Section A: Clarification on effectiveness data

A1. **Priority Question:** For the metformin add-on comparison, no standard meta-analyses of studies 14 and 12 were conducted, based on differences in the baseline HbA1c rates (p.105). Similarly, for the insulin add-on network meta-analysis (NMA) the TZD RCT was excluded due to the high baseline HbA1c rate (p.132). Please clarify whether these decisions (i.e. exclusion of studies with high baseline HbA1 rates) were pre-specified at protocol level. Would it be possible to have a copy of the protocol?

Response:

In accordance with good practice, a treatment*covariate interaction term was pre-specified in the project protocol (copies of the protocols are attached) based on a previously observed potential for co-variates modifying the effect of anti-diabetic agents. Baseline HbA1c was identified as the most important potentially modifying effect, based on previously reported association baseline HbA1c and HbA1c decline from baseline (DeFronzo et al, 2010), and a potential interaction seen between baseline HbA1c and treatment in Study 14 (described below). Furthermore, HbA1c was used as a stratification variable in a number of the RCTs included in the systematic review (Bergenstal et al, 2010; Taskinen et al, 2011; DeFronzo et al, 2005), which is a standard approach for handling effect modifiers. (Sun et al, 2012).

Due to the small number of RCTs in both the insulin network meta-analysis, and the pairwise meta-analysis of studies 14 and 12, we were unable to adjust for the impact of baseline HbA1c. Therefore, although the protocol specified that we would adjust for this effect, it was infeasible to do so, leading to the post-hoc choice not to pool results from RCTs having considerably different baseline HbA1c values

Add-on to metformin: In the subgroup analysis of Study 14, a potential effect of baseline HbA1c on the treatment effect for the change in HbA1c was identified, with larger relative differences observed among patients with higher baseline HbA1c. In Section 5.7.5, the rationale and methodology for incorporating an adjustment factor in the network meta-analysis (NMA) is described. However, in the pairwise analysis of the RCTs involving dapagliflozin, two RCTs were insufficient for incorporating an empirically estimated adjustment variable. Therefore, the pooled estimates for these two RCTs are not presented in Section 5.6; however, they are presented in Section 5.7.9 for comparison against the results of the NMA and assessment of consistency.

Add-on to insulin: Of the four RCTs that were eligible for meta-analysis, three enrolled a patient population with a mean baseline HbA1 ranging from 8.5% to 8.7%. The fourth RCT, which was the only RCT involving a TZD, included a patient population that had a mean baseline HbA1c of 9.8%. As this was the only RCT involving TZD, the treatment effect could not be disentangled from the effect of baseline HbA1c, and a reliable coefficient could not be estimated from the available evidence. As described in above, there is evidence to suggest that baseline HbA1c can modify the effect of antidiabetic agents (DeFronzo et al 2010; Bailey et al 2010). This evidence was considered as the basis for an informed prior distribution; as was the posterior distribution of the coefficient in the metformin add-on network (Section 5.7.6.1). However, the data were considered insufficient for this purpose.

A2. **Priority Question:** In the metformin add-on NMAs outcomes were analysed at 24 weeks (+/- 6 weeks) and at 52 weeks (+/- 6 weeks). In the insulin add-on NMA outcomes were analysed at 24 weeks (+/- 8 weeks) (p.114).

- Please clarify the rationale for choosing these exact time intervals
- Please clarify why a different time interval was chosen for the two comparisons?
- Please clarify whether these decisions were made at protocol level? If they were, is it possible to provide details of the protocol.

Response:

The decision to run two networks, one at 24 weeks and another at 52 weeks, was a pre-specified decision in the protocol

The rationale for stratifying by time point was based on an analysis of relative effect sizes over time and was pre-specified in the protocol (copies of the project protocols are attached). The mean change in HbA1c from baseline was found to vary over time, in a manner that was inconsistent across comparators (Charbonnel 2005; Matthews 2010). Subjects enrolled into the sulfonylurea arm of RCTs tended to have a large initial drop in HbA1c during up-titration in the first four to six months following treatment initiation. This drop is not usually sustained; the mean HbA1c value usually increases over the following six to eighteen months (Charbonnel 2005; Matthews 2010). This observed trajectory is termed a 'J-curve', and is pronounced among the class of secretagogues, but not in other drug classes. As a result of different trajectories over time among the different drug classes, the relative effect size of HbA1c reduction at 24 weeks is often different from that at 52 weeks.

For the outcome of mean body weight change from baseline, trajectories for mean body weight change from baseline over the first year following randomization were presented by Nauck et al (Nauck 2007). The relative difference in the change from baseline weight was different over the first six month interval, while subjects' weight was changing, compared with the second six month interval, when subjects' body weight became relatively stable. Little information regarding the relative effects over time is available for the outcomes of systolic blood pressure (SBP) or rates of hypoglycaemia; therefore, in the absence of strong evidence to support the assumption of a constant relative effect over time, we maintained the stratified analysis (at six months and one year) for all outcomes.

For the add-on to metformin analyses, a 6 week window around these durations was permitted, meaning that the 24 week network included RCTs of 18 to 30 weeks, and the 52 week network included RCTs of 46 to 58 weeks. This decision was approved by a team of clinicians, after reviewing trajectories of serially collected data to ensure that the relative effect size can be assumed to be the same within this defined window. For add-on to insulin, this interval was lengthened post-hoc to an 8 week window (RCTs of 16-30 weeks) as TZDs are a key comparator of interest in the UK, and the main trials are 16 weeks (for example, Rosenstock 2002). Extending the time window by two weeks on either end was not expected to meaningfully impact heterogeneity and no studies of longer than 26 weeks were ultimately available for inclusion in the network (actual range 16 to 26 weeks). The change from 6 weeks to 8 weeks was recorded as a formal protocol amendment. There were several amendments noted in this document in order to better reflect UK clinical practice, clarification on studies that up-titrate insulin (discussed in A3) the inclusion of saxagliptin (licence since approval), and removal of metformin as a comparator of interest.

A3. **Priority Question:** In the insulin add-on NMA, RCTs that allowed titration of insulin were excluded (p.115). However, without titration, insulin is not being used to best effect and so this would reduce the applicability of the results to routine care. Please explain the underlying rationale behind this decision.

Response:

The dapagliflozin studies, similar to studies undertaken for other approved treatments (e.g. Rosenstock, 2002 for TZD), were designed to gauge the actual effects of treatment. Titration was permitted provided certain criteria were met and a greater increase in dose was observed in the comparator arm compared to the dapagliflozin arms in the trials described in the submission. In clinical practice, it would be expected to titrate insulin downwards in order to minimize the risk of hypoglycaemia, and the CHMP guidelines state that the insulin dose should be maintained unchanged.

The change in the background insulin dose over the course of the RCT included in the MTC and the approach used by investigators for insulin dose titration was also technically evaluated to assess the impact of differential dose titration that occurred across trial arms in the MTC analyses that preceded the protocol amendments noted in Question A2. The learnings from this were applied to the updated analyses undertaken after the protocol amendment and presented in the NICE submission.

Prior to the protocol amendment for the UK setting, an NMA was performed using all eligible studies involving agents added on to insulin. In this analysis, RCTs that involved insulin up-titration were initially pooled with RCTs that were designed to maintain a stable dose.

Variability in the design of the RCTs across the network with respect to insulin titration was considered to compromise the consistency assumption of the NMA. Insulin up-titration was considered to modify the effect of the active treatments. Therefore, four methods were considered as a post-hoc. analysis on the outcomes of HbA1c and weight, to reduce the bias introduced by the difference in insulin across the included RCTs. These were

1) A qualitative assessment of the anticipated direction of each included RCT

2) Adding a treatment*covariate interaction term, using the binary covariate of “stable dose”: “Stable dose” refers to the trial design set out by the study investigators. In some RCTs, investigators required that subject maintain the same insulin dose throughout the study, whereas other investigators did not restrict the insulin dose in this way.

3) Adding a treatment*covariate interaction term, using the continuous covariate of the difference between arms in insulin dose (IU/day) change from randomization to study end:

    a) If the change in insulin dose for the active treatment arm over the study period was -1.2 IU/day, and

    b) The change in the placebo arm over the study period was +5.1 IU/day,

c) Then the study-level covariate representing the difference between arms in the insulin dose change would then be 6.3 IU/day

4) Restricting the network to only RCTs with an approach to insulin dose titration that was considered similar to that of the dapagliflozin RCT. With no closed loops, the relative effect sizes for each comparator compared with placebo were minimally influenced by the inclusion or exclusion of other comparators versus placebo when fitting the model.

After critical evaluation, the fourth approach was considered to best represent clinical reality and produced the least biased estimates of relative effect size. Outcomes data for the excluded studies are provided in Tables 125, 127, 129, and 131 for HbA1c, weight, SBP, and hypoglycaemia.

A4. **Priority Question:** Please clarify why a mixture of adjusted (24 weeks) and unadjusted results (52 weeks) have been presented for the change from baseline in HbA1c (%) for all drug classes in Tables 27 and 28 (p.127).

Response:

As indicated in Table 25 in the submission, for the add-on to metformin NMA the adjusted random effects model offered a better fit model at 24 weeks based on a priori criteria for model selection that are described on page 124 of the submission. At 52 weeks the unadjusted random effects model offered a better fit. Tables 27 and 28 provide a summary of the results from the best fitting models and so present a mixture of adjusted and unadjusted analyses. Tables 38-41 provide results for all models.

A5. **Priority Question:** Please explain why no formal meta-analyses of adverse events (other than simple pooling) were conducted (pp.155-182). Information on the source of data for each set of adverse event results presented in the submission is not very detailed. For the UTI and cancer adverse events please clarify which studies are included in each set of results presented on pages 157-161.

Response:

The rationale for not presenting pooled estimates for the dapagliflozin RCTs is provided in Section 5.6.1. Furthermore as the meta-analysis of safety data remains methodologically contentious, such analyses were not prespecified in the project protocol (with the exception of hypoglycaemia), this was a result of our understanding of the inherent reporting bias and severe heterogeneity. Four key methodological concerns were regarding using safety data within a MTC were identified; the non-reporting of safety outcomes, particularly for rare events; method of collection as spontaneously reported outcomes may be more biased than routinely collected pre-defined outcomes, particularly in open label studies; heterogeneity of safety outcome definition, which tends to be more pronounced in safety outcomes than in efficacy outcomes; and finally some adverse events may be too rare or too long-term to be captured within the RCT follow-up period. Despite some degree of heterogeneity in the definition of hypoglycaemia across RCTs, hypoglycaemia is a relatively common and well-established adverse event of anti-diabetic agents and was therefore

frequently included as a pre-defined safety outcome of RCTs, rather than a spontaneously reported event. For this reason, hypoglycaemia was meta-analysed. For other safety outcomes, the choice of whether or not to meta-analyse safety data was subjective and the protocol-specified approach was to summarise the reported outcomes in a tabular format.

