1.742 |

Paralleling the risk factor evolution equations, the BMI at diagnosis within the congestive heart failure event equation is taken to be the trial baseline value minus the arm specific treatment effect, and so differs between arms. The DSU has confirmed that the C++ draws these BMI values from the DCEM *Biannual_Risk_Factors Input* worksheet, with the BMI values both differing between the arms and increasing through time. Since the BMI treatment effect of dapagliflozin is typically somewhat better than that of the comparator arm, this may have biased the analysis in favour of dapagliflozin.

Any bias arising from this is not limited to congestive heart failure. Congestive heart failure has a feedback loop, raising the risk of both myocardial infarction and stroke. Any overestimation of the rate of congestive heart failure will also result in the overestimation of myocardial infarction and stroke. Any overestimation of these quantities further results in an overestimation of event fatalities, the myocardial infarction fatalities and the stroke fatalities.

Within the C++ of the DCEM the DSU has also identified an error in the implementation of the Ln(TC:HDL) within the event equations. Given the transformation of TC:HDL=TC:HDL–5.23 this should be implemented in the C++ as Ln(TC:HDL–5.23). But it is implemented as Ln(TC:HDL)–Ln(5.23)=Ln(TC:HDL/5.23).

There may be a further concern about possibly having to treat HbA1c, SBP and TC:HDL as moving averages as per the definitions of table 1 of the UKPDS 68 rather than as levels. But the impact of this upon the event equations is likely to be very small.

The implementation of the UKPDS 68 event equations within the DCEM may be incorrect due to:

- Not applying the BMI at diagnosis, but rather a BMI base value based upon the trial data
- Differentiating the BMI base value by arm
- Applying Ln(TC:HDL/5.23) rather than Ln(TC:HDL–5.23)
- Not treating HbA1c, SBP and TC:HDL as moving averages

Note that the last bullet also applies to the event equations for amputation, blindness in one eye and renal failure.

There may also be some concerns about the application of the event equations within the context of the DCEM having a six monthly cycle.

*Implementation of UKPDS 68 mortality equations and relationship to UKPDS 66 event mortality*

The UKPDS 68 provides a set of interlinked equations that are most naturally seen as being implemented together as a coherent whole. The UKPDS 68 equation 8 and equation 9 are particularly closely linked. Equation 8 calculates the mortality risk in the year that any of the following events occurs: myocardial infarction, congestive heart failure, stroke, amputation and renal failure. Equation 9 calculates the mortality risk in the years subsequent to the incident year of any of these events.

Within the DCEM only equation 8 is implemented, and this is apparently only called for incident events of congestive heart failure, amputation and renal failure. But note that equation 8 is called for each incident event, so will double count in years that more than one event is incident. For incident events of myocardial infarction and stroke the DCEM relies upon equations derived from the UKPDS 66.

The UKPDS 66 estimated risk equations for fatal myocardial infarction and fatal stroke for the UKPDS Risk Engine. Note that the UKPDS Risk Engine is distinct from the UKPDS 68 and the UKPDS Outcomes Model. The UKPDS 66 examined differences in risk factors within two years of diagnosis of diabetes between those with fatal myocardial infarction and non-fatal myocardial infarction, and between those with fatal stroke and non-fatal stroke. Myocardial infarction events and stroke events were defined as fatal if death occurred within six month of the event. The risk factors "*were measured at diagnosis with the following exceptions: For each individual, HbA1c, systolic*

*blood pressure (SBP), lipid ration (total/HDL cholesterol), BMI, urinary albumen, and triglycerides were defined as the mean of values taken 1 and 2 years after diagnosis of diabetes*".

The β of the probability of a myocardial infarction being fatal, conditional upon a myocardial infarction having occurred, within the UKPDS 66 is given as:

Where TTE is the time to event. This results in:

The β of the probability of a myocardial infarction being fatal is implemented within the DCEM as:

Where $HbA1c_t$ appears to be implemented as the HbA1c at time t. This also sets the time to event equal to 1. As such it appears to be the correct UKPDS 66 equation for the probability of a myocardial infarction in the year subsequent to diagnosis being fatal. But it does not seem to be correct for the probability of a myocardial infarction subsequent to the year of diagnosis being fatal.

