Meindert Boysen
Programme Director
Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

22nd February 2013

Dear Meindert,

Single Technology Appraisal – Appraisal Consultation Document: Dapagliflozin in combination therapy for the treating of type 2 diabetes

Bristol-Myers Squibb and AstraZeneca herewith provide a full response to the Appraisal Consultation Document for the dapagliflozin Single Technology Appraisal (ID427), issued to us on 25 January 2013. The ACD reflected a number of themes of crucial importance to patients with Type II diabetes:

- Clinical specialists confirmed that a new treatment providing an additional option would be valued by clinicians
- Changes in weight were recognised as an important outcome of diabetes treatment (e.g., one reason for the diminishing use of sulphonylureas is the weight gain associated with their use)
- The Committee understood the view of patient experts stating that dapagliflozin will provide a further treatment option for patients who are reluctant to start insulin, or who wish to avoid insulin therapy due to fear of hypoglycaemia
- Hypoglycaemia (and fear of hypoglycaemia) affects patients deeply, especially if driving, and can therefore be a highly significant factor in their lifestyle or livelihood

In addition, the committee sought a number of clarifications from us within the ACD, which we are very happy to provide. We have addressed all the concerns raised by the Committee in this response document and trust that our responses and additional analyses will reassure the Committee of the robustness of the results generated by the network meta-analyses and economic model. This additional work provides further support for the cost-effectiveness of dapagliflozin as an important therapeutic option for patients with Type 2 Diabetes.

To summarise:

- The Committee requested that we revise the programme coding for the network meta-analyses to that recommended by NICE. We have completed this in full. As is expected when using different methods, there are some minor differences between the analyses, but not such as to cause any meaningful changes to the conclusions and with a minimal impact on the results. These continue to show that dapagliflozin is a highly cost-effective intervention for this indication.
- The Committee asked us to re-consider the utility values associated with dapagliflozins's adverse events. We have thoroughly reviewed these and updated the economic model

accordingly. Again, in the additional analyses using the alternative utility values, dapagliflozin remains highly cost-effective against key comparators.

- The Committee wanted to see a number of revisions to the economic model, and to compare the model's output to that obtained from using the CORE model. We have adapted the model exactly as requested, and shown that the results obtained from the economic model are similar to those seen from the CORE model.

Having made all requested changes to the clinical evidence analyses, and to the economic model, we are able clearly to demonstrate that dapagliflozin is still highly cost-effective, with ICERs well below NICE's established cost-effectiveness thresholds. Dapagliflozin has demonstrated efficacy in glycaemic control, and, associated with its novel mechanism of action, has the key advantages of a low risk of hypoglycaemia and clear weight loss benefits compared to current treatments used in combination therapy. The evidence presented in our original submission and in this response document supports the use of dapagliflozin in clinical practice as dual therapy with metformin but also in combination with insulin later in the patient treatment pathway.

Our responses to the Appraisal Committee's questions, along with the additional analyses provided in this response document, should provide the necessary reassurance and evidence to allow a positive recommendation to be made for the use of dapagliflozin as an option in appropriate patients with type 2 diabetes.

We have divided our response into three parts:

In **Part 1** we have responded to each of the questions raised by the Appraisal Committee covering whether all the relevant evidence has been taken into account, whether the summaries of dapagliflozin's clinical and cost-effectiveness are reasonable interpretations of the evidence, whether the provisional recommendations are a sound and suitable basis for guidance to the NHS, and consideration of equity and equality issues.

In **Part 2** we have provided a summary response to each of the specific requests for clarifications and additional analyses within sections 1.2 to 1.4 of the ACD. In these summaries we have addressed each of the specific concerns of the Committee.

In **Part 3** we present detailed technical responses to each of the specific clarification and additional analyses questions in sections 1.2 to 1.4 of the ACD.

Please do not hesitate to contact me should you require any further information or clarification.

Regards,

Steven Lister

Senior Health Economist, Bristol-Myers Squibb Ltd.

Part 1: Bristol-Myers Squibb and AstraZeneca overall response to the ACD

In this part we provide a summary of our comments on the content of the ACD in the context of a preliminary minded no recommendation for dapagliflozin. Specifically, we address the general questions specified on section 1 the ACD.

1.1 Has all the relevant evidence been taken into account?

When the Appraisal Committee make their decision, they can be confident that all the relevant clinical and economic evidence have been provided throughout the process; as part of the original submission, response to the ERG and DSU reports, and in this document responding to the ACD. With these sources combined, and the additional analysis requested by NICE (including: the revised network meta-analysis, updates to the economic model, and a comparison with the CORE model), the Appraisal Committee should be reassured of the clinical and economic value of dapagliflozin used in combination with metformin or insulin for type 2 diabetes.

1.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The concerns raised by the committee have been carefully evaluated and addressed in this detailed response document. The Committee made a number of summary conclusions in the ACD relating to the clinical and cost effectiveness evidence.

Evidence for clinical effectiveneness (Section 4, page 51-52 of summary of Appraisal Committee key conclusions):

- "The Committee concluded that there was significant uncertainty about the validity of the results of the network meta-analyses"
- "The Committee concluded that, although dapagliflozin in dual therapy as an add-on to metformin therapy, and as add-on to insulin therapy, appeared to offer benefits in terms of weight loss and a similar effect on glycaemic control compared with other antidiabetic therapies, given their concerns these results should be reproduced in a revised network meta-analysis"

Evidence for cost-effectiveness (Section 4, page 55 of summary of Appraisal Committee key conclusions):

- "The ICERs for dapagliflozin in combination therapy compared with other antidiabetic drug therapies were all below £20,000 per QALY gained. The ERG's exploratory analyses, which included changes to the utility values associated with weight change and hypoglycaemic

events and the annual costs of pioglitazone and diabetic complications, resulted in higher ICERs, although they were all below £30,000 per QALY gained.

However, the Committee considered that the ICERs presented by both the manufacturers and the ERG were obtained from an economic model that could not be adequately replicated by the DSU. The Committee also noted that these ICERs were obtained from analyses that did not account for its concerns about the network meta-analysis or the utility values applied to changes in weight, hypoglycaemic events and urinary tract and genital infections"

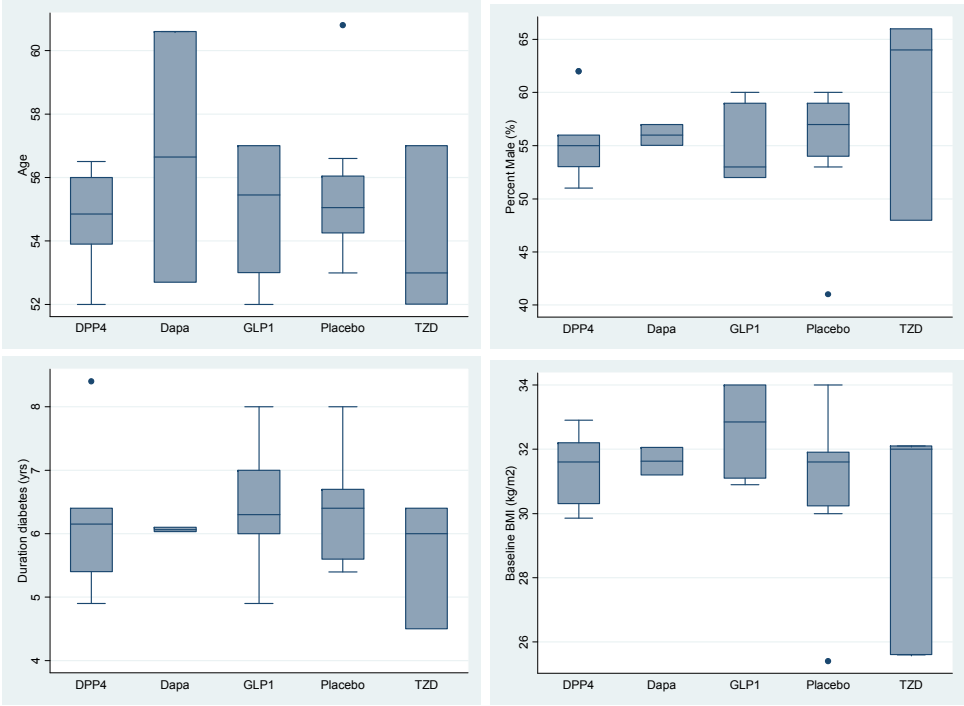
In response to these concerns the Appraisal Committee requests have been fully addressed by BMS/AZ. We have supplied additional evidence in this response document that should reassure the Committee of the robustness and validity of both the network meta analyses and the Dapagliflozin Cost-effectiveness model (DCEM). We have re-run the NMA using the DSU recommended code. We have also reconsidered the utility values relating to weight change and conducted analyses using the ERG preferred values. We have also addressed concerns relating to UTI/GI disutilities and the fear of hypoglycaemia disutility applied.

The combined outcome of these revisions has been that we have addressed all the major concerns of the Committee, and produced revised results that continue to demonstrate the cost-effectiveness of dapagliflozin in its use in different parts of the treatment pathway.