For dapagliflozin, the primary assessment of safety in subjects with T2DM was based on pooled analysis of three Phase 2b and twelve Phase 3, double-blind, placebo/active-controlled, randomized clinical studies . Dapagliflozin was administered as:

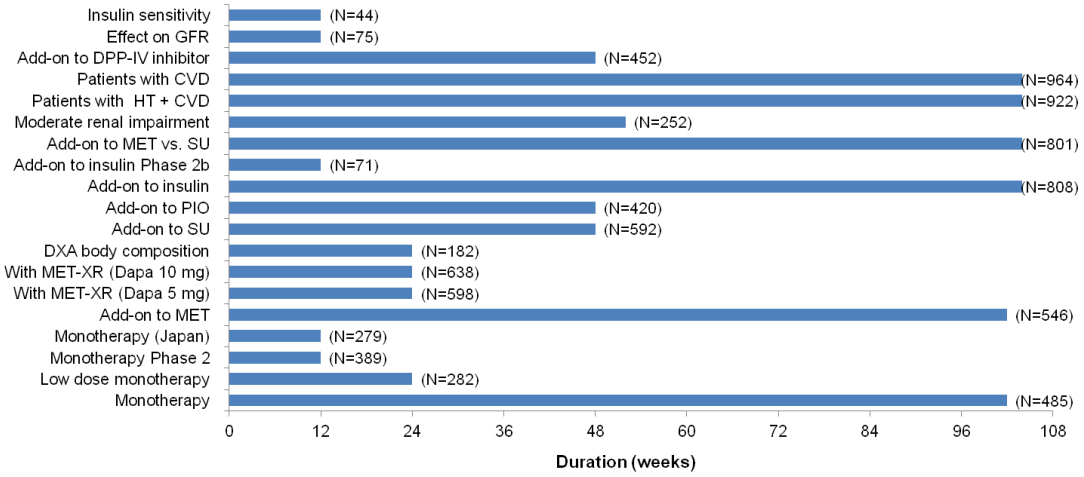
- Monotherapy in 4 studies.
- Add-on combination therapy with a wide variety of other antidiabetic medication in 6 studies.
- Initial combination therapy with metformin in 2 studies.
- A direct comparison with SU in one study.

Most of these studies had 3 study doses (2.5, 5 and 10mg). For the more commonly reported or the actively monitored adverse events such as UTI, Genital tract infections, renal safety, volume depletion, only results for the 10mg dose (1,193 patients on dapagliflozin and 1,393 on placebo) are shown as this is the recommended daily dose in clinical practice.

For the more rare events such as neoplasms, the data set was expanded to pool the more recent trial data as it emerged and includes 19 Phase2b/3 trials(including long-term data up to 2 years of follow-up)

Figure 1 below illustrates the source of this data.

Figure 1. Clinical trials in the dapagliflozin clinical program



Monotherapy=NCT00528372
Low dose monotherapy = NCT00736879
Monotherapy Phase 2=NCT00263276
Monotherapy (Japan)=NCT00972244
Add-on to MET=NCT00528879
With MET-XR (DAPA 5 mg)=NCT00643851
With MET-XR (DAPA 10 mg)=NCT00859898
DXA body composition=NCT00855166
Add-on to SU=NCT00680745
Add-on to PIO=NCT00683878
Add-on to insulin=NCT00673231
Add-on to insulin Phase 2b=NCT00357370
Add-on to MET vs SU=NCT00660907
Moderate renal impairment=NCT00663260
Patients with HT + CVD=NCT01031680
Patients with CVD=NCT01042977
Add-on to DPP-IV inhibitor=NCT00984867
Effect on GFR=NCT00976495
Insulin sensitivity=NCT00831779

Combinations with MET-XR were active (MET) controlled studies; For the purposes of the placebo-controlled pool, only 2 groups were included and the MET group was designated as PBO + MET. NCT00673231 and NCT00855166 studies (total study duration=2 years), and NCT00660907 (total study duration=4 years). N=number of randomized patients. CVD=cardiovascular disease, DPP-4=depeptidyl peptidase, DXA=dual X-ray absorptiometry, GFR=glomerular filtration rate, HT=hypertension, INS=insulin, MET=metformin, PBO=placebo, PIO=pioglitazone, SU=sulphonylurea, XR=extended release.

For pages 157-161, UTI and GI tables are based on the short-term (up to 24 weeks) placebo controlled pool, the same is true for renal events and volume depletion, neoplasm and specific cancers are based on the all Phase 2b/3 pool.

A6. **Priority Question:** Please clarify whether any further evidence about the risk of cancer in patients treated with dapagliflozin, has become available since the FDA review in July 2011?

Response:

The data presented in the submission from the July 2011 cut correspond with the most recent data submitted to the EU regulatory authorities. The overall rates of all cancers in both comparator/placebo and dapagliflozin arms were balanced. From the mechanism of action and the pre-clinical studies of dapagliflozin, there are no obvious pathways which would cause an increase in cancer risk. In addition there were too few events of bladder or breast cancer to establish causality.

In rendering its opinion, the CHMP reviewed the evidence and concluded that during the dapagliflozin clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3 of NICE submission). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non clinical studies as well as the short latency between first

drug exposure and tumour diagnosis, a causal relationship is considered unlikely (SmPC dapagliflozin).

A7. **Priority Question:** In the dapagliflozin RCTs as well as in the RCTs included in the NMA, mean change in HbA1c (%) from baseline was analysed. However, an important issue related to diabetes trials is the definition of the best target level. The current clinical consensus is moving towards 7% in type 2 diabetes (rather than the 6.5% in NICE CG 87). Please clarify whether the proportion of patients with glycaemic control according to this target level was considered as an outcome for inclusion in the RCTs and the rationale for analysing mean change in HbA1c (%)?

Response:

Candidate endpoints identified in the systematic review protocol were prioritised, based on i) clinical relevance of outcome; ii) availability of data (availability of studies reporting that outcome for each pair of comparators); iii) qualitative heterogeneity of outcome definition; iv) relevance of the outcome with respect to the cost-effectiveness assessment of dapagliflozin; v) requirements for health technology assessment submissions. HbA1c; body weight; systolic blood pressure; and hypoglycaemia.

The proportion of patients achieving a target threshold is undoubtedly an important endpoint. The proportion of patients reaching target HbA1c of 7% in patients initially at a baseline ≥7% was a prespecified secondary endpoint of most of the trials. For example, in the head to head study of dapagliflozin vs glipizide (study 04), a similar proportion of patients reached 7% (27.4% vs 32% difference (NS))

The rationale for using change from baseline was to assess the efficacy of the drug, in a manner consistent with EMA guidance (EMA, 2012). If a treat to target approach was used, a comparison to a drug requiring titration would result in underdosing of the SU arm in good responders. This would favour the dapagliflozin arm which is given as a single dose. Baseline HbA1c also impacts the ability to reach a target when a treat to target approach is taken. Our historical understanding of what an appropriate target is has changed over time as has practice patterns and guidelines. A trial initiated today would have a different target than one set up 10 years ago.

If a primary endpoint of reaching a target of 7% was chosen, it would be easier to recruit patients with low initial HbA1c baselines. However, the trial programme was set up to include a wide range of patients and therefore included patients with baseline HbA1c ranging from 6.5-7% to 10-11%.

It should also be noted that NICE as well as the newer EASD/ADA guidelines recommend tailoring treatment targets to the patient. E.g. a low target of 6.5% may not be appropriate in a 75 year old patient with CV co-morbidities while a 45 year old, less complicated patient may benefit from the reduced glycaemic burden, resulting in better rates of microvascular complications. Finally, HbA1c has been recognised by NICE in previous submissions and is well-established as a gold standard diagnostic measurement for chronic glycaemic control. It is also an accepted surrogate marker for the risk of microvascular diabetic complications (UKPDS 38, 1998).

A8. **Priority Question:** In the triple therapy addendum, treatment line duration for the MET+SU+dapagliflozin strategy was compared with the MET+SU+GLP-1 strategy (p.20). For the MET+SU+GLP-1 strategy, a duration of 14.7 years is reported as third line therapy. Based on previous appraisals and clinical guideline 87, the ERG would assume 5 years effectiveness of GLP-1. Please clarify the rationale for assuming a treatment duration of 14.7 years for GLP-1.

Response:

The treatment sequence that was submitted is as follows (Table 1):

Table 1: Treatment sequence for the triple therapy analysis

	Treatment arm		**Control arm**
First line	MET+SU		MET+SU
Second line	MET+SU+Dapagliflozin	**vs**	MET+SU+GLP1
Third line	MET+INS		MET+INS
HbA1c switching threshold	Same as HbA1c baseline (i.e. 7.72%) for both possible switches; from first line to second line and from second line to third line		

The duration per treatment line and per treatment strategy (dapagliflozin arm or control arm), was an output of running the model (Table 2a and b).

Table 2a: Treatment duration for the triple therapy analysis (dapagliflozin arm)

Treatment lines for dapagliflozin arm		**Treatment duration (years)**
1st line	MET+SU	3.71
2nd line	MET+SU+Dapagliflozin	2.74
3rd line	MET+INS	15.03
Total		21.48

Table 2b: Treatment duration for the triple therapy analysis (Comparator arm)

Treatment lines for control arm		**Treatment duration (years)**

1st line	MET+SU	3.71
2nd line	**MET+SU+GLP1**	**3.51**
3rd line	MET+INS	14.27
Total		21.50

As presented in the above tables, we would like to clarify that the treatment strategy "MET+SU+GLP1" is applied as second line treatment, and not as third line as stated in the question A8 above. The treatment duration with "MET+SU+GLP1" (as reported in the submission triple therapy addendum), corresponds to 3.51 years and not 14.7 years as stated in question A8 above.

The duration of each treatment line is determined by the HbA1c level of the patient over time. A patient receives a treatment as long as his HbA1c level is below a certain HbA1c switching threshold. The HbA1c switching threshold (the level of HbA1c above which the patient switches treatment) was set to 7.72% for both the switch from first to second line and from second to third line. First line treatment is assumed to be MET + SU. Once a patient exceeds an HbA1c level above 7.72%, the patient switches (to the second treatment line which is "MET+SU+GLP1" (control arm) or "MET+SU+dapagliflozin" (dapagliflozin arm). Under the same rationale the patient remains on the second treatment line or switches to the third line treatment of MET +INS when HbA1c exceeds 7.72%.

Taking into consideration these clarifications upon the treatment sequences and the treatment lines' duration, we consider that the reported durations are valid assumptions and in line with the ERG's expectation for duration of treatment with GLP-1.

A9. Please clarify the reason why certain results are in bold text (some based on the NMA and others not) within the overall summary (pp.152-153).

Response:

As described on pages 152-153 of the submission, estimates in bold represent the best estimate based on an assessment of a priori model choice, model fit, and assessment of the posterior distribution of the between studies variance. For clarity, the results of all analyses (fixed effects, random effects, adjusted and unadjusted analyses) are also reported in Tables 38-41.

A10. In the triple therapy addendum, please clarify why results from the Canadian (CADTH) review from August 2010 have been presented without any attempt to update this with more recent studies.

Response:

The add on therapy combinations for which BMS/AZ are seeking an approval at launch are; add on to metformin, add on to SU and add on to insulin. The efficacy

and safety of dapagliflozin after metformin and SU are still being evaluated in a prospective, randomised controlled trial (RCT) which is expected to complete in late 2013 [NCT01392677]. At the time of writing, these data are not yet available.

Following discussion with NICE (21 June, 2012), BMS/AZ provided an addendum to allow consideration of the use of dapagliflozin in the triple therapy setting. Originally BMS/AZ did not intend to provide such analyses (and as such did not prepare a de novo systematic review) because, as noted above and in our response to the scope, the relevant RCT has not yet reported and consequently approval for the triple therapy indication was not being sought at the time being.

The CADTH was selected as a recently published high quality systematic review in the triple therapy population which could be incorporated alongside the data from Studies 18 & 19 in high-risk CV patients into the *exploratory* triple therapy analysis submitted specifically to meet NICE's request for this analysis. Clearly new data may have been published since. Two studies are known (Owens 2011 and Moses 2012) and both report similar efficacy and safety findings to those of the single sitagliptin study included in the systematic review so are unlikely to influence the findings of the MTC. There may, of course, be other studies that would be identified by a systematic search but the impact of additional publications must be considered alongside the likely greater impact of other caveats outlined on page 4 of the Addendum.

Section B: Clarification on cost-effectiveness data

General

B1. There appears to be no outline of the role of elements such as the target values in the model manual supplied with the submission. Please clarify this point, and also whether there is a more comprehensive manual available?

Response:

A manual has been provided in Appendix A at end of this document.

B2. Please clarify the colour coding of cells within the various worksheets. As these do not always appear consistent between the worksheets and the codings key.