The β of the probability of a first stroke being fatal, conditional upon a stroke having occurred, within the UKPDS 66 is given as:

The β of the probability of a first stroke being fatal is implemented within the DCEM as:

As for myocardial infarction, this would seem to be the correct UKPDS 66 equation for the probability of a stroke in the year subsequent to diagnosis being fatal.

Whether it is reasonable for these equations from the UKPDS 66 to be rebased from the year of diagnosis to the year of incidence to yield estimates for the incident fatality rates is not clear. But the requirement for these equations from the UKPDS 66 given those of the UKPDS 68 is questionable. The UKPDS 68 equation 8 accounts for myocardial event mortality and stroke mortality in the year of the event. Only calling equation 8 for incident events of congestive heart failure, amputation and renal failure seems peculiar and loses some of the overall coherence of the UKPDS 68.

As previously noted, it also appears that since the DCEM may not apply the UKPDS equation 9 it may not model the mortality risk from previous events of myocardial infarction, congestive heart

failure, stroke, amputation and renal failure. This appears to be confirmed in section 2.5.3 of the DSU report.

*HRQoL impacts of weight changes*

In response to ERG clarification questions B26 the manufacturer provides the study 12 baseline mean EQ-5D HRQoL values using the UK social tariff and their changes from baseline, the mean values at 24 weeks and the mean changes from baseline at 24 weeks. In response to ERG clarification questions B27 the manufacturer also provides the estimated changes in HRQoL from baseline at 24 weeks that result from applying the parameter estimate from Lane et al[79] to the weight changes observed in study 12. These are summarised below.

**Table 43 Observed and estimated changes in HRQoL from study 12**

| **Study 12** | **Placebo+Met** | | **Dapagliflozin+Met** | |
|---|---|---|---|---|
| **n** | **91** | | **89** | |
| | **mean** | **s.e.** | **mean** | **s.e.** |
| EQ-5D UK Social Tariff | | | | |
| Baseline | 0.837 | 0.016 | 0.867 | 0.017 |
| 24 week | 0.884 | 0.016 | 0.885 | 0.019 |
| Change from baseline to 24 weeks | 0.047 | 0.014 | 0.018 | 0.016 |
| Lane TTO | | | | |
| Change from baseline to 24 weeks | 0.000 | 0.003 | 0.016 | 0.002 |

For reasons that are not clear, within the placebo arm it appears that there was a statistically significant increase of 0.047 in the EQ-5D HRQoL between baseline and 24 weeks. While the central estimate for the dapagliflozin arm suggested some improvement, this was not statistically significant. Turning to Lane et al, the situation reverses. Applying the Lane et al HRQoL coefficients to the weight changes observed suggests that there is no change in HRQoL in the placebo arm, but that there is a statistically significant increase in HRQoL in the dapagliflozin arm.

The ERG clarification question B30 asked whether any analysis of changes in weight/BMI and changes in the EQ-5D HRQoL values had been conducted during the trial programme. ERG clarification question B30 also noted that even a simple comparison of the changes in the EQ-5D UK social tariff values and the changes in weight, possibly sub-grouped by those gaining and those losing weight, might be of interest. Unfortunately, table 14 of the manufacturer response appears to only reports the mean values of the EQ-5D rather than changes. As a consequence, the data is of limited interest. But the response to ERG clarification question B30 states that the "*EQ-5D is a generic*

*instrument developed to measure health status and is not an appropriate tool to detect utility changes due to weight change*".

Note that as per the response to the ERG clarification question B25, the manufacturer is also supporting the very large SHIELD study in America with 14,378 respondents with diabetes or at risk of developing diabetes. Rather than relying upon Lane et al,[79] this might have provided a source of HRQoL data in line with the NICE reference case. The ERG has not reviewed any of the seven SHIELD references provided by the manufacturer.

CG87, while not having access to the work of Lane et al,[79] preferred the utility decrement per BMI point of 0.0061 drawn from Bagust et al[85] with a sensitivity analysis that applied an adjusted coefficient of 0.0038 derived from the transformation of data applied by Bagust et al. Baghust et al undertook a multivariate regression using EQ-5D UK social tariff values that controlled for most of the complications of diabetes[85].