We have a number of specific comments on parts of the ACD not covered by our additional clarifications and analyses in Part 2 and 3 of the response. These are provided in the following table 1.1

Table 1.1 Additional comments on specific sections of the ACD

ACD section	Comment
3.33	***The ERG commented that it was not clear whether studies of between 30 and 46 weeks or greater than 58 weeks follow-up were identified in the review.*** No RCTs between 30 and 46 weeks or greater than 58 weeks were excluded from the NMA on grounds of duration of follow-up. The references for all RCTs identified in the systematic review are provided in Table 7 (metformin) and Table 8 (insulin) of the original submission: o <u>Metformin add-on:</u> ▪ No RCTs in the stratum labelled "Duration of study: 12 to 17.9 weeks" were included in the NMA. ▪ In the stratum labelled "Duration of study: >30 weeks", all RCTs involving add-on to metformin were included in a 52 week NMA. o <u>Insulin add-on:</u> ▪ As noted by the ERG, a protocol change was implemented to expand the range of the 24 week NMA from 18 to 30 weeks to 16 to 32 weeks; ▪ In the stratum labelled "Duration of study: 12 to 17.9 weeks", only the RCT by Rosenstock *et al*. (16 week RCT) was included in the NMA. All other RCTs in this stratum were excluded on the grounds of: ▪ Duration of follow-up of less than 16 weeks (Wilding 2009; Mudiliar 2010); • Comparator (Strowig 2002; Schiel 2007; Remplio 1998; Osei 1984; Lewitt 1989); or • Non-stable insulin (Asnani 2006 [also Mudiliar 2010]).
3.34	***The ERG commented that no attempt was made to adjust the analyses for any other variables.*** Prior to selecting adjustment factors for the analysis, both a visual assessment of heterogeneity was conducted among key characteristics, and clinical input as to the potential of effect modification was provided. Clinical and patient characteristics considered for model adjustment included: age, sex, duration of diabetes, baseline BMI, duration (leading to the decision to stratify by duration of follow-up), HbA1c (leading to the decision to adjust for HbA1c). Data were provided in tabular format in the submission (Appendix Tables 111 to 123), and key characteristics are presented graphically below (Figure 1.1):

ACD section	Comment
	 **Figure 1.1 Box plots, by class, among RCTs included in the 24 week metformin add-on network meta-analysis.** For any all potential sources of heterogeneity (e.g. outlying data points, wide variation within or across classes), we further investigated: the potential impact of that variable on relative effect sizes; correlation with HbA1c; and feasibility for adjusting the model. *Notes:* The RCT having the highest mean age also had the lowest mean baseline HbA1c; duration of diabetes was negatively correlated with baseline HbA1c; the RCT having the lowest baseline BMI was the only RCT comparing TZD with placebo and no clear impact of baseline BMI could be assessed within other drug classes. NMA models were not fit for all baseline variables to avoid spurious correlations, and to avoid using the same data for model selection and estimation. ***The ERG commented that the manufacturers' approach to model selection lacked transparency and that insufficient***

ACD section	Comment
	justification was provided about whether or not adjusted results were presented. The *a priori* selection was to use an adjusted, using treatment-specific coefficients. No network had sufficient data for estimating treatment-specific coefficients (requires approximately 10 data points per comparator); When insufficient evidence was available to reliably estimate a treatment-specific coefficient, then a model using a common coefficient for all treatments vs. the reference was fit. In the 52 week network, the reference treatment was an active control (sulphonylureas) and the assumption that a common coefficient could be applied for all treatments vs. sulphonulreas was less tenable than in networks involving placebo as the common treatment. When insufficient evidence was available to reliably estimate a common coefficient, a model having no coefficient was selected. o 24 week metformin network: ▪ The random effects coefficient was estimated to be -0.30 (95% CrI: -0.62 to 0.01), and was included in the final selected model. o 52 week metformin network: ▪ The random effects coefficient was estimated to be 0.02% (95% CrI: -0.23 to 0.24). The magnitude of this coefficient, relative to the uncertainty, led to the decision not to include this adjustment in the final selected model. o 24 week insulin network: ▪ The fixed effect coefficient was estimated to be -5.87% (95% CrI: -17.14 to 6.56). The uncertainty around this coefficient led to the decision not to include this adjustment in the final selected model. ▪ *Note*: this model was fit using only four RCTs for three comparator agents. In selecting between the fixed and random effects models, the *a priori* choice was the random effects model, and was selected, unless: i) the fixed effect model offered <u>better</u> model fit according to the DIC (defined as more than 3 units less than the random effects model); or ii) the posterior distribution of the between-studies variance was similar to the prior distribution, indicating that there was insufficient evidence to reliably estimate the between-studies variance (due to a sparse network).
3.36	It states "… Overall, the ERG considered that the HbA1c threshold levels for switching treatment applied in the model reduced its relevance to UK clinical practice." Please see response xx in Part 2 for further clarification.
3.37	It states "…However, the ERG was unable to validate the adverse event and discontinuation data provided for the dual therapy analyses." AstraZeneca and Bristol-Myers Squibb have already provided additional information to address this perceived gap in the Manufacturer's Submission in the response to ERG's request for further clarification
3.39	It states "…The ERG considered that these alternative utility values, which were applied in the manufacturers' scenario analyses, to be more reasonable." However, in Section 3.28 they acknowledge that we had already presented a scenario in which the Bagust utility (0.0061) was used. It should also be acknowledged here.

ACD section	Comment
4.13	It states "...It noted that the most common adverse events were urinary tract and genital infections." Two sentences later it states "However, the Committee heard from the manufacturers that the recurrence of these events in the clinical trials was low." The focus has been on these AEs specifically because they are related to the mechanism of action, were specifically collected within the trials, and showed greater differences between study arms, but not because they were most frequent. The current Forxiga SmPC states that 'the most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%)'.
4.19	It states "The Committee considered that applying the treatment effect on weight loss gradually over the first year would have been more plausible." We believe it would be more plausible for the Committee to consider the speed of weight loss as observed in dapagliflozin's study programme.
4.19	It states "It considered that it was more plausible that any initial differences in weight change between treatments would converge over time." Our interpretation of this statement is that the Committee believe that patients who receive dapagliflozin will experience greater weight gain that those patients who receive alternatives, following a treatment switch. This statement does not seem plausible and requires revisiting before being updated into the FAD

1.3 Are the provisional recommendations a sound and a suitable basis for guidance to the NHS?

We note that the Appraisal Committee are minded not to recommend dapagliflozin, but have requested the additional clarifications in order to determine a final recommendation. We have provided all the additional analyses requested by NICE within the revised economic model as well as provided clarifications to concerns outlined in the ACD, and this has shown dapagliflozin to be a cost-effective option in combination with oral anti-diabetic drugs, specifically metformin, and in combination with insulin for patients with type 2 diabetes at different points in the patient treatment pathway:

- The ICER for dapagliflozin in dual therapy in combination with metformin (after revisions requested by the NICE Appraisal Committee, including the requested ERG changes to utilities for weight change and costs of diabetes without complications) is £7.7k/QALY vs SU and £3.3k vs DPP-4. Even after the revisions requested dapagliflozin has demonstrated cost-effectiveness against these comparators as an add-on to metformin.

- The cost-effectiveness results for dapagliflozin in combination with insulin after revisions requested by the NICE Appraisal Committee shows that it dominates DPP-4. Hence, it can be concluded that dapagliflozin represents a cost-effective use of NHS resources as add-on therapy to insulin.

- The revised analysis performed for the use of dapagliflozin in triple therapy (in addition to metformin and SU) has also shown it to dominate each relevant comparator (DPP-4, TZD and GLP-1).

A summary of the revised DCEM analyses and results are presented in Part 2 of this response (2.3.2), with full disaggregated results in part 3 (3.2.9).

By providing the clarifications to concerns raised by the DSU, and additional analyses based on revisions to the DCEM, and by demonstrating the reproducibility of the results using the CORE model, we have reduced the level of uncertainty concerning the ICERs reported. The results/conclusions from the DCEM and the CORE Model continues to support the cost-effectiveness of dapagliflozin and provides added assurance that dapagliflozin remains within acceptable bounds of cost-effectiveness with sufficient certainty in appropriate positions within type 2 diabetes treatment pathway. Hence, the ICER results we have generated and reported in this response provide a strong basis for a positive recommendation by NICE for dapagliflozin in final NICE guidance.

1.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

There are no particular aspects of the current recommendation or of a potential positive recommendation for dapagliflozin that are likely to result in unlawful discrimination issues against any group of people.

Part 2: Summary response to the questions in section 1.2 – 1.4 of the ACD

2.1 Overview

The provisional recommendation in section 1.1 of the ACD is that the committee is minded not to recommend dapagliflozin in combination therapy for treating type 2 diabetes, but requires further information from the manufacturer relating to a number of requests as presented in sections 1.2, 1.3 and 1.4 of the ACD.

The additional requests can be grouped into two components:

I. Clarification requests in ACD section 1.2**:** requesting further details about methods and data inputs in the economic model and network meta-analysis (NMA).