Response:

In general, the following colour coding is used (as specified on the "demographics" worksheet):

Key to colour coding	
	These cells may be modified by the user
	These cells should be modified by experienced users only
	These cells should not be changed
	Note: References for input parameters located in end worksheet

There are other colours used in the model to signify the following:

- The various colours used in the worksheet “Results” are solely to make the output clearer and differentiate between control, treatment and difference between control and treatment.

- In the sheet “Effectiveness and AE” the cells in yellow represent those inputs that should be adjusted manually before a scenario relating to the parameter concerned is performed. For example, the “years to loss of weight effect” is an input that should be adjusted depending on the scenario being investigated. Similar cells for probability of discontinuation are coloured yellow to remind the user to amend these when conducting scenario/sensitivity analysis on this parameter.

C++ programming code

B3. Multiple versions of the model have been supplied - one within the zip file named “add-on to INS_basecase”, four within the zip file named “add-on to MET model_basecase, and five within the “Triple therapies models” folder of the zip file named “Triple therapy_UK_13July2012”. Please clarify whether the only variations between these versions are the treatment options selected within the Demographics sheet of the Excel file, and that there are no differences in the worksheet calculations, VBA code, DLLs or C++ code provided.

Response:

Each of these files is a copy of the original model; various copies of the original generic DCEM were created for the user’s convenience. The only variation is the selected treatment lines of the control and treatment arm and the corresponding HbA1c thresholds of first and second switch in the sheet “Demographics” (under “therapy pathways” section). There are no differences in the worksheet calculations, VBA code, DLLs or C++ code.

B4. Please describe in full any differences between these models outside of the treatment options selected in the *Demographics* worksheet.

Response:

The model structure is the same across all models as specified in the response to B3.

The only differences between the add on to MET models submitted are in the "Therapy Pathways" and "Threshold HbA1c%" cells selected on the Demographics sheet. This was for user convenience to enable separate assessment of each of the comparisons of relevance.

There are additional differences with the inputs to the add-on to INS model in the following fields:

- Treatment options in "Therapy Pathways" and the "Threshold HbA1c%" (on the Demographics sheet)
- Baseline patient characteristics (on the Baseline profiles sheet)
- Drug specific parameters (on the Effectiveness and AE sheet).

B5. Please clarify whether the “Diabetes1.dll” is used by any of the models or whether it is redundant within the analyses conducted to inform the manufacturer submission.

Response:

The file “Diabetes1.dll” is redundant and not used by any of the models.

B6. Please clarify whether the source code provided within the zip file named “dapa source code” is that used to create “Diabetes2.dll”.

Response:

This is the correct source code.

B7. Five DLLs have been provided; Diabetes2.dll, Diab2User.dll, Diab2Tornado.dll, Diab2Sampling.dll and Diabetes1.dll. Please provide all files that are necessary to compile and debug these DLLs. This should include for example (but not be limited to) C++, header, compiler project files, libraries and any third party products.

- These files should be the exact versions used to generate the DLLs provided in the submission.
- If a specific compiler is required, please provide details of this compiler and supply a temporary product license covering the anticipated timeframe of the appraisal. This compiler should allow step by step debugging.
- It should be possible to compile these DLLs from the files provided without errors or significant warnings.

Response:

All of the relevant source code has been provided (*Dapa dll source code.zip*) in the reference pack accompanying this response document. Microsoft Visual C++ version 6 software was used to compile the code. We would be very happy to provide a laptop with this software already installed, with the additional support of a technical analyst, if this would be helpful to the ERG.

Clinical effectiveness and baseline characteristics

B8. Please confirm that the baseline prior history of IHD, MI, CHF, stroke, amputation, nephropathy, proliferative diabetic retinopathy and blindness was not recorded during any of the dapagliflozin trials, hence the base case assumption of these all being zero.

Response:

The baseline characteristics of the patients included in the dapagliflozin studies were balanced across the placebo and dapagliflozin arms and are presented in the tables below. Unfortunately this level of detail was not consistently reported for all the trials included the MTC. Given similar inclusion and exclusion criteria stipulated for inclusion in the MTC, similar baseline characteristics could be expected across the included RCTs: this anticipated similarity would affect all comparators with minimal impact on overall cost-effectiveness, hence values were reset to zero

24 week MTC – Add on to metformin vs placebo (study 14):

52 week MTC – Head to head vs SU on a background of metformin (study 4):

24 week MTC - add on to insulin (study 6):

Model structure

B9. **Priority Question:** Please present the equations calculating how the various risk factors change over time along with the underlying reference(s) these are drawn from. Please also summarise what happens to these risk factor equations as a result of a change in therapy. Please also outline if the risk factor equations subsequent to a change in therapy measure time from the baseline or from the time of therapy change.

Response:

Table 3 below provides full details of the equations used to generate the annual risk factor values for each therapy line. The key references the risk equations and weight progression estimates are based on are as follows:

- ***UKPDS 68 reference:*** Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, Matthews DR, Stratton IM, Holman RR; UK Prospective Diabetes Study (UKDPS) Group*. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68).* Diabetologia 2004; 47: 1747-59

  The natural progression of HbA1c, blood pressure (SBP) and cholesterol (total:HDL cholesterol) are modelled via the implementation of the UKPDS 68 equations.

- ***UKPDS 33 reference:*** UK Prospective Diabetes Study Group*: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).* Lancet 1998; 352: 837–853

This study was used as the basis for estimating the average natural progression of weight in patients with type 2 diabetes, modelled as an increase of 0.1kg per year. We can also clarify that the risk factor equations subsequent to a change in therapy measure time from the time of therapy change.

Table 3 Risk factor equations as used in the model

Risk Factor Profile Equations	
Risk Factor	**Equation**
HbA1c	**<u>Therapy 1:</u>** ***Year 1:*** HbA1c (1) = baseline + (level change for defined therapy) x (months benefit for defined therapy) / 12 ***Year 2:*** If (delay in creep > 1 year) then HbA1c(2) = HbA1c (1); Else HbA1c(2) = -0.024 + 0.144 * Log(2 + duration of diabetes) + (HbA1c (1) - 7.09) x (slope for defined therapy) + 0.085 * (BASE - 7.09) + 7.09; Where BASE = HbA1c (1) ***Year n:*** If (delay in creep > (n-1) years) then HbA1c(n) = HbA1c (n-1); Else HbA1c(n) = -0.024 + 0.144 * Log(n + duration of diabetes) + (HbA1c (n-1) - 7.09) x (slope for defined therapy) + 0.085 *

	(BASE - 7.09) + 7.09 **<u>Therapy 2:</u>** ***Year 1:*** HbA1c (1) = BASELINE + (level change for defined therapy) x (months benefit for defined therapy) / 12 Where BASELINE = HbA1c value that exceeded therapy 1 threshold value; Or therapy 1 baseline if the threshold value is not exceeded. ***Year 2:*** If (delay in creep > 1 year) then HbA1c(2) = HbA1c (1); Else HbA1c(2) = -0.024 + 0.144 * Log(2 + duration of diabetes) + (hbA1c (1) - 7.09) x (slope for defined therapy) + 0.085 * (BASE - 7.09) + 7.09; Where BASE = HbA1c (1) ***Year n:*** If (delay in creep > (n-1) years) then HbA1c(n) = HbA1c (n-1); Else HbA1c(n) = -0.024 + 0.144 * Log(n + duration of diabetes) + (HbA1c (n-1) - 7.09) x (slope for defined therapy) + 0.085 * (BASE - 7.09) + 7.09 **<u>Therapy 3:</u>** As Therapy 2 but using: Where BASELINE = HbA1c value that exceeded therapy 2 threshold value; Or therapy 2 baseline if the threshold value is not exceeded.
Total Cholesterol	**<u>Therapy 1:</u>** ***Year 1:*** tc(1) = baseline + (level change for defined therapy) x (months benefit) / 12 ***Year 2:*** If (months benefit = 12) then tc(2) = HDL-C x Total-C:HDL-C for year 2 else tc(2) = baseline + (level change for defined therapy) ***Year n:*** tc(n) = HDL-C x Total-C:HDL-C for year n **<u>Therapy 2:</u>** As therapy 1 but baseline set to Therapy 1 value for year of therapy switch. **<u>Therapy 3</u>**: As therapy 2 but baseline set to Therapy 2 value for year of therapy switch.
HDL Cholesterol	**<u>Therapy 1:</u>** ***Year 1:*** hdl(1) = baseline + (level change for defined therapy) x (months benefit) / 12 ***Year 2:*** If (months benefit = 12) then hdl(2) = hdl(1) else hdl(2) = baseline + (level change for defined therapy) ***Year n:*** hdl(n) = hdl(n-1) **<u>Therapy 2:</u>** As therapy 1 but baseline set to Therapy 1 value for year of therapy switch. **<u>Therapy 3:</u>** As therapy 2 but baseline set to Therapy 2 value for year of therapy switch.
Total-C:HDL ratio	**<u>Therapy 1:</u>** ***Year 1:*** total:hdl(1) = tc(1) / hdl(1) Where tc(1) and hdl(1) are the first year values for Total-C and

	HDL-C. ***Year 2:*** = If (months benefit = 12) then total:hdl(2) = (-0.021+0.526 x (total:hdl(1) -5.23)+0.252*(BASE -5.23))+5.23; Else total:hdl(2) = tc(2) / hdl(2) ***Year n:*** total:hdl(n) = (-0.021+0.526 x (total:hdl(n-1) - 5.23)+0.252*(BASE -5.23))+5.23 Where BASE = total:hdl(1) **Therapy 2:** As therapy 1 but baseline set to Therapy 1 value for year of therapy switch. **Therapy 3:** As therapy 2 but baseline set to Therapy 2 value for year of therapy switch.
SBP	**Therapy 1:** ***Year 1:*** sbp(1) = baseline + (level change for defined therapy) x (months benefit) / 12 ***Year 2:*** If (months benefit = 12) then sbp(2) = 0.03+0.039xlog(2+duration of diabetes)+0.717*(sbp(1)-135.09)/10+0.127x(sbp(1)-135.09)/10)x10+135.09 else sbp(2) = baseline + (level change for defined therapy) sbp(n) = 0.03+0.039xlog(n+duration of diabetes)+0.717*(sbp(n-1)-135.09)/10+0.127x(BASE - 135.09)/10)x10+135.09 else Where BASE = sbp(1) **Therapy 2:** As therapy 1 but baseline set to Therapy 1 value for year of therapy switch. **Therapy 3:** As therapy 2 but baseline set to Therapy 2 value for year of therapy switch.
Weight	**Therapy 1:** ***Year 1:*** wt(1) = baseline + (level change for defined therapy) x (months benefit) / 12 ***Year 2:*** If (months benefit = 12) then wt(2) = wt(1) + (annual weight gain defined for therapy) else wt(2) = baseline + (level change for defined therapy) ***Year n:*** wt(n) = wt(n-1) + (annual weight gain defined for therapy) **Therapy 2:** As therapy 1 but baseline set to Therapy 1 value for year of therapy switch. **Therapy 3:** As therapy 2 but baseline set to Therapy 2 value for year of therapy switch.

B10. **Priority Question:** Please present the equations calculating the incidence of events as functions of the risk factors along with the underlying reference(s) these are drawn from. Please also summarise what if anything happens to these event equations as a result of a change in therapy. Please also outline

if the event equations subsequent to a change in therapy measure time from the baseline or from the time of therapy change.

Response:

Table 4 below shows details of the event equations used in the model. The risk of macrovascular and microvascular events in diabetic subjects is estimated using risk equations developed in UKPDS 68 (reference as in response to B9), using a 2 step process: 1) to calculate β for each eventor event fatality, and 2) to calculate the result for the estimated β.

For each year an individual is processed through the simulation the event equations are used to calculate the probability of an event occurring. A randomly generated number (in the interval [0 .. 1)) is tested against the value derived from the equation and if it is less the event is deemed to have occurred. Once an event has occurred then a test for fatality is made if appropriate for the event.