*HRQoL impacts of hypoglycaemic events*

As summarised above, the values implemented in the model derived from Currie et al[81] may be too high and not relate to the 3 month data duration of Currie et al.[81]

While CG87 considered Currie et al as a possible source, it applied a QALY decrement of 0.01 per severe hypoglycaemic event avoided per year.[81]

*HRQoL impact of adverse events*

The manufacturer response to the ERG clarification question B24 outlines that the four respondents that were excluded from the Lane study[79] of HRQoL and weight were excluded for the following reasons:

- Participant was willing to trade more to avoid the health state 'diabetes base case' than they were to avoid the health states 'diabetes base case + genital infection'
- Participant was willing to trade more time to avoid the health state 'diabetes base case' than they were to avoid the health states 'diabetes base case + urinary tract infection'
- Participant was willing to trade more time to avoid the health state 'diabetes base case' than they were to avoid the health states 'diabetes base case + urinary tract infection' or the health state 'diabetes base case + genital infection'
- Participant was willing to trade more time to avoid the health state 'diabetes base case' than they were to avoid the health states 'diabetes base case + urinary tract infection' or the health state 'diabetes base case + genital infection'

Whether these patients should have been excluded from the study for the purposes of estimating the impact of weight upon HRQoL is a moot point. But the above clearly suggests that the Lane study was commissioned by the manufacturer to examine both the HRQoL impact of weight changes and the HRQoL impact of UTIs and GIs.[79] None of the UTI and GI data has been presented despite having been commissioned by the manufacturer, and the manufacturer noting an absence of estimates for GIs in their supplementary literature search.

*Costs of the complications of diabetes*

The DSU report section 2.7 highlights that the annual costs in the incident year of an event are not halved to correspond with the 6 monthly cycle of the model and then applied over two cycles, but are applied in full immediately upon the event occurring. The maintenance costs are then applied in the 6 month cycle following the event. This will increase the incident annual costs of events by half of the event's annual maintenance costs.

*Cost per severe hypoglycaemic event*

As noted in the summary of Hammer et al[84] above, this was an industry sponsored study and the sampling of respondents was non-random. There may be grounds for believing that the 50% proportion of patients within the sample who required medical attention for their severe hypoglycaemic event may have been unrepresentatively large. Since respondents were identified by medical practitioners, whether 25% of severe hypoglycaemic events require hospital attention at an average cost of £952 in 2011 prices is equally unclear. CG87 assumed that only 25% of events would require medical attention. Reducing the proportions seeking medical attention from 50% to 25%, with these still being equally balanced between non-hospital and hospital care, reduces the average cost per severe hypoglycaemic event from £320 to £178 in 2011 prices.

CG87 relied upon the study by Leese et al[88] of medically managed severe hypoglycaemic events, which as the manufacturer notes included both patients with T2DM and patients with T1DM. The balance between events among patients with T2DM and patients with T1DM was roughly equal. CG87 calculated an average cost of £335 per event which uprated to 2011 prices using the HCSPPI results in £360 per event. Applying the CG87 25% would result in an average cost per event of only £90.

### 5.4 Exploratory and sensitivity analyses undertaken by the ERG

Due to the concerns about the model implementation as summarised above, both within the visual basic and the C++ of the model, the ERG has not undertaken any further modelling using the DCEM and has not attempted to explore the impacts of addressing the model implementation issues.

The input values have been reasonably well explored within the manufacturer sensitivity analyses, and in particular the HRQoL impact of weight changes. Changes to HRQoL impact and the average cost per severe hypoglycaemic event would result in proportionate changes to the total costs, total QALYs, net costs and net QALYs reported above.

### 5.5 Conclusions of the cost effectiveness section

Describe the completeness of the MS with regard to relevant cost effectiveness studies and data described in any de novo economic evaluations. Does the submission contain an unbiased estimate of the technology's ICERs in relation to relevant populations, interventions comparators and outcomes? Are there any remaining uncertainties about the reliability of the cost effectiveness evidence? Reference should also be made concerning the extent to which the submitted evidence reflects the decision problem defined in the final scope.

# 6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has not undertaken any further exploratory and sensitivity analyses using the DCEM. Many of the concerns of the ERG, and those of the DSU, which cross checked the C++ coding of the model, relate to the model structure, choice of risk equations and implementation of risk equations within the DCEM. Due to the inter-related nature of the Excel, Visual Basic, and C++ the ERG has not attempted to resolve any of these elements of the DCEM.