II. Additional and revised analyses using the economic model in ACD section 1.3, and also reproduced using the CORE model in ACD section 1.4.

Bristol-Myers Squib and AstraZeneca (BMS/AZ) have addressed all the requests and questions raised in sections 1.2 to 1.4 of the ACD in some depth. Our detailed response to each specific bulleted request is provided in Part 3 of this response. However, in order for the Committee to obtain the key findings from the clarification requests and additional analyses, in Part 2 below we provide a summary of our responses, together with an interpretation of the implications for the NICE appraisal of the clinical and cost-effectiveness of dapagliflozin as add-on to metformin, and as add-on to insulin therapy. Hence, this will enable an informed final recommendation by the NICE Appraisal Committee for dapagliflozin in combination therapy for treating type 2 diabetes. More detailed information on the responses to each request is provided in Part 3 of this response.

2.2 Summary of response to clarification requests (Section 1.2 ACD)

The clarification requests in section 1.2 of the ACD covered the following requests, with our summary response:

A response to the Decision Support Unit (DSU report) on the Dapagliflozin Cost-Effectiveness Model (DCEM), including explanations about the reproducibility of the model and the stability of the results (bullet 1, section 1.2 ACD).

BMS/AZ Response:

- We have explored the concerns of the DSU relating to the reproducibility of results and why the DCEM was not producing stable results with 100 runs. We have however been able to replicate the results provided in the submission, and have produced stable results with 1000

simulations, which is the standard number of runs required by such models to achieve convergence. Further details are provided in Part 3.1.1.

- The DSU were concerned that the model using mean values did not produce the same results to the PSA results when the PSA parameter values are set to their mean values. We have re-run the analysis and produced identical results. We have re-checked this to try and understand why the DSU were finding differences, and have made some suggestions in the detailed response in part 3 (section 3.1.1).
- We have also addressed other concerns of the DSU. such as relating to implementation of the UKPDS risk factor progression equations, the implementation of UKPDS equations relating to mortality, discrepancies with sampled variables for the PSA drawn from the gamma and beta distributions, a minor error with how event probabilities were being estimated, and the handling of all-cause mortality in the model. Although we have modelled appropriately and in accordance with other major models in type 2 diabetes, we have made a number of small structural changes to the DCEM to address these DSU concerns. Details of the structural changes can be found in 3.1.1.
- In summary, by addressing the concerns of the DSU, we have demonstrated the robustness and reliability of the DCEM so that the DSU and NICE can have confidence in the results produced by the model. All the above checks and structural changes have had only a small impact on the cost-effectiveness results, and do not change the conclusions that dapagliflozin in combination therapy has a high probability of being cost-effective at £20,000 per QALY gained (as noted also in ACD section 4.26). This is also borne out by the re-analysis conducted at the Committees request using the revised model, which is summarised in part 2.3 below.

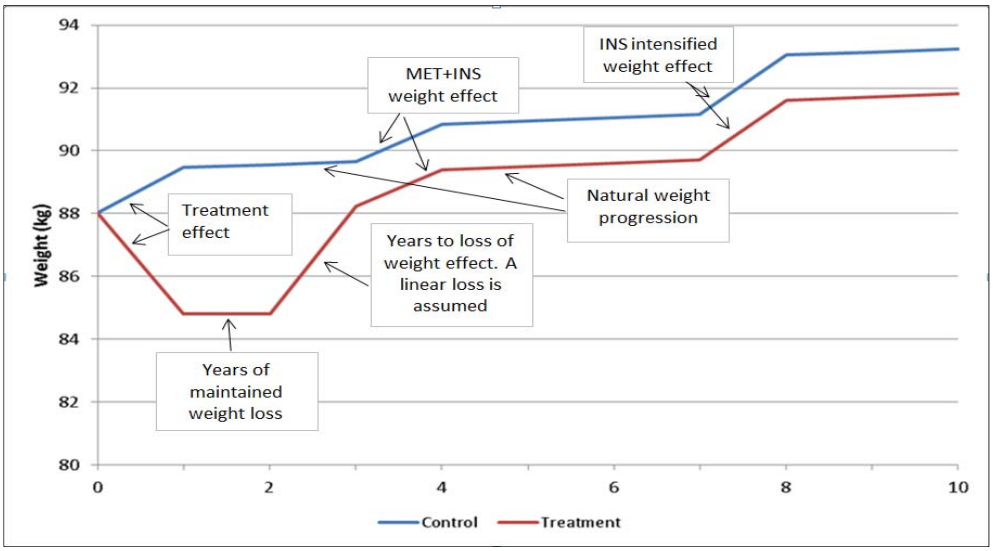
Further explanation on how changes in weight are modelled over time for different treatments, and justification for differences assumed between lines of therapy (bullet 2, section 1.2 ACD).

BMS/AZ Response:

- For dapagliflozin, the 1 year treatment effect on weight loss derived from the dapagliflozin clinical trials is applied in the model, in year 2 it is assumed the weight loss is maintained (based on 2 year trial follow-up data from trials in add-on to metformin (Study Code: D1690C00004 - Del Prato, 2011), and add-on to insulin (Study Code D1690C00006), and then weight is regained fully in a linear manner over the time to next treatment switch. Following that weight increases in the model at a natural progression rate of 0.1kg per year. The same modelling approach is used for comparator treatments that are associated with some weight loss (e.g. DPP-4's), despite there not being longer term data showing durable weight loss.
- For comparator treatments that are associated with weight gain (TZD, SU) the weight increase is assumed for 1 year, followed by natural weight progression.

- After treatment switch the weight effect of the next line of treatment is modelled accordingly. Figure 2.2.1 presents an overview of how weight change is modelled

Figure 2.2.1 Illustration of dynamic body weight profile implemented in the model; the scenario illustrates MET+dapagliflozin vs MET+SU→MET+INS→INS



x axis = years

- Weight loss is a key clinical benefit associated with dapagliflozin in patients with type 2 diabetes. However, our assumptions modelling weight change have been conservative and have not been overly favourable to dapagliflozin for the following reasons:
    - The two year data showing the durability of weight loss supports the assumptions for weight loss effect in the model.
    - However, we assume that weight loss is regained after this period which is conservative especially as there is now data becoming available from the phase III study versus SU showing that weight is maintained over 4 years on dapagliflozin + MET (see Appendix 3).
    - A more extreme scenario would be that the weight of patients on dapagliflozin and comparator treatments such as SU and TZD converge at year 3. However, this would imply that not only do patients on dapagliflozin gain weight, but those on SU/TZD could lose weight by year 3, which seems implausible and counter to the data now coming out for the weight loss durability of dapagliflozin.

- BMS/AZ would contend that the way in which weight change has been modelled is appropriate and for the reasons specified above has not produced favourable outcomes for dapagliflozin. Hence, the economic analyses performed and results generated using the approach adopted to modelling weight change provide an appropriate and robust base case. Full details of the modelling approaches adopted in the submission for weight change are described in part 3 of this response (3.1.2).

- In the revised economic analysis presented below we present illustrative scenarios in which weight is maintained with dapagliflozin for 4 years in line with the emerging evidence.

Further clarification of the sources of the treatment-related adverse events and discontinuation rates included in the economic model (bullet 3, section 1.2 ACD).

BMS/AZ Response:

- It was not possible to meta-analyse adverse events and discontinuation rates from the NMA's for add-on to metformin and add-on to insulin. The data was sourced from trials covered by the NMA's – the specific sources for dapagliflozin and the comparators are fully explained in part 3.1.3 of this response.
- The rates used in the model are plausible for the base case, but are not key drivers of the cost-effectiveness results for dapagliflozin.

Further clarification of how the effect of treatment on risk factors evolves in the economic model and the impact of this on how long these effects are maintained in the model (bullet 4, section 1.2 ACD).

BMS/AZ Response:

- When modelling the impact of diabetes treatments, strict interpretation of the original risk equations is virtually impossible due to a lack of full information on post diagnosis risk factors, hence in the original DCEM post treatment HbA1c, SBP and TC;HDL were used. This is consistent with other validated type 2 diabetes models.
- For the revised analysis requested by the NICE Appraisal Committee we have also modified the model to use pre-treatment baseline risk factor values as suggested in the DSU report, which has not had a significant impact on the risk factor progression results (see part 3.1.4 for the graphical presentation of impact on risk factor progression).

Further explanation of why variations in baseline characteristics and risk factors of simulated patients were not accounted for in the model (bullet 5, section 1.2 ACD).

BMS/AZ Response:

- When running the model in 'PSA' mode, the model does account for variations in baseline characteristics and risk factors as these parameters are subject to sampling (i.e. in order to quantify 2nd order uncertainty). The misunderstanding may have arisen as the model can

also be run in 'mean values' mode, where there is no parameter sampling (i.e. only 1st order uncertainty is addressed in this mode).

- Further details are provided in part 3.1.5.

A review of utility values associated with urinary tract and genital infections, with further justification for the values chosen (bullet 6, section 1.2 ACD).