Event equations measure time from baseline and the impact of therapy changes are captured by changes in risk factor profiles that change with each subsequent therapy change.

Table 4: Type 2 diabetes complication – event equations used in the model (estimated from risk equations in UKPDS 68)

Event Equations	
Event	**Equation**
IHD event	**1. Calculate β**: β = -5.310 + 0.031 x (age at diagnosis – 52.59) - 0.471 x (gender) + 0.125 x (hbA1c – 7.09) + 0.098 x (sbp - 135.09)/10 + 1.498 x log (total:hdl – 5.23) **2. Calculate result:** Result = exp(1.15 x log(year of simulation) + β) x CV risk factor x BMI risk factor
MI event	**1. Calculate β:** β = -4.977 + 0.055 x (age at diagnosis – 52.59) - 0.826 x (gender) - 1.312 x (ethnicity) + 0.346 x (smoking status) + 0.118 x (hbA1c – 7.09) + 0.101 x (sbp - 135.09)/10 + 1.190 x log (total:hdl – 5.23) + 0.914 x (IHD) + 1.558 x (CHF) where IHD = 1 and CHF = 1 if history of IHD or CHF, 0 otherwise **2. Calculate result:** Result = exp(1.257 x log(year of simulation) + β) x CV risk factor x BMI risk factor
CHF event	**1. Calculate β:** β = -8.018 + 0.093 x (age at diagnosis – 52.59) + 0.066 x (bmi – 27.77) + 0.157 x (hbA1c – 7.09) + 0.114 x (sbp - 135.09)/10 **2. Calculate result:** Result = exp(1.711 x log(year of simulation) + β) x CV risk factor x BMI risk factor Note that if Rosiglitazone is current therapy then the result is further multiplied by the value defined for the CHF risk factor
Stroke event	**1. Calculate β:** β = -7.163 + 0.085 x (age at diagnosis – 52.59) - 0.516 x (gender) + 0.355 x (smoking status) + 0.128 x (hbA1c – 7.09) + 0.276 x (sbp - 135.09)/10 + 0.113 x (total:hdl – 5.23) + 1.428 x

	(ATRFIB) + 1.742 x (CHF) where ATRFIB = 1 if atrial fibrillation at diagnosis, 0 otherwise and CHF = 1 if history of CHF, 0 otherwise **2. Calculate result:** Result = exp(1.497 x log(year of simulation) + β) x CV risk factor x BMI risk factor
Amputation	**1. Calculate β:** β = -8.718 + 0.435 x (hbA1c – 7.09)+ 0.228 x (sbp - 135.09)/10 + 2.436 x (PVD) + 1.812 x (BLIND) where PVD = 1 if peripheral vascular disease at diagnosis, 0 otherwise and BLIND = 1 if history of blindness in one eye, 0 otherwise **2. Calculate result:** Result = exp(1.451 x log(year of simulation) + β) x BMI risk factor
Blindness	**1. Calculate β:** β = -6.464 + 0.069 x (age at diagnosis – 52.59) + 0.221 x (hbA1c – 7.09) **2. Calculate result:** Result = exp(1.154 x log(year of simulation) + β) x BMI risk factor
Renal event	**1. Calculate β:** β = -10.016 + 0.404 x (sbp - 135.09)/10+ 2.082 x (BLIND) where BLIND = 1 if history of blindness in one eye, 0 otherwise **2. Calculate Result:** Result = exp(1.865 x log(year of simulation) + β) x BMI risk factor
Event Fatality	**1. Calculate β:** β =-3.251 + log(AGE EVENT - 52.59) + 0.114 x (HbA1c - 7.09) + 2.640 x (MI) + 1.048 x (STROKE) where AGE EVENT = age at occurrence of first diabetes-related event elevating risk of mortality and MI = 1 if occurrence of MI event and STROKE = 1 if occurrence of Stroke event **2. Calculate result:** Result = exp(β) / (1 + exp(β)) ***Note***: Event Fatality is checked when an event that may be fatal occurs. Equations to test for an MI or Stroke fatality are handled separately (see below).
MI Fatality	**1. Calculate β:** β = 0.713 - 0.048 * (age at diagnosis - 55) - 0.178 x (HbA1c - 6.86) - 0.141 x (sbp - 141)/10 - 0.104 **2. Calculate Result:** Result = 1/(1 + exp(β))
Stroke Fatality	**1. Calculate β:** β = 1.684 - 0.249 x (sbp - 141)/10 **2. Calculate Result:** Result = 1/(1 + exp(β))

B11. **Priority Question:** Please confirm whether the model only simulates the incidence of the first event, or whether a patient can experience multiple events of the same type, e.g. multiple MIs?

Response:

The model simulates primary events only; a patient can only experience one MI, one stroke or other complications over a lifetime in keeping with other assumptions in diabetes models used in previous NICE appraisals. However, this option can be over-ridden by the user and multiple events predicted

B12. **Priority Question:** In a hypothetical scenario, the baseline patient weight is X kg, the treatment arm is associated with a weight loss of Y kg and the comparator arm is associated with a weight gain of Z kg, the weight loss of Y kg as a result of treatment lasts for 2 years. Please clarify whether it is possible within the model structure to equalise the patient weight between the two treatment arms at 2 years? If so, how?

Response:

Dapagliflozin has demonstrated a sustained weight at two years demonstrating that weight does not equalise at 2 years. Therefore, it is not realistic to equalize weight at 2 years. Hypothetically for the weight to equalize in year 3 and beyond two major assumptions have to be made:

- Treatment arm weight loss of Y kg disappears; and
- Weight gain caused by comparator arm treatment of Z kg disappears (must now change to a weight loss effect) and come down to the baseline weight while on treatment , thereby, conferring a weight loss attribute to a comparator drug shown to cause weight gain

We strongly feel that the hypothetical scenario outlined in B12 is not a valid scenario.

In response to the question, it is not possible to produce the exact hypothetical scenario presented in Question B12 within the model structure.

It is, however, possible to conduct a similar scenario in which the weight loss of Y kg is nullified within 1 year after the 2 years of sustained weight loss (1 year weight loss based on NMA data, 1 year weight loss maintained). Similarly weight gain of Z kg over 1 year, maintained in year 2 and then nullified within 1 year can be modelled. Hence, in this scenario the weight between the two treatment arms is equalised at Year 3 (at a weight that includes natural weight progression over time compared to baseline). This can be done by adjusting the parameters “Years of maintained weight loss” and “Years to loss of weight effect” on the “Effectiveness and AE” sheet in the model as shown below.

To explain the base case values used in the model for comparator treatments that are weight-increasing, by default, the parameter “Years of maintained weight loss” (which in fact for these treatments should read as “years of maintained weight change”) is set to 1 and the parameter “Years of loss to weight effect” is set to 0, under the assumption that the weight gained in the first year of therapy will not be lost in subsequent years. Based on 2-year evidence, the “Years of maintained weight loss” of dapagliflozin is set to 2 years in the base case. The same value is applied for other weight-lowering comparator treatments, despite a lack of 2-year evidence for sustained weight loss of the comparator treatments.

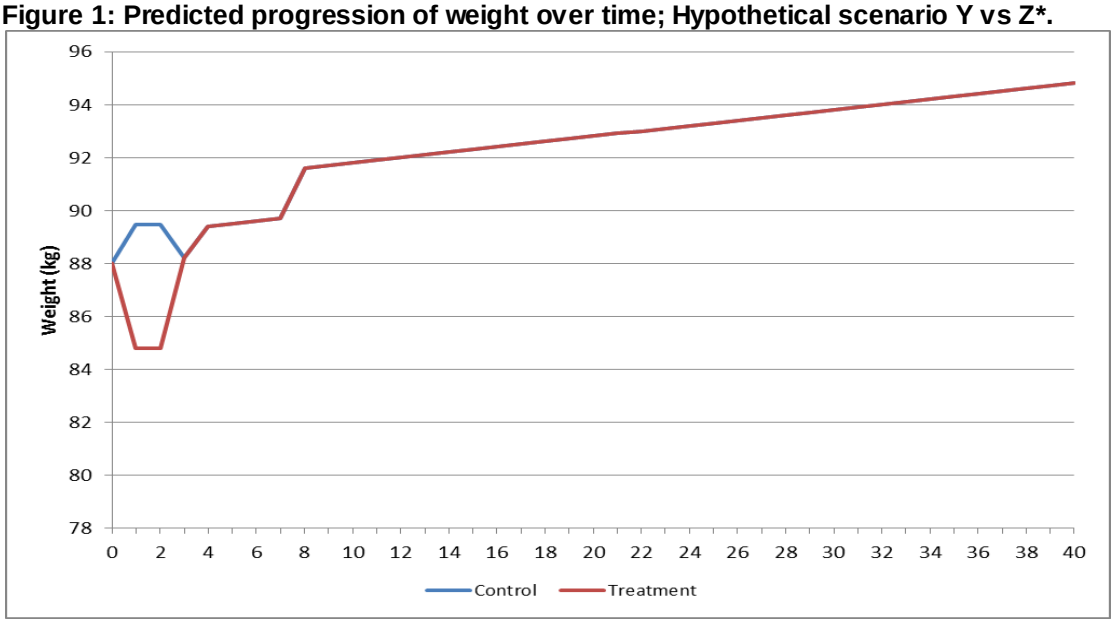
The value of “Years to loss of weight effect” for dapagliflozin and weight-lowering comparator treatments can then be varied in scenario analyses, but with each scenario based on the assumption of a linear, gradual loss of that weight effect. This is explained in more detail in the response to Question B15. Note that all treatment effects (with respect to weight) in the model are applied in their entirety during the first year of treatment as a change from the baseline values; this cannot be adjusted by the user.

In order to conduct the scenario in which the weight loss of Y kg is nullified within 1 year after 2 years of sustained weight loss, and the weight gain of Z kg is assumed to be nullified after 2 years of maintained weight gain, with weight being equalised between the two arms at Year 3, the parameter settings should be as follows:

	"Years of maintained weight loss" (/gain)	*"Years to loss of Weight effect"*
Treatment Y (Y kg weight loss)	*2*	*1*
Treatment Z (Z kg weight gain)	*2*	*1*

A profile of weight over time for the hypothetical scenario is presented in figure 1 below, taking Y and Z to be -3.22 kg and +1.44 kg respectively.

Figure 1: Predicted progression of weight over time; Hypothetical scenario Y vs Z*.



*Note that the change in weight at year 7 is as a result of treatment escalation modelled in this illustrative scenario, and is not associated with 1st line therapies Y and Z.

Figure 1 shows that, indeed, in this scenario weight is equalised between the two arms at Year 3. However, this is only possible if both the weight loss of Y kg and the weight gain of Z kg are nullified within 1 year after the 2 years of sustained weight effect. Thus, in this case we assume that a patient will lose any weight gained due to a weight-inducing treatment while still on that treatment. This seems unlikely and hence should be considered an extreme scenario.-However, without that assumption, it is not possible to simulate equal weight between the two arms by adjusting the parameters "Years of loss to weight effect" and "Years of maintained weight loss".