In terms of the main uncertainties around the input values that should be used the ERG considers the HRQoL impacts of weight changes, the HRQoL impacts of severe hypoglycaemic events and the costs of severe hypoglycaemic events as the inputs that have the most questionable values applied in the manufacturer base case. Within the constraints of the structure of the DCEM the manufacturer has undertaken a wide range of sensitivity analyses, and has explored the impacts of changing the HRQoL associated with weight changes. The other key input, as it gives rise to the majority of the costs offsets, is the annual £34,806 cost of renal failure.

## 7 OVERALL CONCLUSIONS

The manufacturer included in the current submission 5 dapagliflozin RCTs; 50 comparator RCTs; and a series of Phase 2 and Phase 3 clinical trials from the dapagliflozin programme for the assessment of adverse events. The quality of the five main dapagliflozin trials, all sponsored by BMS/AZ, was good.

Dapagliflozin has been assessed as second-line treatment option (when blood glucose is not adequately controlled with metformin) and as third-line treatment option (when blood glucose is still not adequately controlled and insulin is initiated).

Dapagliflozin is a novel first-class agent with an insulin independent mechanism of action (it removes glucose via the kidneys and does not rely on β-cell function). It can be taken once daily at any time of day with or without food.

Our conclusions were that dapagliflozin was clinically effective in reducing HbA1c levels, facilitating weight loss and lowering systolic blood pressure. Furthermore, it did not result in higher number of hypoglycaemic episodes.

With regard to safety, participants receiving dapagliflozin 10 mg had a higher incidence of genital and urinary tract infections (but infections were reported to be mostly mild). Genital and urinary tract infections are consistent with the dapagliflozin mechanism of action which eliminates glucose in the urine and causes a mild loss of fluid.

The incidence of bladder, prostate, and breast cancer was higher after dapagliflozin treatment than would be expected in the normal T2DM population. With the current available data it is unclear whether dapagliflozin is associated with an increased risk of cancer.

*Limitations of the current clinical evidence*

One of the main weaknesses is the lack of head-to-head comparisons between dapagliflozin and the DPP-4 inhibitors, which could be regarded as one of the main comparator interventions. The ERG would expect SUs, which are well-established, inexpensive, and safe drugs, to be used in the T2DM care pathway before dapagliflozin and not as comparator treatments.

For the assessment of diapagliflozin in triple therapy, GLP-1 analogues (e.g. exenatide) were not considered suitable comparators.

All clinical trials were of relative short duration, whereas T2DM is a long-lasting condition. Therefore, we cannot draw conclusions on the long term effects of dapagliflozin (especially on

safety). However, given the non-insulin-dependent mechanism of action, there may be a particular place for the SGLT2 inhibitors in long-standing T2DM where beta-cell capacity has declined to the point where drugs whose effect is in whole or in part through stimulating insulin secretion (SUs, GLP-1 analogues, DPP 4 inhibitors), have lost effectiveness.

*Summary of cost-effectiveness issues*

There is no obvious justification presented for the revision to the cohesive set of risk equations of the UKPDS 68 and the introduction of other risk equations. This may have tended to downplay the role of HbA1c and increase the role of SBP within the DCEM.

The implementation of the UKPDS 68 risk evolution equations and some of the UKPDS 68 event risk equations does not appear to be in line with a literal reading of the UKPDS 68. Initial treatment effects upon some of the risk factors in the first year are maintained for the patient lifetime. This also applies to the differences in patient weights estimated between the treatment sequences that arise from any initial weight gains in the first year.



The ERG views the estimates of the direct HRQoL impacts from weight changes as too large given the results of other published studies and previous NICE assessments. The ERG would also be interested in whether the study these are drawn from collected data on UTIs and GIs, and whether any exploration of the impacts of these upon HRQoL was conducted.

The modelling of a common prior line of dual therapy within the consideration of the triple therapy comparisons is peculiar. The manufacturer justification for this lacks credibility.

Pairwise comparisons are undertaken but this may be a poor guide to the optimal sequence of treatments. It may be most cost effective to try a safe cheap drug first and check whether there is a sufficient response before trying a new more expensive drug, regardless of the estimated cost effectiveness of the direct pairwise comparison. There may also be some concerns around the treatment sequences which have been modelled, and the assumption that once having started dapagliflozin patients will be willing to discontinue treatment with dapagliflozin when going onto insulin therapy.