BMS/AZ Response:

- A focused literature review was performed and we identified five studies, including one recently published systematic review that reported utility for UTI's, but none for GI's.
- Hence, we have used the range of UTI values identified and also applied these for GI's in the revised economic analysis reported below (part 2.3).
- Further details are provided in part 3.1.6

2.3 Additional analyses requests (Section 1.3 and 1.4 ACD)

2.3.1 Requests in section 1.3 of the ACD

In section 1.3 of the ACD the Appraisal Committee have requested a number of additional analyses, as follows:

Revised Network meta-analyses (NMA) for dual therapy and add-on to insulin therapy (bullet 1, section 1.3 ACD).

BMS/AZ response:

- The NMAs have been re-run in full using programme code reported in the DSU Technical Support Document (TSD 2), and in a validation exercise these have been compared with the results produced using the original code. Using the DSU code compared to that reported in the original submission has shown small numerical differences in results and no changes to the conclusions. We have also performed a further validation exercise to compare the original code with the DSU recommended code using an independent data set, which produces similar results irrespective of the code used. Full details of the validation exercise completed are presented in 3.2.1 and are available in Appendix 4. The revised NMAs, using the DSU code, have been incorporated into the revised economic analyses, and this does not change the results or conclusions that dapagliflozin in combination with other key therapies is cost-effective (see table 2.3.2.1).

The Appraisal Committee have also requested a number of other revisions to the economic analyses:

For dual therapy cost-effectiveness analyses, use the same baseline characteristics and risk factors for each analysis (bullet 2, section 1.3 ACD).

BMS/AZ response:

- We have re-run the analysis using the same baseline characteristics and risk factors, as requested. In the original submission, data were taken from the head-to-head RCT for the comparison versus SU, and from the NMA for all other comparators, resulting in two sets of baseline characteristics and risk factors. To use only one set of baseline characteristics and risk factors, we must obtain estimates of treatment effect versus all comparators from one source. Hence, this has been achieved by using data from the 52 week NMA, which has the added benefit of providing the longest follow-up
- Combined with the revised NMA and other revisions requested (switch threshold, DSU structural revisions – see below) the resulting ICERs show that dapagliflozin in dual therapy as an add-on to metformin is highly cost-effective against key comparators (see table 2.3.2.1 below).

For all cost-effectiveness analyses, apply the same baseline risk factors for both treatment groups rather than the baseline value minus the treatment-specific effect (bullet 3, section 1.3 ACD).

BMS/AZ response:

- The revised analysis has been based on applying the same baseline risk factors for both treatment groups, drawn from the relevant NMA for each analysis.
- Combined with the revised NMA and other revisions requested (switch threshold, DSU structural revisions – see below) the resulting ICERs clearly demonstrate that dapagliflozin in dual therapy and add-on to insulin is highly cost-effective against each key comparator considered (see table 2.3.2.1 below).
- Full details are reported in part 3.2.3

For all cost-effectiveness analyses, for the decision to switch or intensify treatment in the model should be based on HbA1c levels that are currently recommended in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87) rather than from the clinical trials included in the submission (i.e. 7.5%) (bullet 4, section 1.3 ACD).

BMS/AZ response:

- A switch threshold of 7.5% has been applied as requested by the Appraisal Committee. This has been applied in the revised dual therapy economic analyses.
- We draw to the attention of the Committee that this threshold may not be reflective of clinical practice in the UK. There is evidence, which we discuss further in Part 3, that as patients only return periodically to their clinician for review their HbA1c levels have increased to higher levels than 7.5% before a switch is initiated.
- In most comparisons applying a switch threshold of 7.5% results in improved ICERs for dapagliflozin as patients spend less time on treatment and the reduction of costs outweighs the loss of QALYs, so improving the ICERs.
- Hence, for dual therapy we perform a scenario analysis using a higher switch threshold of 8.04% in addition to the requested 7.5% threshold . For triple and add-on to insulin therapy where the likelihood is that a switch will only occur at higher HbA1c levels we apply a switch threshold of 8.61% and 9.04% respectively as a base case, and for add-on to insulin therapy explore the impact of 7.5% in scenario analysis.
- Full details are reported in Part 3.2.4.

For the triple therapy cost-effectiveness analyses, the sequence of treatments should be revised so that the starting treatment is triple therapy rather than dual therapy (bullet 5, section 1.3 ACD).

BMS/AZ response:

- We have revised the triple therapy analysis to start with triple therapy.
- This has not had a major impact on the analysis. In the revised analysis incorporating other structural changes to the model, dapagliflozin is shown to be highly cost-effective versus the comparators considered (see part 2.3.2 below)

The changes proposed by the Evidence Review Group (bullet 6, section 1.3 ACD):

- ***reducing the loss in QALYs associated with hypoglycaemia to −0.012 for a severe event and −0.004 for a symptomatic event.***
- ***reducing the annual cost of pioglitazone to £112.18***
- ***including an annual cost of £483 for people not experiencing diabetic complications and***
- ***using utility values associated with weight change of ±0.0061 per unit of BMI.***

BMS/AZ response:

- The above analyses have been run separately and, with the exception of the QALY loss associated with hypoglycaemia, combined to present the impact on the ICER results for dual therapy and add-on to insulin therapy using the revised DCEM.

- We have run the scenario with hypoglycaemia disutilities and although it has been misinterpreted how this data has been derived, we have correctly applied the values in the original model (see part 3.2.6 for a full explanation).
- The implication of applying the ERG revisions using the revised DCEM is that dapagliflozin remains highly cost-effective in dual therapy and add-on to insulin therapy against each key comparator, with the exception of pioglitazone as a comparator in dual therapy. In each case the ICER with the combined ERG changes is below £20,000 for dual therapy vs DPP-4 and vs SU, and in add-on to insulin therapy vs DPP-4. The driver for weaker cost-effectiveness vs TZD in dual therapy is due to the lower generic price for pioglitazone. However, our evidence is that the most used drugs for dual therapy in clinical practice are SUs and the DPP-4's against which dapagliflozin remains highly cost-effective (see table 2.3.2.1).

Changes to the model as a result of responding to the DSU report and the revised network meta-analyses (bullet 7, section 1.3 ACD).

BMS/AZ response:

- We have revised the NMA and model to reflect the requests from the Appraisal Committee and the DSU, and presented the evidence in this response. The structural changes made to the DCEM, and the revised NMA, do not impact the cost-effectiveness findings for dapagliflozin, and provide support for the conclusion that dapagliflozin is cost-effective against key comparators currently used in different stages of the treatment pathway (see part 2.3.2 below).
- However, the structural changes we have made to the DCEM as reported above in response to DSU concerns, and the revised NMA using the DSU code has not impacted on the cost-effectiveness findings for dapagliflozin and provide support for the conclusion that dapagliflozin is cost-effective against key comparators currently used in different stages of the treatment pathway (see part 2.3.2)
- Full details are provided in part 3.2.7

Analyses using the upper and lower estimates of utility values associated with urinary tract and genital infections identified in the review requested in 1.2 (bullet 8, section 1.3 ACD).

BMS/AZ response:

- We have applied the UTI/GI disutility range identified after a literature search, and this has little impact on the ICERs as presented in tables 2.3.2.1 and 2.3.2.2 below.

2.3.2 Revised model ICERs

Based on the changes above we have re-run the DCEM in order to generate revised ICER results for dapagliflozin in dual therapy, triple therapy, and as an add-on to insulin as requested. The topline ICER results are presented below for each comparison, and show that with the revised analysis dapagliflozin is a cost-effective treatment option for patients with type 2 diabetes in different parts of the treatment pathway. The detailed disaggregated results are presented in part 3 of this response.

Revised dual therapy ICERs

The results for the dual therapy comparisons are presented in Table 2.3.2.1. The Appraisal Committee's requested analyses are presented, along with the results of additional sensitivity analyses pertaining to weight regain and maintenance to 4 years based on new data for this duration for dapagliflozin (see parts 2.1 above, and part 3.2.9 for full results).

Table 2.3.2.1: Summary of ICERs from the revised DCEM and additional analyses requested

	ICERs (Cost/QALY)		
	Dapa+MET vs SU+MET	**Dapa+MET vs DPP-4+MET**	**Dapa+MET vs TZD+MET**
Original submission ICERs	**£2,689**	**Dominant**	**Dominant**
Revised ICER (A) with: • DSU/NMA revisions • 52 week NMA results • HBbA1c switch threshold of 7.5% • 2 years weight maintenance • Same baseline characteristics and risk factors	**£1,498**	**£689**	**£5,342**
A+ERG change (i): revised utilities for hypoglycaemia	£1,537	£690	£5,527
A+ERG change (ii): Reducing cost of pioglitazone	N/A	N/A	£26,083
A+ERG change (iii): Cost for diabetes w/o complications	£1,495	£680	£5,306
A+ERG change (iv):utilities of +/- 0.0061 for BMI change	£7,748	£3,378	£15,919
Combination of (ii), (iii) and (iv)* (B)	**£7,735**	**£3,337**	**£77,615**
Scenario analysis around ICER (A):			
on UTI/GI disutilities: -0.0104 to both UTI and GI -0.000657 to both UTI and GI	 £1,503 £1,496	 £696 £687	 £6,021 £4,865
on switch threshold:	£17,219	£4,138	£5,070

8.04%**			

*The revised utilities for hypoglycaemia are not applied in the combined scenario as these were not incorrectly applied in the original analysis (see part 3 for full explanation)
** based on 52 week NMA baseline value

As can be seen from Table 2.3.2.1, the estimated ICERs are well below the threshold of £20,000, even after the ERG requested changes for the comparison with SU (£7.7k/QALY) and with DPP-4 (£3.3k/QALY), the primary comparators based on current practice for add-on to metformin. The recent lower price for pioglitazone that was not available at the time of our submission increases the ICER for this comparison. The ICER results vs SU are quite sensitive to assuming a higher switch threshold, although this is still below £20k/QALY (Table 2.1).