An alternative, more plausible approach to equalise weight in the model can be adopted, which is explained below:

Using time to switch to next treatment to equalise weight: Within the model it is possible to equalise the patient weight between two treatment arms at the time of switch to a next therapy line (which is determined by the HbA1c level), by manipulating the treatment effect on weight, associated with that next therapy line, such that the resultant weight is equal in both arms. To illustrate how this is performed, an example of one of the scenario analyses that was included in the submission dossier is presented below. This is the scenario analysis of dapagliflozin add-on to metformin vs. SU add-on to metformin in which weight was assumed to be equal between the two treatment arms after the switch to the third therapy line. In

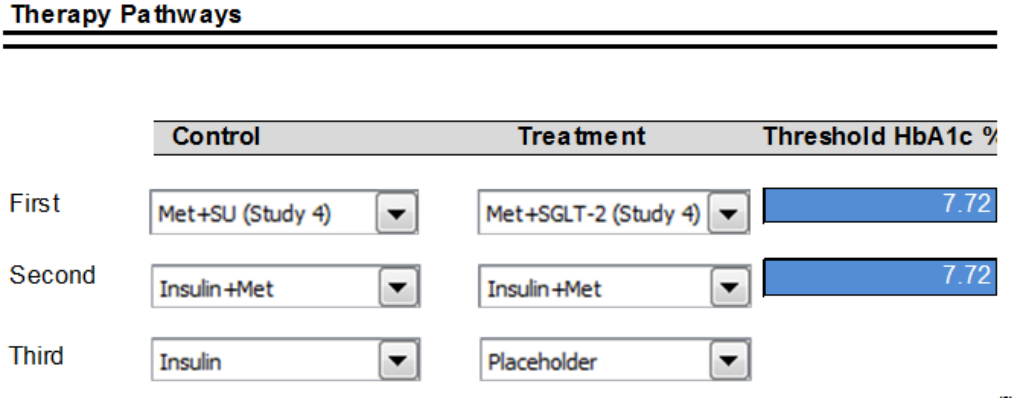
order to conduct this scenario analysis, the treatment effect on weight of the 3rd therapy line (i.e. intensified insulin) was manipulated on the "Effectiveness and AE sheet" of the model, as shown in Table 5 below.

Table 5: Example of adjusting the value of treatment effect on weight on the "Effectiveness and AE" sheet of the cost-effectiveness model, with the aim to conduct "equal weight" scenario analyses.

	Control	**Treatment**	**Treatment**
	Base case and Scenario analysis	**Base case**	**Scenario with equal weight after switch to 3rd line**
First line	Metformin+Sulphonylurea (Study 4)	Metformin+Dapagliflozin (Met+SGLT-2) (Study 4)	Metformin+Dapagliflozin (Met+SGLT-2) (Study 4)
	Weight: +1.44 kg	Weight: -3.22 kg	Weight: -3.22 kg
Second line	Insulin+Metformin (Insulin+Met)	Insulin+Metformin (Insulin+Met)	Insulin+Metformin (Insulin+Met)
	Weight: +1.084 kg	Weight: +1.084 kg	Weight: +1.084 kg
Third line	Insulin	Insulin	Insulin (Placeholder) *
	Weight: +1.9 kg	Weight: +1.9 kg	Weight: +3.34 kg This is the 1st line weight gain of Met+SU (+1.44 kg) added to the weight gain associated with 3rd line intensified insulin (+1.9 kg) in order to equalise the weight between the Control and Treatment arm.

* Use a "Placeholder" field on the "Effectiveness and AE sheet" in the model; apply the same values as in the "Insulin" field to the Placeholder entries, except for the value of Weight effect (> enter 3.34 instead of 1.9 kg).

Select the corresponding Therapy Pathways on the "Demographics" sheet of the model. In the underlying scenario example these would be:



The graphs of weight over time of this scenario analysis compared to the base case are reproduced in the figures below.

Figure 2 Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Base case

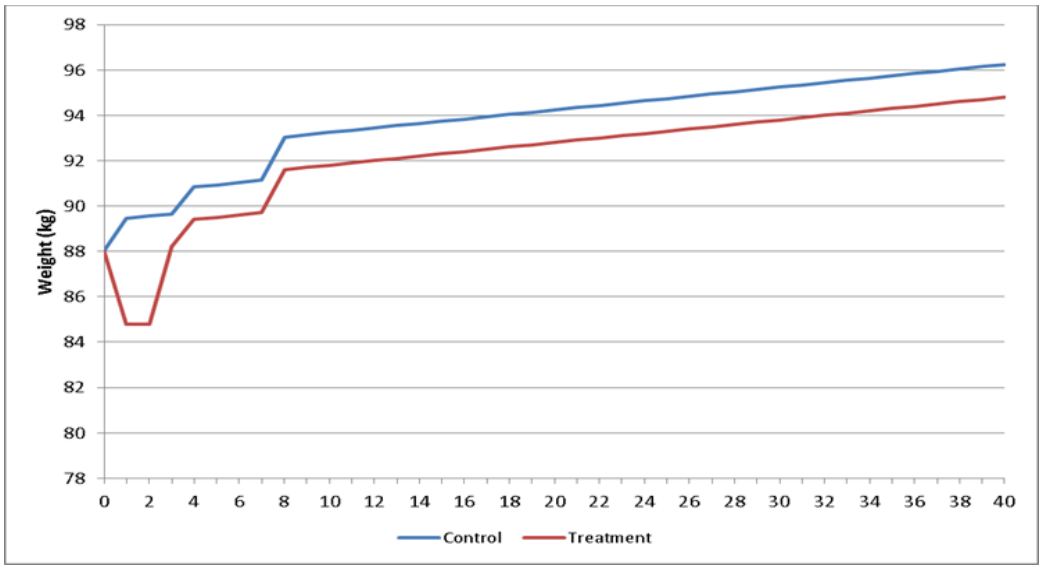
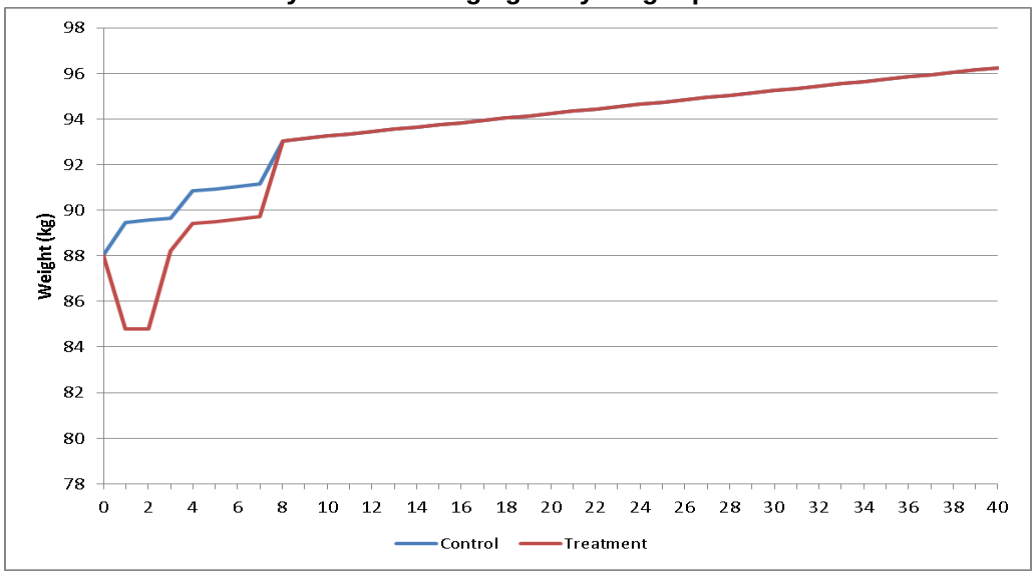


Figure 3 Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Scenario analysis of converging body weight profiles after switch to 3rd line.



In the same manner as presented for the above scenario, patient weight could be equalised after the switch to 2nd line therapy, either by taking the weight of the treatment arm to be equal to the weight of the control arm or vice versa, as shown in the figures below.

Figure 4: Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Weight of Treatment arm equal to Control arm after switch to 2nd line therapy.

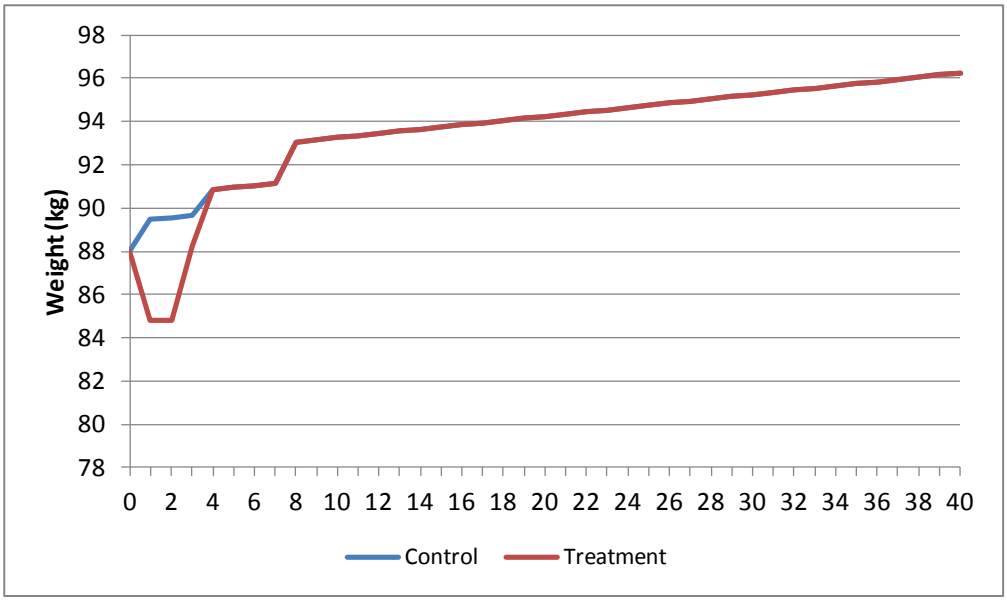
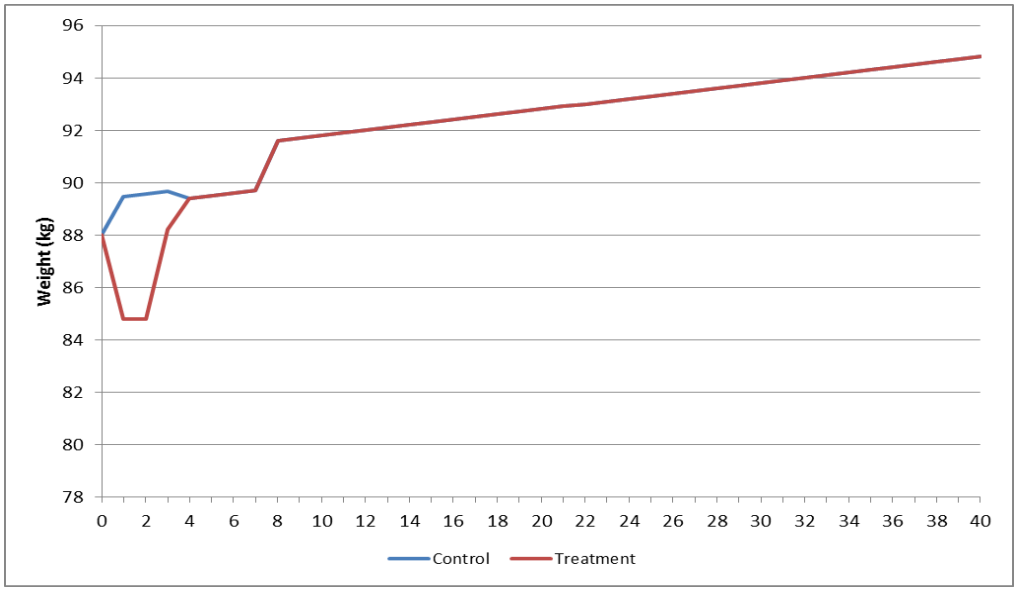


Figure 5: Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Weight of Control arm equal to Treatment arm after switch to 2nd line therapy.



B13. Given the distributions placed upon each of the parameters and in particular the patient characteristics at baseline, which if any variables are sampled within the "deterministic" modelling. For instance, the patient baseline BMI appears to be associated with a distribution. Is this BMI distribution sampled within the "deterministic" modelling (Run model using mean values)? Is this BMI distribution sampled within the "probabilistic" modelling (Run probabilistic sensitivity analysis)?