The HbA1c therapy switching values that are applied within the base case modelling are quite far above the 7.5% of the NICE guideline. The manufacturer does undertake sensitivity analyses around this. The scenario analyses that apply switching values more in line with the NICE guideline, coupled with other changes including some patients having prevalent events at baseline and applying the direct

HRQoL impact of weight changes that was used for the NICE guideline, worsens the cost effectiveness estimates quite noticeably.
The DCEM should cost the inpatient and outpatient costs from the UKPDS 68 for those without complications.

There may be a number of errors in the DCEM C++ coding.

The November drug tariff and the November electronic version of the Monthly Index of Medical Specialities (MIMS) suggest a somewhat lower cost for pioglitazone. The revised annual cost may be as little as £139.16 compared to the £437.53 of the manufacturer drawn from the July 2012 tariff: i.e. only 32% of the drug cost used within the DCEM.

- For the dual therapy comparison of dapagliflozin with pioglitazone this results in the modelled cost of pioglitazone being reduced from £2,538 to £807. This in turn results in the net overall cost shsu141aving of £58 being turned into a net overall cost of £1,670, which results in the estimated cost effectiveness being revised from dapagliflozin being estimate to dominate pioglitazone to an ICER of £3,980 per QALY.
- For the triple therapy comparison of dapagliflozin with pioglitazone this results in the modelled cost of pioglitazone being reduced from £1,412 to £449. This in turn results in the [redacted] being turned into a [redacted], which results in the estimated cost effectiveness being revised from dapagliflozin being estimate to dominate pioglitazone to an ICER of £1,409 per QALY.

### 7.1 Implications for research

There is a need for large, well-designed RCTs comparing directly dapagliflozin with the DPP-4 inhibitors (dual therapy).

Current pathways are based on adding more drugs in an effort to ensure good glycaemic control. There is some evidence from a Danish study that at the point of switching from combination therapy with oral agents, to starting insulin, an intensive lifestyle intervention programme may be as effective as insulin in reducing hyperglycaemia[15] and possibly better in reducing some cardiovascular risk factors.[89] The ERG recommends that this study be repeated in the UK with larger numbers and longer follow-up.

Should dapagloflozin be approved by NICE, it is worth noting that the second in this group, canagliflozin, is not far behind and a head-to-head trial of the two drugs, independent of the manufacturers, would be useful.

We currently lack data on the effect of dapagliflozin on cardiovascular outcomes. A meta-analysis by the manufacturers was reported at a recent conference.[90] It reports a meta-analysis of 14 phase 2 and phase 3 studies, using a composite outcome of cardiovascular events, but has few events (no 78) and therefore very wide confidence intervals around a hazard ratio of 0.6 (95% CI 0.36 – 1.0). Moreover, this study appears to include all doses (i.e. including 2.5, 5 and 10mg).

Long-term safety data are needed especially to assess the risk of cancer.

For future NICE submissions, the scope should emphasise the need for trials that reflect the possible real life use of the medication. It is necessary for all new drugs, once introduced into the market, to show not only benefits in terms of glycaemic control, but also non-detrimental effects with regards to cardiovascular mortality. This might take time to prove and during that period the new drug is unlikely to be placed at an earlier step on the escalation of therapy to well-established therapies in current use. Therefore, drugs need to show that they are at least non-inferior to sulphonylureas (+/- DPP-4 inhibitors).

There is also a need for updating the current diabetes complication models to reflect a real life general population cohort or at least the more modern large trials in T2DM (i.e. ACCORD, ADVANCE and VADT).[91-93]

There is also a requirement for more accurate estimates of quality of life on acute and chronic complications of diabetes.

Future research should also confirm whether the improved glycaemic control, weight reduction, and lower blood pressures translate into cardiovascular benefits.

While there remain concerns with the implementation of the DCEM, the ERG views the approach adopted during this assessment as a good model for assessing the validity of any T2DM models submitted to NICE. But this needs to be read alongside the reported probable imminent acceptance for publication of a revised second UKPDS outcomes model with additional risk factors, which also permit second events. A revised software implementation of the UKPDS Outcomes Model using these risk equations is also apparently under development. Given the preponderance of the current UKPDS 68 in all the T2DM models this may be a game changer in the field of health economics modelling of treatments for T2DM. It may also be an opportunity to reset the clock in terms of NICE acceptance and methods of review of models submitted for T2DM, on the assumption that most will be revised in the light of the revised UKPDS risk equations.