Revised add-on to insulin ICERs

The results for the add-on to insulin comparison is presented in Table 2.3.2.2. As with dual therapy the Appraisal Committee requested analyses are presented, along with the results of additional sensitivity analyses pertaining to weight maintenance to 4 years based on new data for this duration for dapagliflozin (see parts 2.1 above, and part 3.2.9 for full results).

Table 2.3.2.2: Summary of dual therapy ICERs from the revised DCEM and additional analyses requested

	ICERs
	Dapa+INS vs DPP-4+INS
Original submission ICERs	**£4,268**
Revised ICER (A) with: • **DSU/NMA revisions** • **24 week NMA results** • **HBbA1c switch threshold of 9.04%*** • **1 year weight maintenance**	**£2,509**
A+ERG change (i): revised utilities for hypoglycaemia	£3,065
A+ERG change (ii):cost for diabetes w/o complications	£2,473
A+ERG change (iv):utilities of +/-0.0061 for BMI change	£5,717
Combination of (ii), (iii) and (iv) (B)**	£5,634
Scenario analysis around ICER (A):	
on UTI/GI disutilities: -0.0104 to both UTI and GI -0.000657 to both UTI and GI	 £2,573 £2,457
on switch threshold: 7.5% based on CG87	Dapagliflozin dominant
Assuming maintenance of weight benefit to 4 years	£1,097

* based on 24 week NMA baseline value as this is more representative of clinical practice for add-on to insulin therapy than 7.5% cited in CG87
**The revised utilities for hypoglycaemia are not applied in the combined scenario as these were not incorrectly applied in the original analysis (see part 3 for full explanation)

Even with the revised analysis dapagliflozin and using a HbA1c switch threshold of 9.04% (based on likely clinical practice - see part 3.2.4) is highly cost-effective compared to DPP-4 as an add-on therapy to insulin at an ICER of £5.7k/QALY gained. Using the requested 7.5% switch threshold improves the cost-effectiveness further (so that dapagliflozin becomes 'dominant' in this scenario) The results are not sensitive to varying the disutilities associated with UTI/GI based on the range identified in the literature (see part 3.2.8). Full results are presented in part 3.2.9 of this response.

Revised triple therapy ICERs

The results from the re-analysis of the triple therapy evaluation using the appropriate sequencing starting with triple therapy as described in (part 3.2.5), incorporating model structural changes and assuming an HbA1c switch threshold of 8.61% (based on ??) produced the following results:

- Dapagliflozin in combination with Metformin and SU is dominant compared with MET+SU + DPP-4, TZD or GLP-1.

Full results are presented in part 3.2.9

2.3.3 Validation against the CORE model (section 1.4 of ACD)

The Appraisal Committee also made the following request:

A comparison should be provided of the results requested in 1.3 with the results that would have been obtained from using the CORE model for all relevant comparisons in dual therapy, insulin add-on therapy and triple therapy, and an explanation of any reported differences (bullet 1, section 1.4 ACD).

BMS/AZ response:

- A comparison of cost-effectiveness results has been performed using both the CORE model and the original base case settings of the DCEM.
- This demonstrates that the ICERs generated by the DCEM for all dual therapy and add-on to insulin comparisons are consistent with those generated by the CORE model (Table 2.3). Using the results from the DCEM based on additional DSU recommended structural changes also demonstrates consistency in the two sets of results (Table 2.3).

Table 2.3 Comparison of dapagliflozin ICERs generated by the DCEM and CORE models (dual therapy and add-on to insulin therapy)

Base case comparison	CORE model ICER	DCEM ICER (original base case)	DCEM (with all structural revisions based on DSU recommendations)**
Dual therapy*			
Dapa+MET vs SU+MET	£8,879	£1,831	£1,498

Dapa+MET vs DPP-4+MET	£2,014	£599	£689
Dapa+MET vs TZD+MET	£7,093	£137	£26,083
Add-on to insulin			
Dapa+INS vs DPP-4+INS	Dapagliflozin dominates	£551	£2,509**

*Using 52 week NMA and 7.5% switch threshold

**ICERS reported above in Tables 2.1 and 2.2

- To explain the differences in ICERs generated by the DCEM and CORE models in Table 2.3, while there is consistency in the prediction of incremental costs by across the two models, the original DCEM consistently predicts higher incremental QALY gains (see Part 3.3 of this response). This is primarily associated with the differences in assumptions for weight change related utilities in the original DCEM and CORE. When utility associated with weight change is set in the DCEM to be the same as in CORE (±0.0061), the DCEM predicts lower incremental QALY gains (see Figure 3.3.1 in part 3).
- It can be seen in Table 2.3 that the ICER results using either model are well below accepted thresholds of cost-effectiveness of £30,000/QALY gained (and all but one are well below the threshold of £20,000/QALY gained), and so the conclusion still holds that dapagliflozin is a cost-effective treatment option for patients with type 2 diabetes as an add-on to metformin or as an add-on to insulin therapy.
- There is limited clinical data currently to enable a meaningful comparison of the results from the CORE and DCEM model for triple therapy. Consequently there are differences in the ICERs predicted by each model. Further details are provided in part 3.3.

In conclusion, the CORE validation exercise has further supported the robustness and reliability of the DCEM, as any differences in results can be largely accounted for by differences in the input variables (primarily weight change utility) used in the original models.

We are not surprised by the findings from this validation exercise as the DCEM model structure has previously been validated at the Mount Hood challenge [Mount Hood 4 Modelling Group], and the changes made for this appraisal based on DSU comments are relatively small and have reinforced the structural validity of the model for determining the cost-effectiveness of type 2 diabetes interventions.

2.4 Conclusions

After taking account of DSU and The Appraisal Committee requests for revisions to the NMA and economic analysis the conclusion remains that dapagliflozin is highly cost-effective with ICERs below £20,000/QALY most revised comparisons performed. We would not expect any remaining uncertainty

for example regarding utility values associated with weight change, or duration of weight loss benefit to alter this conclusion.

We have provided the committee all requested assistance and more to aid in its task of interrogating the evidence provided. We express confidence that our analyses and responses will enable the committee to make a positive recommendation for dapagliflozin.

Part 3: Detailed response to additional requests from NICE

3.1 Clarification requests (section 1.2 ACD):

3.1.1 Clarification request 1 (Section 1.2 ACD, bullet 1): *Response to the report produced by the Decision Support Unit (DSU). This should include explanations about the reproducibility of the model and the stability of the results.*

Below we provide a detailed response to the concerns raised and further explanations requested in the DSU report.

Reproducibility of the model

The DSU identified three key questions regarding the 'mean parameter value' dynamic link library Diabetes2.DLL and the probabilistic sensitivity analysis (PSA) library Diab2Sampling.dll.

a. Why the supplied source code, when compiled by the DSU, provided different results from the results provided in the original submission?
b. Why the QALY values did not stabilize within 100 runs?
c. Why the results from the model using mean values did not produce the comparable results to the PSA results when all parameter values in the PSA are set to their mean values?