Response:

Within the “deterministic modelling” (Run model using mean values), the model runs are initiated with the mean values of the baseline patient characteristics. None of the baseline patient characteristics, including BMI, are sampled from a distribution.

Baseline patient characteristics, including BMI, were not sampled from a distribution within the “probabilistic modelling” (Run probabilistic sensitivity analysis). The parameters that were sampled from their distribution within the probabilistic sensitivity analysis are: first-line treatment effects on HbA1c, weight, SBP, total cholesterol and HDL cholesterol, the number of symptomatic hypoglycaemic events and the probability of a severe hypoglycaemic event, adverse event rates (urinary tract infection and genital infection), utilities and costs. Please refer to Probablistic Sensitivity Analysis (PSA) Parameters table in the Manufacturer’s Submission.

B14. Please clarify what impact the age dependent baseline utility function in figure 28 (p.229) has within the modelling. Does it reduce the value of any additional survival? Does it reduce the value of avoiding events with the event decrements being proportionate to the age dependent utility profile? Given the age dependent baseline HRQoL, how is this subsequently conditioned by the age specific EQ-5D utility values?

Response:

The age dependent baseline utility function is solely used to define the starting utility of the cohort in the simulation, conditional on mean age of the cohort at baseline. Utility decrements applied to events are constant with respect to age; as such, the age dependent baseline utility has no impact on the value of avoiding events.

It could be argued that the value of the baseline utility has an indirect impact on the value of any additional survival, since a higher/lower baseline utility would lead to greater/lesser utility gains associated with patients living longer. However, survival is not a key driver of the cost-effectiveness results.

B15. The description of the modelling of weight states that: “*After Year 2, weight is assumed to be fully regained by the time of switch to the next treatment line in a linear manner*” (p.212). Please clarify what is meant by “*in a linear manner*” and how this is implemented and over what time frame in the model.

Response:

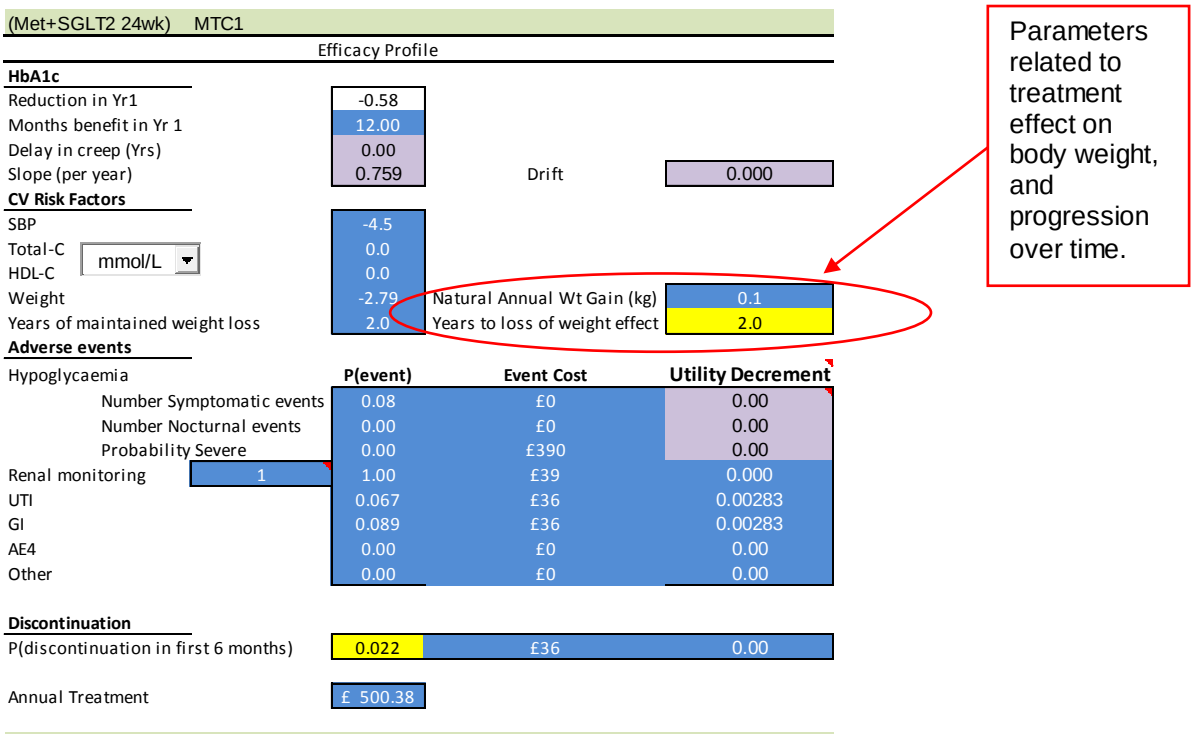
By “in a linear manner” it is meant that weight rises with an even, gradual slope until patient’s weight is at a level that it would be if the patient would not have experienced any weight loss due to dapagliflozin treatment. It has been shown in the clinical studies that the weight lowering effect of dapagliflozin is maintained while on dapagliflozin treatment. Based on 2-year data from the long-term extension of the dapagliflozin vs glipizide as add on to MET trial (Study Code D1690C00004; Del Prato, 2011), and on long-term data of the placebo-controlled dapagliflozin add-on to INS trial (Study Code D1690C00006) the sustained weight loss is assumed for at least the first two years of dapagliflozin therapy. To date there is no data on body weight beyond two years of treatment with dapagliflozin. While it can be assumed that weight loss is maintained throughout the whole duration of dapagliflozin treatment, a more conservative approach has been followed in the cost-effectiveness

analyses by assuming that the weight-lowering effect decreases with time on dapagliflozin treatment. Since there is no data available on the rate at which the effect would disappear, if at all, a linear, gradual loss of weight effect has been assumed. Alternative time frames can be defined from 1 year upwards for the gradual but linear change in weight. Therefore, within the model structure there is no "slope" parameter for the weight effect. Instead, the linear loss of the dapagliflozin weight reduction is implemented in the model as described below.

In the cost-effectiveness model, 5 parameters determine the course of patient body weight over time:

- baseline weight at model entry
- treatment effect on weight
- number of years during which the treatment effect on weight is maintained
- number of years that it takes from the end of the maintained weight effect until the effect has disappeared completely
- natural annual weight gain.

The last four of these parameters can be changed for each treatment on the "Effectiveness and AE" sheet in the model, as shown below.



The effect on body weight is derived from the appropriate sources for each treatment option in the model, and applied in the first year after treatment initiation. For dapagliflozin, and weight-lowering comparator treatments, the "years of maintained weight loss" is set by default to 2 years, based on the evidence as explained in B13. In the absence of a slope parameter to regulate the rate of loss of weight effect, in order to simulate a linear, gradual regain of weight, the "years to loss of weight effect" were set to a value such that weight is fully regained by the time of switch to the next treatment line. By "fully regained" it is meant that the patient weight is at a level that it would be if no weight effect had occurred in the first year after therapy start (i.e. baseline weight plus weight gained since baseline due to natural weight progression).

In the model, the time of switch to the next treatment line is determined by the HbA1c reduction and the user-defined HbA1c switching threshold. As these two parameters vary in the analyses depending on the treatments and scenarios under investigation, the parameter "Years to loss of weight effect" on the "Effectiveness and AE" sheet needs to adjusted to achieve the linear weight regain by the time of switch to 2nd line therapy. The parameter setting for the base case analyses is shown in table 6 below.

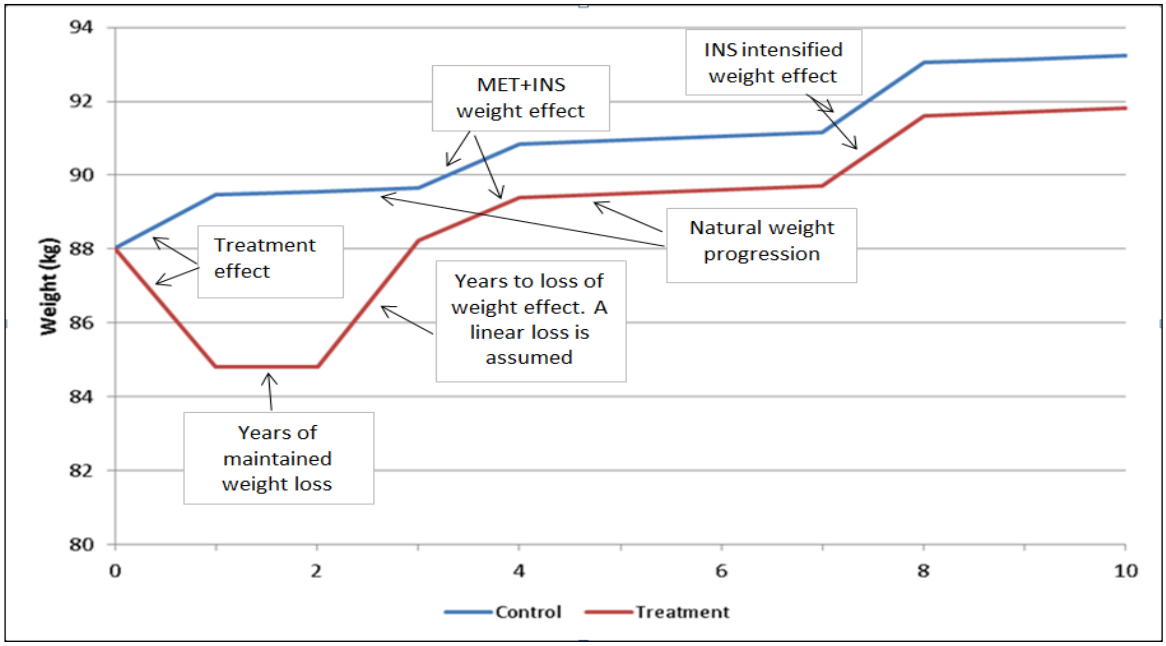
Table 6: Base case parameter settings for years to weight effect loss

Treatment	Met+SGLT2 Study 4	Met+SU Study 4	Met+SGLT2 (24wk MTC)	Met+DPP4 (24wk MTC)	Met+TZD (24wk MTC)	Ins+SGLT2	Ins+DPP4
Years to loss of weight effect	Set to 1	Set to 0*	Set to 2	Set to 3	Set to 0*	Set to 5	Set to 0*
Comment	In the case of an HbA1c switching threshold of 7.72	* Tx associated with weight gain	In the case of an HbA1c switching threshold of 8.17	In the case of an HbA1c switching threshold of 8.17	* Tx associated with weight gain	In the case of an HbA1c switching threshold of 8.9	* Tx associated with weight gain

It should be noted that for treatments associated with weight gain (Met+TZD, Met+SU, Insulin+DPP4, Met+Insulin (2nd line), intensified insulin (3rd line)) the "Years to loss of weight effect" is set to zero. For these treatments it is assumed that the initial weight gained in the first year of therapy will not be lost in subsequent years.

The course of body weight over time and the parameters that determine the course of body weight in the model are illustrated in figure 6 below, which is reproduced from our submission (for the base case of dapagliflozin vs SU).

Figure 6. Illustration of dynamic body weight profile implemented in the model



B16. In regard to the model therapy target values in cells Q29:Q31 of the *Demographics* worksheet, please clarify whether a change of therapy occurs if

any of the 3 target values are met, only if all the 3 values are met or something else? Further please clarify what happens if these cells are empty? And how do the targets of these cells differ from the threshold HbA1c of cells L29 and L31 in the same worksheet? Do 3 lines of therapy always have to be specified even if only second to last or last line is being considered?