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# 9 APPENDICES

## Appendix 1 Description of the manufacturer's search strategies and critique

The sources searched for this review were appropriate; however there are several factors which suggest that the electronic searches may not have achieved the optimal sensitivity required for a systematic review of clinical effectiveness. Indeed 14 of the published studies were identified, not from the searches, but from reference lists or from contact with the manufacturer, which would suggest this to be the case (Figure 2 in the manufacturer's submission).

The manufacturer states that they searched MEDLINE, MEDLINE in-process, EMBASE and CENTRAL in May 2011 along with 2010 conference proceedings of five major diabetic and cardiology meetings. They also searched the main registers of ongoing trials (Current Controlled Trials, Clinical Trials.gov, ICTRP and Clinical Study Results). Full details of the search strategies used are detailed in Appendix 2 of the submission and are reproducible. In section 5.1 of the submission the manufacturer states that the searches in MEDLINE, EMBASE and CENTRAL were updated in June 2012 for metformin and July 2012 for insulin. However, the manufacturer subsequently included three further studies (see Section 5.2.3), which had been published in full after the search execution date for the systematic review (in 2011 and in 2012). These three studies (representing three of the five main dapagliflozin RCTs considered by the manufacturer) were not included in the systematic review flow diagram (Figure 2 of the submission). Appendix 2 of the submission also gives the search date as May 2011. This would suggest that a systematic update of the searches was not carried out in June and July 2012 and it is unclear what method(s) was used to identify the additional papers. Another later study (Barnett 2012) was also included in the analysis but is not mentioned as an additional study and no details are provided as to how this was identified either. It thus appears that recent studies may have been excluded because systematic literature searching stopped in May 2011.

The search strategies used for MEDLINE, EMBASE and CENTRAL are reproduced in full in Appendix 2 of the submission. The structure of the searches was the same for each: the results sets from searching for four concepts (drugs included in the analyses, drug combinations, diabetes, and trials) were combined using the Boolean operator 'AND'. The trials section was omitted for CENTRAL which was appropriate. Within each facet (or concept), a combination of controlled vocabulary terms and text terms were used.

The inclusion of the 'drug combination' facet in this manner has the potential to be too restrictive since it relied on all relevant studies either being indexed with the drug combination term used or including, in the title or abstract ,one of a small and very specific selection of phrases such as

'combination therapy' or 'multiple drugs'. The sensitivity of this section would have been improved by relaxing the adjacency operator and hence retrieving a wider selection of phrases, and by using additional terms such as 'add-on'. Furthermore, important controlled vocabulary terms were omitted. The MEDLINE search did not include the MeSH term *Drug therapy, combination/* (although it was used in the CENTRAL search) and the EMBASE search omitted the use of the EMTREE floating subheading *cb.fs*. Instead the MEDLINE and EMBASE search used only the term *exp drug combinations/* which in MEDLINE would identify only single preparations containing two or more active agents (and the use of the exploded function would retrieve irrelevant chemotherapy and antiviral drug combinations). The sensitivity of this section of the search would have further benefited from searching for records where either metformin or insulin as well as any of the add–on therapies was mentioned in the title or abstract or was indexed as such. By doing this, retrieval of relevant studies would not have relied on an explicit statement of drug combination in the records or on accurate indexing,

In other sections of the search, incorrect EMTREE and MeSH were used. While the Ovid mapping function would compensate for this in EMBASE (e.g. *thiazolidinediones/* used rather than the correct EMTREE term *2,4 thiazolidinedione derivative/* and *Sulphonylurea Derivative/* rather than the EMTREE *sulfonylurea derivative/)* in MEDLINE and CENTRAL the use of *Sulphonylurea Compounds/* or *Sulphonylurea Derivative/* does not map to the correct MeSH *Sulfonylurea Compounds/* and would not retrieve any records. In general, the selection of text terms used was fit-for-purpose.

The trials section of the search used the sensitivity and precision maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE. The EMBASE strategy was appropriate, however restriction to human studies would have been improved by using the search string *nonhuman/ not human/.*

The search strategies used for the conference abstracts and trials registers were fit-for purpose.