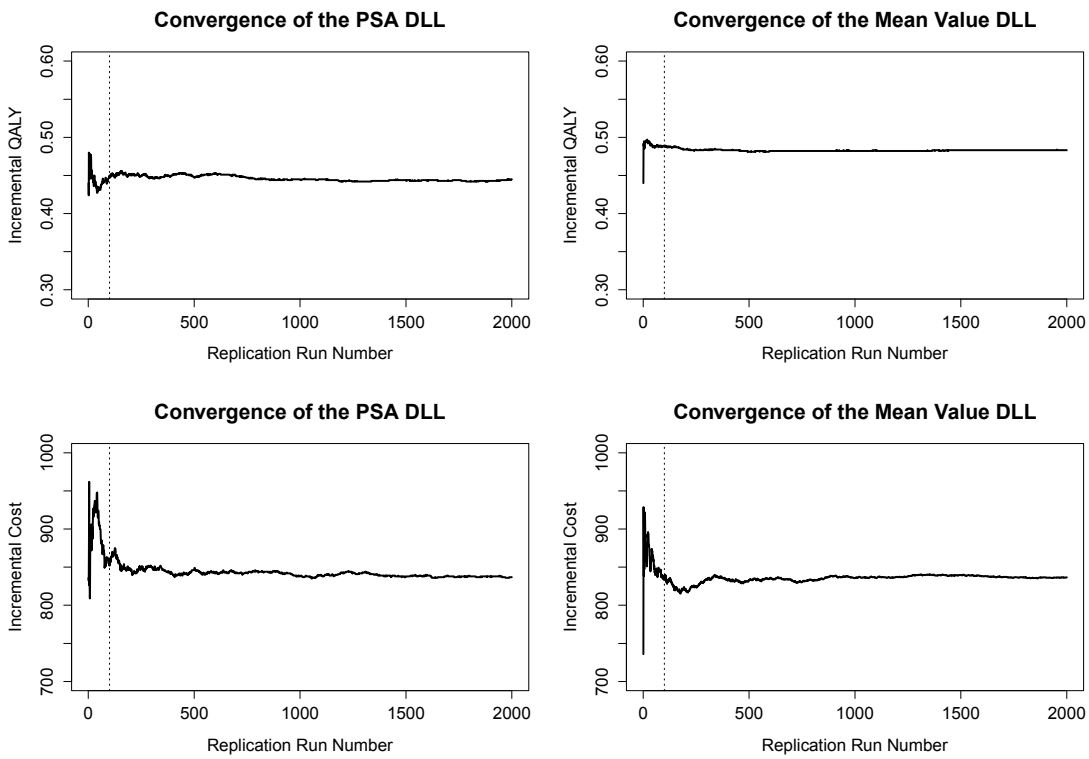
Compiling the source code

We were unable to reproduce the DSU finding. We would suggest that this is most likely due to the Excel interface that the DSU were working with, having slightly different settings to the version used in the submission (DCEM version 2.2), rather than the compiled dll file differing in any way. It is worth noting that the differences observed were relatively small (difference in costs £37 and difference in QALYs 0.008). It is quite conceivable that this difference is due to stochastic variability; as detailed below, model convergence typically requires more than 100 replications, and as stated below the economic model requires around 1000 simulation replications (runs) to achieve convergence.

Model stability and convergence

The analysis undertaken for the DSU report demonstrated that for metformin plus dapagliflozin versus metformin plus sulphonylurea scenario the predicted incremental QALYs did not appear to stabilize (converge) after 100 simulation runs (replications). The DSU were not able to identify why the incremental QALYs did not converge. Figure X1 illustrates the results obtained from the original model (prior to any ACD related changes requested) for both mean values and PSA dynamic link libraries for incremental QALYs and incremental costs. The vertical dotted line in each graph illustrates the point at which 100 simulation runs have been completed. These plots demonstrate that the model requires around 1000 simulation replications (runs) to converge. The actual number is dependent on whether the model is run using mean values or with sampled input values via the PSA module. It is also dependent on the size of the treatment effect being modelled. The smaller the treatment effect the greater the number of replications required. It is noteworthy that this is a fundamental feature of patient level stochastic simulation models. In the re-analysis submitted to NICE the updated economic model uses 1000 replications and the rate of convergence of the updated model is similar to the previous version.

Figure 3.1.1.1: Convergence of the DCEM to a steady state solution using Diabetes2.DLL (mean values) and Diab2Sampling.dll (PSA) comparing metformin plus dapagliflozin to metformin plus sulphonylurea over a 40-year time horizon using the version of the model evaluated by the DSU. Vertical line (at replication run number =100) shows the point at which DSU assessed model convergence.



Comparability of mean values DLL(Diabetes2) and PSA (Diab2Sampling) DLL

The DSU noted that the PSA DLL and mean values DLL should produce identical results when the PSA analysis is run without sampling variation. Appendix 3 Figures A4 and A5 of the DSU report showed plots of the incremental QALYs and costs that differed between the two dll modules. The DSU commented that they would expect the results to be similar but not identical, yet the results they obtained demonstrated that the two models they tested were not equivalent.

Shown below (Table 3.1.1.1) are the results obtained when running the same dll files as evaluated by the DSU for 1000 patients with 10 simulation replications using the mean values dll and PSA dll with no sampling selected in the PSA worksheet. These results are identical. One potential reason for the discrepancy identified in the DSU analysis is that the DSU made changes to the 'PSA map' worksheet. This worksheet is a hidden worksheet and the PSA within the DCEM should be controlled from the 'PSA' worksheet; it is therefore possible that the PSA scenario ran by the DSU contained some sampling variation and this accounts for their observation.

Table 3.1.1.1: Comparison of incremental QALYs and costs when using the 'run model with mean values' and 'run probabilistic sensitivity analysis' with no parameters sampled

	Mean Values (Diabetes2.dll	PSA Values (Diab2Sampling.dll)
Cost	£2,004 (1424.74 to 2582.89)	£2,004 (1424.74 to 2582.89)
Benefit	0.489 (0.385 to 0.593)	0.489 (0.385 to 0.593)
ICER	£4,100	£4,100

Risk-Factor Progression

The DSU queried the implementation of the HbA1c, SBP and TC:HDL ratio risk factor progression equations (UKPDS equations 11,12 and 13 respectively from the UKPDS 68 publication[Clarke et al, 2004)) in the economic model. These changes made had minimal impact on the results, see Table 3.1.1.2.

Table 3.1.1.2: Comparison of incremental costs and QALYs using original base case analysis and updated risk factor progression equations.

Incremental Result	Previous risk factor progression		Updated risk factor progression		Difference
	Mean	95% CI	Mean	95% CI	
Cost	£1,296	(£1140-1451)	£1,083	(£842-1324)	-£213
Benefit	0.486	(0.454-0.519)	0.414	(0.381-0.448)	-0.072
ICER	**£2,663**		**£2,614**		**-£49**

Event Equations

The DSU/ERG report noted that equations 8, 9 and 10 from the UKPDS 68 publication were not implemented consistently. The DCEM utilizes the UKPDS 66 mortality equation (Stevens et al, 2004) and life tables to model mortality. The reason for this is because the DCEM was initially developed prior to the publication of UKPDS 68 and as the model is used in multiple countries the use of life tables facilitates implementation in other countries. This approach is consistent with other diabetes models such as the CORE model (Palmer et al, 2004) . To address concerns expressed by the ERG and DSU regarding the loss of coherence regarding the full implementation, equations 8,9 and 10 from UKPDS 68 have been fully coded into the model (see appendix 1 for source code). This structural change to the model results in the model predicting slightly shorter life years but makes minimal difference to the incremental results. All re-analyses presented utilise the UKPDS mortality equations (8,9 and 10). .

Parameter sampling

The DSU identified discrepancies with sampled variables drawn from the gamma and beta distributions. Previously a gamma random deviates were sampled utilizing information on the mean, minimum and maximum of the distribution. We have updated the way in which gamma deviates are created by using a more standardized approach, namely generating gamma deviates using the inverse gamma function. We first formulate alpha and beta parameters from the mean and standard error values and then apply the inverse gamma function to generate the deviates. The following formulae are used to generate alpha and beta:

$$Alpha = E[x]^2/SE^2$$

$$Beta = 1/(\frac{Alpha}{E[x]})$$

The PSA code has now been modified and Figure X6 shows simulated random deviates drawn from the Normal, Gamma and Beta distributions for a variety of profiles. These are contrasted with simulated deviates generated in the statistical package R [[1]] using the rnorm, rgamma and rbeta

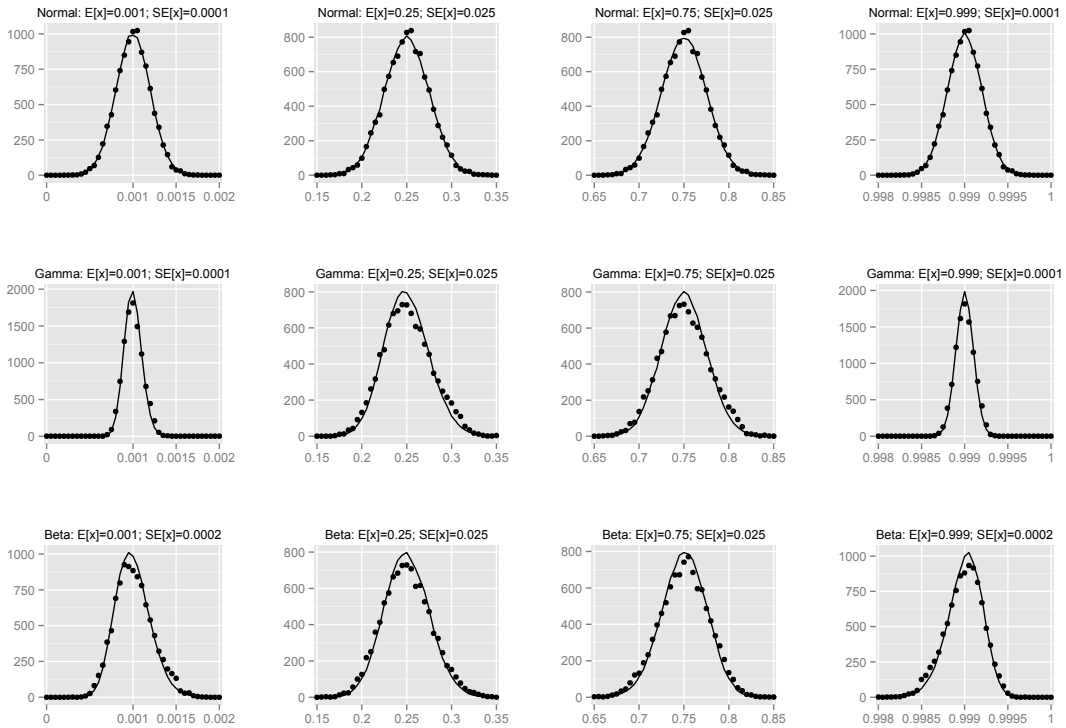
[1] R version R-2.15.2 available at www.r-project.org

functions. The impact of this change makes minimal difference to the model's results (Table 3.1.1.3). The source code used to produce these distributions is documented in the Appendix.