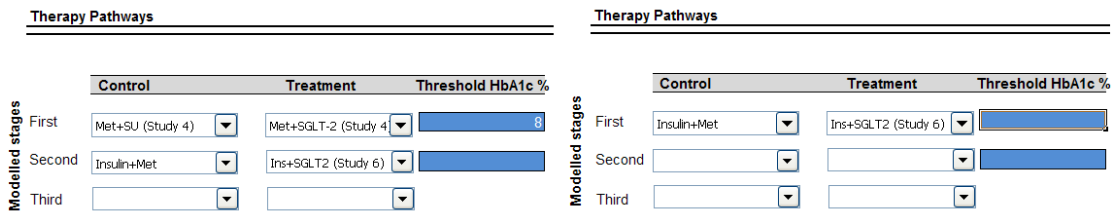
Response:

The target values in cells Q29:Q31 of the *Demographics* worksheet have no impact on the cost-effectiveness modelling and are relevant only for the reporting of specific outcomes (i.e. on the "*Results"* and "*Results (5YR)"* worksheets . For example, setting user defined targets for HbA1c, SBP or weight levels in cells Q29:Q31 will produce estimates of the numbers of patients meeting the targets ("*Results"* sheet), or number of years below/at target at 5 (or less) years ("*Results*" (5YR) sheet). No changes in therapy are modelled as a result of exceeding any particular target defined in cells Q29:Q31 of the *Demographics* worksheet. If no target values are defined the model will run with zero values and will therefore lead to results for patients meeting the target and years below the target reflecting a zero value threshold for each parameter. However, as above this will not affect the cost-effectiveness results.

Therefore, the threshold values in Q29:Q31 do not relate to the HbA1c thresholds in cells L29 and L31, which do have an impact on the modelling of cost-effectiveness as these values determine the time at which therapy escalation occurs. To summarise each treatment arm (i.e. 'treatment' and 'control') is comprised of **up to** three therapy lines. The simulated subjects will receive a particular therapy until their HbA1c crosses the specified threshold (switching threshold defined in cells L29 and L30), at which point they cease receiving that therapy and move onto the next therapy. HbA1c levels are checked at the end of each year to determine when switches are made in therapy lines.

All three therapy lines do not have to be filled for each run of the model. If only the second to last and last lines of therapy are to be modelled, then selections should only be made in the therapy pathways section of the *Demographics* worksheet for the first and second modelling stages, and only the first HbA1c threshold should be completed. If only the last line of therapy is to be modelled, only the first modelling stage should be selected and no HbA1c thresholds should be entered (see Figure 7 below).

Figure 7: Therapy pathway set-up for modelling of second to last (left) and last (right) therapy lines only



Model validation

B17. **Priority Question:** Please outline which studies within table 1 of the Cardiff (DCEM) model validation report are drawn from Mt Hood challenges.

To what extent do the values reported in table 1 comprehensively report the disaggregated and aggregated event rates modelled in each of the Mt Hood challenges? Has the Cardiff (DCEM) model changed between the Mt Hood challenges?

Response:

The Mt Hood challenges have previously included validation exercises from ASPEN, ACCORD and ADVANCE. The format for Mt Hood is for each model to predict the endpoints that each model is capable of predicting. MI and stroke are common to all models but endpoints such as angina, revascularisation and secondary events are not uniformly predicted by participating models.

The Cardiff model has been updated since the Mt Hood 4 challenge - but the underlying event rate calculations remain the same. Furthermore, validation of model updates undertaken has demonstrated consistent results between model versions.

The event rates shown in table 1 of the validation report are those trial endpoints that the DCEM is capable of predicting and, therefore, not the full range of trial endpoints.

B18. **Priority Question:** The observed and predicted events presented in table 1 of the Cardiff (DCEM) model validation report do not obviously correspond with those presented in table 1 of the published Mt Hood 4th modelling group report (Diabetes Care 2007 (30):6;1638-1646). Please provide a summary of and reconciliation between these two sources of the Cardiff (DCEM) modelled and observed CARDS study events.

Response:

The validation undertaken for the DCEM was conducted independently and without reference to the Mt Hood 4 modelling exercise. The only endpoint reported in both studies is stroke and in the Mt Hood 4 paper the Cardiff model reports a 4 year incidence of ~2.5% compared with ~1% in the recent validation exercise. The lower incidence is unlikely to be due to the history of disease at commencement of the model as only CHD and AF increase stroke risk. Validation results are sensitive to the variability in demographic and risk factor input parameters and it is possible that these distributions were set up differently between the two applications. In response to B20, the input profiles used in the model are specified.

B19. Please tabulate the values that are plotted in figures 5 and 6 of the Cardiff (DCEM) model validation report.

Response:

The values plotted in figures 5 and 6 of the Validation Report are tabulated below in Table 7.

Table 7 Tabulated values for Figures 5 in the Validation Report

Event	Legacy	No Legacy	UKPDS	LCL	UCL
Any	0.895	0.9782	0.91	0.83	0.99
DMRD	0.827	0.9675	0.83	0.73	0.96
MI	0.918	0.981	0.85	0.74	0.97
Stroke	0.915	0.9852	0.91	0.73	1.13
PVD	0.659	0.9519	0.82	0.56	1.19
MVD	0.798	0.9634	0.76	0.64	0.89

Table 7.1 Tabulated values for Figure 6 in the Validation Report

	ICER		QALY's		Total Cost (£)			
Scenario	CDM	DCEM	CDM	DCEM	CDM (D)	CDM (S)	DCEM (D)	DCEM (S)
A1	7,105	8,452	0.587	0.413	14,592	10,420	13,822	10,333
A2	18,689	19,934	0.223	0.175	14,592	10,420	13,822	10,333
A3	7,151	8,502	0.608	0.410	14,370	10,277	13,817	10,329
A4	18,025	20,178	0.227	0.173	14,370	10,277	13,817	10,329
A5	6,916	8,265	0.607	0.417	15,755	11,555	15,714	12,271
A6	16,775	19,256	0.250	0.179	15,755	11,555	15,714	12,271
A7	7,062	8,403	0.590	0.411	15,724	11,554	15,700	12,245
A8	16,604	19,879	0.251	0.174	15,724	11,554	15,700	12,245
A9	7,062	9,098	0.547	0.410	14,460	10,277	13,957	10,228
A10	6,378	7,764	0.650	0.440	14,421	10,277	13,747	10,329
A11	29,438	26,755	0.139	0.128	14,370	10,277	13,747	10,329
A12	7,570	9,417	0.586	0.365	14,700	10,277	13,769	10,329

B20. Please tabulate each of the baseline percentages of : AF, PVD, IHD, MI, CHF, Stroke, Amputation, Blind, ESRD that were inputted for each of the Mt Hood challenges, also identifying which study these relate to in table 1 of the CARDIFF (DCEM) model validation report.

Response:

The model is capable of running with multiple CV events (over-riding the primary event only equations) and allowing subsequent events to be predicted. In the validation studies performed the history of CV events were set to 0 as an alternative to invoking multiple event predictions. In Appendix B, an embedded spreadsheet sets the input profiles modelled for the validation study.

B21. Within the CORE Diabetes model, it is usual for the treatment effect of only the initial therapy to apply with the subsequent therapies having no effect; i.e. there is only an initial drop from the first therapy and no subsequent change in the risk factors at therapy switches subsequent to the first therapy. This appears to be a key difference between the Cardiff (DCEM) model and the CORE model. Please confirm if this interpretation of the CORE model implementation applies to the CORE modelling of the two validation reports.

Response:

This is not the case. The description above related to the treatment tree approach used by the CORE model. Validation between the two models was used with the treatment line approach in the CORE model that allows for treatment effects to be applied in subsequent therapy lines.

B22. Please clarify whether the CORE modelling for validation applied a therapy HbA1c threshold to determine the timing of switch of therapy or applied a fixed duration of therapy prior to therapy switch.

Response:

The CORE model also used an HbA1c threshold to control therapy escalation.

Modelling submitted

B23. In the triple therapy addendum, the treatment sequences appear to consider MET+SU as first-line therapy prior to any of the comparisons of interest.. Please provide the rationale for the inclusion of MET+SU within the treatment sequences under consideration.

Response:

Data used in the triple therapy addendum is pooled from two studies: Study 18 & 19. Those receiving triple therapy are sub-populations and neither Study 18 or 19 was designed to evaluate the efficacy of dapagliflozin in a triple therapy setting per se. As the baseline characteristics of the patients in these sub-populations is unrepresentative of patients we expect to receive dapagliflozin as part of a triple therapy regimen in routine practice, we felt it would be inappropriate to use these characteristics directly in the model for the assessment of the cost-effectiveness of dapagliflozin in this setting. Therefore, in order to better reflect routine clinical practice we adopted a pragmatic approach using data from Study 4 including Met + SU for baseline characteristics and treatment comparisons, with patients then 'progressing' onto triple therapy at the HbA1c threshold for switching. While this approach blurs the principle research question (adding 4-5 years of costs for dual therapy and over discounting the costs and effects of triple therapy) it was felt this was less of a limitation than basing the patient cohort on inappropriate baseline characteristics.

Health-related quality of life

B24. **Priority Question:** The study by Lane et al (2012) removed 4 patients of the 100 patients interviewed due to illogical responses. Please provide further reasoning for the removal of each of these 4 patients.

Response:

The reasons are given below for each of the 4 patients:

Excluded respondent 1 – illogical TTO response – 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'*

Excluded respondent 2 – illogical TTO response – 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'*

Excluded respondent 3 – illogical TTO response – 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'*

Excluded respondent 4 – illogical TTO response – 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'*

B25. **Priority Question:** Please confirm whether the manufacturers are aware of any studies of the effect of weight upon HRQoL in T2DM that have been previously undertaken or supported by them, or that they are currently undertaking or supporting?

Response:

This is a list of all the studies of the effect of weight upon HRQoL in T2DM that the manufacturers are aware of. No other studies are being undertaken at the moment. The manufacturers are involved in the SHIELD Study Group.

The table also includes the corresponding PDF files of the studies.

Table 8. List of all published studies of the effect of weight upon HRQoL in T2DM of which the manufacturers are aware.

Publications
Grandy S, Fox KM, Bazata DD, for the SHIELD Study Group. Association of self-reported weight change and quality of life, and exercise and weight management behaviors among adults with type 2 diabetes mellitus. *Cardiol Res Pract* 2012;2012:892564
Grandy S, Fox KM, Hardy E, for the SHIELD Study Group. Impact of self-reported weight change on quality of life among individuals with type 2 diabetes mellitus. Poster presented at the 9th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease, Los Angeles, California, November 3-5, 2011.
Grandy S, Fox KM. EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: Findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Health Qual Life Outcomes* 2008;6:18.
Gavin JR III, Rodbard HW, Fox KM, Grandy S, for the SHIELD Study Group: Association of overweight and obesity with health status, weight management, and exercise behaviors among individuals with type 2 diabetes mellitus or with cardiometabolic risk factors. *Risk Management and Healthcare Policy* 2009;2:1-7.
Rodbard HW, Fox KM, Grandy S, for the SHIELD Study Group: Impact of obesity on work productivity and role disability in individuals with and at risk for diabetes mellitus. *Am J Health Promot* 2009;23:353-360.
Green AJ, Fox KM, Grandy S, for the SHIELD Study Group. Impact of regular exercise and attempted weight loss on quality of life among adults with and without type 2 diabetes mellitus. *J Obesity* 2011 Article ID 172073 doi:10.1155/2011/172073.
Grandy S, Fox KM, for the SHIELD Study Group. Change in health status (EQ-5D) over 5 years among individuals with and without diabetes. Poster presented at the 47th Annual Meeting of the European Association for the Study of Diabetes, Lisbon, Portugal, September 12-16, 2011.

B26. **Priority Question:** For the patient level data from the dapagliflozin study 12 using the UK social tariff weights for EQ-5D please provide:

- the mean (s.d.) baseline EQ-5D utility by treatment arm?
- the mean (s.d.) 24 week EQ-5D utility by treatment arm?
- the mean (s.d.) change between baseline and 24 weeks in EQ-5D utility by treatment arm?