Table3.1.1.3: Comparison of incremental costs and QALYs using original base case analysis and updated PSA sampling distributions.

Incremental Result	Previous PSA sampling		Updated PSA sampling		Difference
	Mean	95% CI	Mean	95% CI	
Cost	£1,225	(£1056-1395)	£1,288	(£1159-1416)	+£62
Benefit	0.559	(0.322-0.795)	0.514	(0.084-0.944)	-0.045
ICER	**£2,193**		**£2,505**		**+£312**

Figure 3.1.1.2: A comparison of simulated random deviates drawn from the Normal, Gamma and Beta distributions from the updated DCEM (dots) and from R (solid line)



Hypoglycaemia

The DSU report concludes that the utility decrement associated with hypoglycaemia fear "is not halved in the same manner as the utility decrements associated with diabetes co-morbidities". Consequently, the DSU assumes the DCEM over-estimates the dis-utility associated with hypoglycaemia. As detailed in the response to question B.28 of the MRCL the model handles hypoglycaemia in the following way:

1. The frequency and severity of hypoglycaemia incidence is used to predict hypoglycaemia fear.
2. Hypoglycaemia fear is linked to health utility

Importantly, (1) is time dependent, (2) is not. The model adjusts the probability and number of events predicted to accommodate the six-monthly time-cycle used in the DCEM. Therefore, the model predicts the appropriate number (and severity) of hypoglycaemia events per cycle; this information is then used to predict a simulated individual's fear of hypoglycaemia. This level of fear is held constant over the relevant time-cycle and is used to drive the level of dis-utility applied. Unlike the hypoglycaemic event itself which is transient, hypoglycaemia fear is not; patients live with the risk and fear of hypoglycaemia permanently. (Frier B. 2000). Consequently, the duration of the study period from where the utilities are drawn (3-months) and the time-cycle modelled (6-month) do not require

reconciliation, because the model is relating a level of fear to a level of utility; conditional upon a given frequency and severity of hypoglycaemia incidence.

Event Probabilities

The DSU noted that cumulative hazards were being used in the model to control disease progression and that the probability of an event occurring during cycle length u should be given by; Transition probability = 1-exp { H(t-u) – H(t) }.

Correcting this error results in a minor change to the overall results predicted by the DCEM. As illustrated shown below, a small change of £14 in the ICER is seen in the illustrative comparison of Met+SU versus Met+Dapa (Table 3.1.1.4).

Table 3.1.1.4

Incremental Result	Using cumulative hazard		Using probability		Difference
	Mean	95% CI	Mean	95% CI	
Cost	£1,296	(£1140-1451)	£1,330	(£1147-1512)	+£34
Benefit	0.486	(0.454-0.519)	0.497	(0.465-0.528)	+0.010
ICER	**£2,663**		**£2,677**		**+£14**

All-cause mortality

The DSU report identified that "the risk of death taken from the life-tables is adjusted to account for the risk of diabetes related death from CHF, renal events and amputations in that cycle, such that the overall risk of death from CHF, renal events, amputations and non-diabetes related death is equal to that given in the life-table. No adjustment is made to account for the risk of fatality from stroke or MI events. This differs from the description of all-cause mortality on page 213 of the MS [*Manufacturer Submission*] where it states that both cardiovascular and diabetes related deaths were subtracted from all-cause mortality."

Correcting the model to ensure that cardiovascular and diabetes related deaths were subtracted from all-cause mortality resulted in a small change to the model's predictions. As shown below, incremental costs and QALYs remain virtually unchanged and a small change of £47 in the ICER is seen in the illustrative comparison of Metformin+SU versus Metformin+SGLT2 (Table 3.1.1.5).

Table 3.1.1.5

Incremental	Without adjustment	With adjustment	Difference

Result	Mean	95% CI	Mean	95% CI	(with-without)
Cost	£1,296	(£1140-1451)	£1,302	(£1157-1448)	+£7
Benefit	0.486	(0.454-0.519)	0.480	(0.446-0.515)	-0.006
ICER	**£2,663**		**£2,711**		**+£47**

Applying transformations to risk factors and moving averages

The ERG and DSU group noted that the risk factor transformation applied to TC:HDL and age were not implemented as per the UKPDS 68 publication. This is because doing so results in the requirement to take the natural log of a negative number, which is undefined. In response to numerous queries from modellers attending the Mount Hood diabetes modelling conference, Philip Clarke (lead author of UKPDS 68) produced an example spreadsheet of how to implement the equations (see Appendix 5). The transformations applied in the DCEM are coded in line with this example spreadsheet..

The use of moving averages in the UKPDS analysis was undertaken to smooth patient level data (HbA1c SBP and lipids) - as diabetes models use simulated (and smooth) data it is unnecessary to take moving averages; this is also consistent with Philip Clarke's example spreadsheet.

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3.1.2 Clarification request 2 (ACD Section 1.2, bullet 2): *Further explanation of how changes in weight are modelled over time for the different treatments, and further justification for differences assumed between lines of therapy*.

Weight change is included in the model as a modifiable risk factor and treatment-related change in weight and is associated with CV risk and a HRQoL impact. UKPDS derived CV risk equations based on BMI are included in the model, hence changes in patient weight over time are converted to a BMI value based on baseline weight and height characteristics. The following section describes how weight is handled over time in the model scenarios. In summary the key components to modelling weight over time are:

- The initial weight loss
- How long weigh loss is maintained
- How weight loss is regained
- The clinical data to support the model scenarios for dapagliflozin.

At the original submission 2 year data supported weight for dapagliflozin and the assumption beyond 2 years is that the weight loss is regained just before switch to next line of therapy occurs. Switch to next line of therapy occurs at different point in time in different scenarios and hence the gradient of weight regain is different in different scenarios. Clinical data now supports that weight is maintained over 4 years on dapagliflozin. The section below describes the different scenarios in more detail.

The implementation in the model of treatment effects on body weight and progression in weight over time are illustrated in Figure 3.1.2.1 Progression of weight in kg over time is based on the initial impact of each treatment on weight over a 12-month period. The treatment effects on body weight were applied in the first year after therapy initiation. The number of years during which the treatment effect will be maintained can be defined in the CEM. In the CE analyses, the weight lowering effect of dapagliflozin was maintained throughout the second year of treatment (red line/Treatment in Figure 3.1.2.1). This was based on 2-year data available at the time of submission from the long-term extension of the dapagliflozin vs glipizide as add-on to MET trial (Study Code D1690C00004), (Del Prato et al, 2012) and on long-term data of the placebo-controlled dapagliflozin add-on to INS trial (Study Code D1690C00006).). After Year 2 weight is assumed to be fully regained by the time of switch to the next treatment line in a linear manner to a level at which it corresponds to the patient's natural weight progression (i.e. the value that weight would be if no weight effect had occurred). A natural progression in weight as the patient ages is included in the model, at a rate of 0.1 kg per year.[2] This assumption is further reinforced with the interim results of the 4 year double blind extension phase which shows that initial weight loss achieved by dapagliflozin is maintained, while weight gain associated with SU is progressive over the period.

For DPP4i, the same assumptions regarding maintenance and loss of weight effect as for dapagliflozin were applied. The other comparators, SU (blue line/Control in Figure 3.1.2.1 and INS+DPP4i, are therapies associated with weight gain rather than weight loss. After the treatment effect in the first year, patients on

[2] A literature search was conducted to identify studies analyzing annual weight gain. Six studies performed in European countries and three in the US and Australia were reviewed. The studies varied in target population, but all demonstrated an annual weight gain varying from 0.04 to 1 kg per year.