Response@

As per ERG request, a statistical analysis was performed by manufacturer's statisticians on the study 12 data where the UK social tariff weights (Kind et al, 1999) for EQ-5D was used replacing the original European norm data (Greiner et al, 2003). The results are presented in table 9.

Table 9 EQ-5D index mean change from baseline at week 24 with UK social tariff weights in study 12.

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Table 2

EQ-5D Index Mean Change from Baseline at Week 24 (LOCF)
Including Data After Rescue
Using UK social tariff weights for EQ-5D
Short-term Treatment Period
Full Analysis Set

	PLA + MET (N=91)	DAPA 10MG + MET (N=89)
SUMMARY STATISTICS		
N#	89	87
BASELINE MEAN (SD)	0.837 (0.1493)	0.867 (0.1583)
WEEK 24 MEAN (SD)	0.884 (0.1517)	0.885 (0.1784)
MEAN CHANGE FROM BASELINE (SD)	0.047 (0.1335)	0.018 (0.1498)

B27. **Priority Question:** Using the patient level data from the dapagliflozin study 12, and applying the parameter estimates of Lane et al (2012) to patient weights/BMIs, what is the implied mean (s.d.) change in utility between baseline and 24 weeks by treatment arm?

Response:

As per ERG request, a statistical analysis was performed by manufacturer's statisticians using the patient level data from the dapagliflozin study 12 where the parameter estimates of Lane et al (2012) were applied. The results are presented in table 10 below.

[redacted]

Table 10. EQ-5D utility mean change from baseline at week 24 in study where the parameter estimates of Lane et al (2012) were applied.

B28. **Priority Question:** Please clarify how the hypoglycaemia utility decrements are applied within the model, with reference to the comparison with DPP4s as an example (taken from the submitted model cells D71:F79 of the *Utilities* worksheet presented below); i.e. what do the following numbers mean and how are they calculated?

Hypoglycaemia fear score and utility equations

	(Table 4) (Excluding Nocturnal	(Table 5) (Including Nocturnal
Number of Symptomatic	1.7727	0.0000
Severe Hypoglycaemia	5.8812	6.3956
HFS value	0.0084	0.0066
Number of Nocturnal	0.0000	1.0540

Please clarify the source reference(s) and the arithmetic underlying the utility decrements within cells D55:M67 of the *Utilities* worksheet.

Response:

The values in the table above (Cells D71:D79) are used to model utility decrement associated with hypoglycaemia in the model's default state. They are taken from a study by Currie et al (2006) in which statistical models were developed that related the fear of hypoglycaemia to changes in health-related utility, conditioned on differing severity and frequency of hypoglycaemic events. These published equations, characterising the relationship between the fear of hypoglycaemia and health-related utility using the EQ5D, were hard coded into the model.

Reference: Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. *Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes.* Current Medical Research and Opinion 2006; 22(8): 15-23.

The derived equations used pooled data from two postal surveys conducted in Cardiff, UK (n=1,305 responses), in which the fear of hypoglycaemia was characterised using the hypoglycaemia fear survey (HFS [eight question worry sub-scale only]), and health-related utility using the EQ-5D index.

The analysis revealed the HFS value to be the best estimate of the EQ-5D, while the number of hypoglycaemic events was found to be an important predictor of the HFS value. Therefore a two-stage approach was adopted to predict EQ-5D; firstly the relationship between frequency of hypoglycaemic events and the HFS value was estimated (as shown in Table 4 of Currie et al). Severe hypoglycaemia resulted in a change of 5.881 units on the HFS. One or more symptomatic hypoglycaemic event over the same period results in a corresponding change of 1.773 units on the HFS. The predicted HFS value was then used to estimate the EQ-5D (as shown in Table 5 of Currie et al). A 1 unit increase on the HFS results in a 0.008 unit decrease on the EQ5D.

In this modelling exercise only severe and symptomatic hypoglycaemic events are modelled and hence only the first column of values in the table included in the question (and those detailed in the description above) are applied in the calculation of health-related utility consequences of hypoglycaemia in the model.

Table 11 Calculation of decrement in health utility associated with hypoglycaemia

Stage of	Equation

calculation	
HFS estimation	HFS = (5.8812*severeHypo) +(1.7727*logSymptomaticHypo) + (0.0000*√nocturnal Hypo) Where; *severeHypo* = 1 if severe hypoglycaemic event occured *logSymptomaticHypo* =0 if no symptomatic hypoglycaemic events occur, or =ln(1+number of symptomatic hypos) if they do *nocturnalHypo*= number of nocturnal hypoglycaemic events = 0 for this analysis
EQ-5D decrement estimation	Utility decrement value = 0.0084* HFS

For example, the utility decrement applied to hypoglycaemia associated with Met+DPP-4 is as follows (taken from 24 week MTC):

Number of symptomatic hypoglycaemia events = 0.049

Proportion severe hypoglycaemia = 0.00005

For a modelled individual, the probability of suffering a severe hypoglycaemic event is compared to a randomly sampled number. If a severe hypoglycaemia event is predicted to occur in that cycle then the value 'severeHypo' is set to 1, otherwise it is set to 0 (Table 12).

Table 12: Example of utility decrement calculations for severe hypoglycaemia

Scenario a: severeHypo=1 *(expected to be true in 0.05% of calculations for a modelled individual on this treatment)*	
HFS estimation	HFS = (5.8812*1) +(1.7727*ln(1+0.046)) + 0 HFS = 5.9609
EQ-5D decrement estimation	Utility decrement value = 0.0084* 5.9609 Utility decrement value = 0.05007
Scenario b: severeHypo=0 *(expected to be true in 99.95% of calculations for a modelled individual on this treatment)*	
HFS estimation	HFS = (5.8812*0) +(1.7727*ln(1+0.046)) + 0 HFS = 0.0797
EQ-5D decrement estimation	Utility decrement value = 0.0084* 0.0797 Utility decrement value = 0.00067

B29. Please clarify which comorbidities of T2DM Lane et al (2012) controlled for in their analyses?

Response:

Utility results were stratified according to the following factors: age, region, current BMI, sex, and weight preference (i.e. desire to lose weight, gain weight, or maintain

current weight). The potential for controlling for these factors was investigated but the final best fitting model selected only controlled for BMI category. Although the frequency of comorbidities was collected for the patient population (see table 13 below), controlling for these comorbidities was not pre-specified in the analysis plan for the study. This was because the comorbidities were not expected to have an impact on utilities associated with weight change (see B30 for further comment)

Table 13: Comorbidities for the type 2 diabetes patients in the Lane study

Comorbidity	Percentage of patients (N=100)
Hypertension	45%
Arthritis	23%
Serious mental disorders	19%
Other chronic conditions	19%
Heart disease	10%
Asthma	6%
Stroke	3%
COPD	2%

B30. Given the use of EQ-5D within the trial programme, please clarify whether any analysis of the trial EQ-5D data and weight changes has been undertaken? If it has please present the results of this. The ERG would be interested in these data even if limited to a comparison of the mean changes of the EQ-5D UK social tariff utility and the mean changes of weight/BMI by arm, with possibly a subgrouping based on patients who lost and who gained weight. If no analysis has been performed please provide a justification for this.

Response:

EQ-5D is a standardized and generic measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL group, 1990). It provides a simple descriptive profile and a single index value for health status and utilities (Brooks, 1996).

Study 12 was not designed to assess the relationship between EQ-5D and weight changes, and therefore, there were no pre-specified analysis of EQ-5D utilities and weight change in study 12.

However, one exploratory post-hoc analysis was performed in study 12, where norm data from six European countries have been used (Greiner et al, 2003). Please note that UK social tariff utility was not used in this analysis.

The association between actual weight reduction at week 24 and EQ-5D (Visual Analogue Scale and index) for dapagliflozin versus placebo was analyzed descriptively in study 12. The results indicate that there were no associations (Table 14).

These results come as no surprise as 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 and additionally study 12 was not designed and powered to measure a relation between EQ-5D utilities and weight change. The few responses in the placebo subgroup weight decrease of 5% or more is expected as very few patients in the placebo group lost that much weight. Therefore, the results in table 14 are difficult to interpret.

Table 14: Association between actual weight reduction at week 24 and EQ-5D (Visual Analogue Scale and index) for dapagliflozin versus placebo in study 12.

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Table 9

Association between actual weight reduction at week 24 (LOCF) (by category) and EQ-5D for DAPA vs Placebo
Including Data After Rescue
Full Analysis Set
PRO Population

	EQ-5D VAS (n, mean and SD)		EQ-5D index (n, mean and SD)	
	DAPA 10MG + MET (N=87)	PLA + MET (N=89)	DAPA 10MG + MET (N=87)	PLA + MET (N=89)
All subjects	n=87, 77.44 (15.207)	n=89, 78.31 (10.651)	n=87, 0.88 (0.171)	n=89, 0.87 (0.159)
Subset of subjects with body weight decrease >=3% of body weight	n=47, 78.60 (12.524)	n=20, 79.65 (11.573)	n=47, 0.88 (0.154)	n=20, 0.88 (0.191)
Subset of subjects with body weight decrease >=5% of body weight	n=27, 76.26 (14.440)	n=4, 83.00 (4.082)	n=27, 0.86 (0.168)	n=4, 1.00 (0.000)
Subset of subjects with no body weight decrease	n=40, 76.08 (17.928)	n=69, 77.93 (10.427)	n=40, 0.88 (0.190)	n=69, 0.87 (0.150)

The Lane et al (2012) study was specifically designed to evaluate utility changes related to weight change (4). Therefore, the analysis that was performed for ERG/NICE clarification question B27, table 3, utilizing Lane et al (2012) utility values with dapagliflozin study 12 patient level data is considered to be the more appropriate analysis to evaluate the change in utility associated with weight change by treatment arm.

Costs

B31. In the triple therapy addendum (p.20), please clarify the source of the costs reported in the add-on to metformin and SU: dapagliflozin versus DPP-4.

Response:

The table "*Add-on to metformin and SU: dapagliflozin versus DPP-4"* in the triple therapy addendum (p.20) is an outcome of the cost-effectiveness analysis. The source of these costs is located in the model within the sheet *"Results"* (cells O2:O30 to T2:T30). The user can replicate these results after conducting the base case analysis. Please note that the costs in the model are presented for the total cohort population that was sampled, whereas in the table presented in the triple therapy addendum, the costs are presented per patient.

The cost inputs that were applied for the triple therapy analyses are the same as for the add-on to MET and add-on to INS analyses, as presented in section 6 of the submission.

References

Bergenstal R, Forti A, Chiasson J-L, et al. Once Weekly Taspoglutide, a Human GLP-1 Analog, Is Superior to Sitagliptin in Improving Glycemic Control and Weight Loss in Patients with Type 2 Diabetes (T2D): Results from the T-emerge 4 Trial. ADA 70th Scientific Sessions , Abstract 58-OR. 2010

Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:2223-33.

Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48:1093-104.

DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. Diabet Med 2010;27:309-17.

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

The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208

Greiner W, Weijnen T, Nieuwenhuizen M, et al. (2003). A single European currency for EQ-5D health states. Results from a six country study. Eur J Health Econ; 4(3):222-231.

Kind, P, Hardman, G and Macran, S (1999). UK Population Norms for EQ-5D. The University of York, Centre for Health Economics. Discussion paper 172

Matthews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes, Obesity and Metabolism 2010;12:780-9.

Moses et al Poster 1094-P, ADA 2012, Philadelphia

Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial. Diabetes, Obesity and Metabolism 9 (2) (pp 194-205), 2007 Date of Publication: Mar 2007:

Owens et al. Efficacy and safety of lingagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24 week randomized study. Diabetic Medicine 2011;28 (11): 1352-1361

Rosenstock J, Einhorn D, Hershon K, et al. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin

therapy. Int J Clin Pract 2002;56:251-7Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72

Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012;344:e1553

Taskinen M, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study. Diabetes, Obesity and Metabolism 13 (1) (pp 65-74), 2011 Date of Publication: January 2011:January.