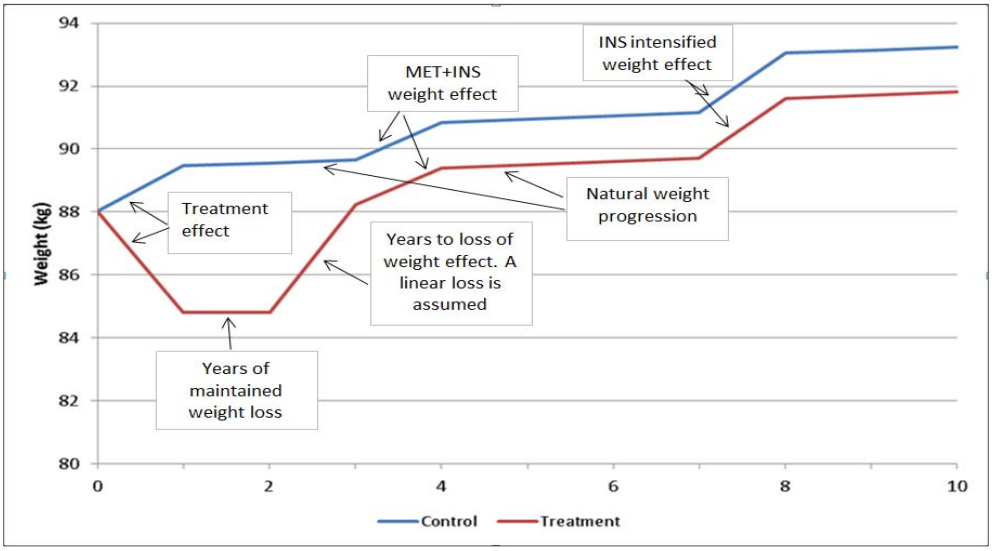
MET+SU therapy or INS+DPP4i therapy will increase in body weight in line with natural weight progression. It has been assumed that treatment-induced weight gain will not be lost in subsequent years.

As an example, the simulated progression of body weight over time for both strategies. MET+dapagliflozin results in a reduction in weight of 3.22 kg in the first year, leading to a decrease from baseline weight of 88 to 84.8 kg. For dapagliflozin, the weight loss is maintained over the second year of treatment. After that, the initial weight reduction obtained on dapagliflozin was assumed to wear off in a linear fashion until patients switched to the next line of therapy. In the MET+SU comparator arm an increase in weight of 1.44 kg is observed in the first year. The initial weight gain of 1.44 kg is maintained in subsequent years. Likewise, subsequent treatment lines are associated with effects on body weight applied in the first year after start of therapy. [redacted].

[redacted]

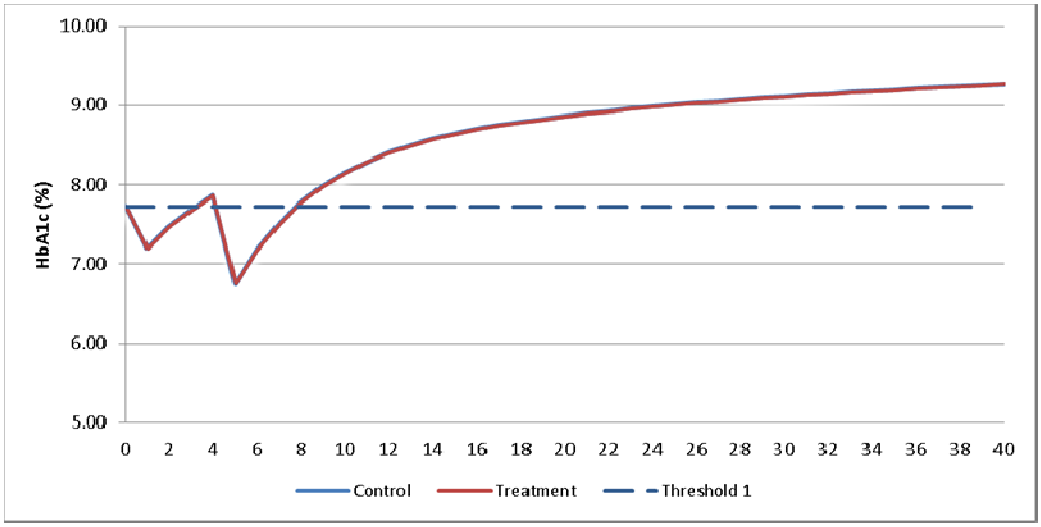
Patients will switch to the next treatment line when HbA1c reaches the HbA1c threshold (defined in the model as 7.72% for the exact comparison illustrated in Figure 3.1.2.2), which happens after 3 years. When patients switches, the weight effect of the next treatment line (e.g. MET+INS) is applied in the first year after treatment with this regimen commences, and natural weight progression is applied afterwards until patients switches to the next treatment line. Finally, patient switches to the last treatment line (e.g. INS, in the exact example) and again the weight effect of the treatment with insulin is applied in the first year and natural progression in applied thereafter as the patient ages.

Figure 3.1.2.1 Illustration of dynamic body weight profile implemented in the model; the scenario illustrates MET+dapagliflozin vs MET+SU→MET+INS→INS



x axis = years

Figure 3.1.2.2 Predicted progression of HbA1c over time; MET+dapagliflozin vs MET+SU



x axis = years

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

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. 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.

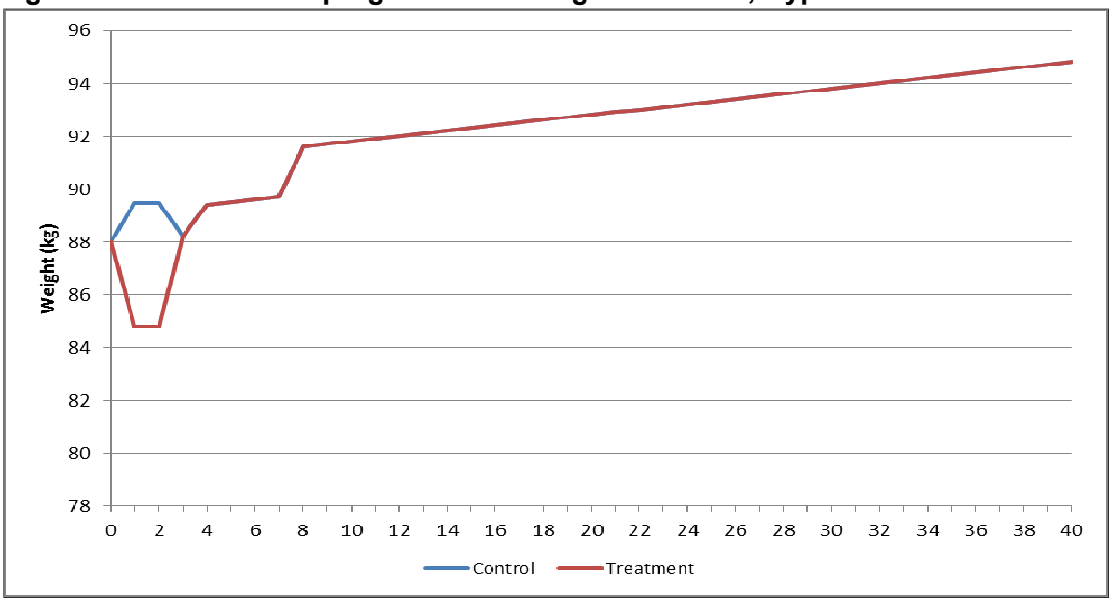
In order to conduct the scenario in which the weight loss of Y kg is nullified within 1 year after 2 years of sustained weight loss, and the weight gain of Z kg is assumed to be nullified after 2 years of maintained weight gain, with weight being equalised between the two arms at Year 3, the parameter settings should be as follows (Table 3.1.2.2):

Table 3.1.2.2: Parameters for weight to be equalised at Year 3

	"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 3.1.2.3 below, taking Y and Z to be -3.22 kg and +1.44 kg respectively.

Figure 3.1.2.3 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 3.1.2.3 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 is unlikely and hence should be considered an extreme unrealistic 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:

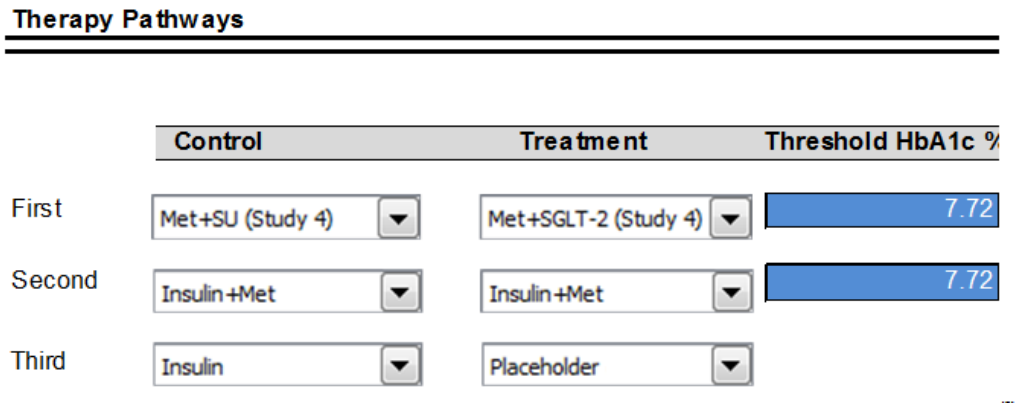
Using time to switch to next treatment to equalise weight: Within the model it is possible to equalise the patient weight between two treatment arms at the time of switch to a next therapy line (which is determined by the HbA1c level), by manipulating the treatment effect on weight, associated with that 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 3.1.2.3 below.

Table 3.1.2.3 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 3.1.2.4 Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Base case

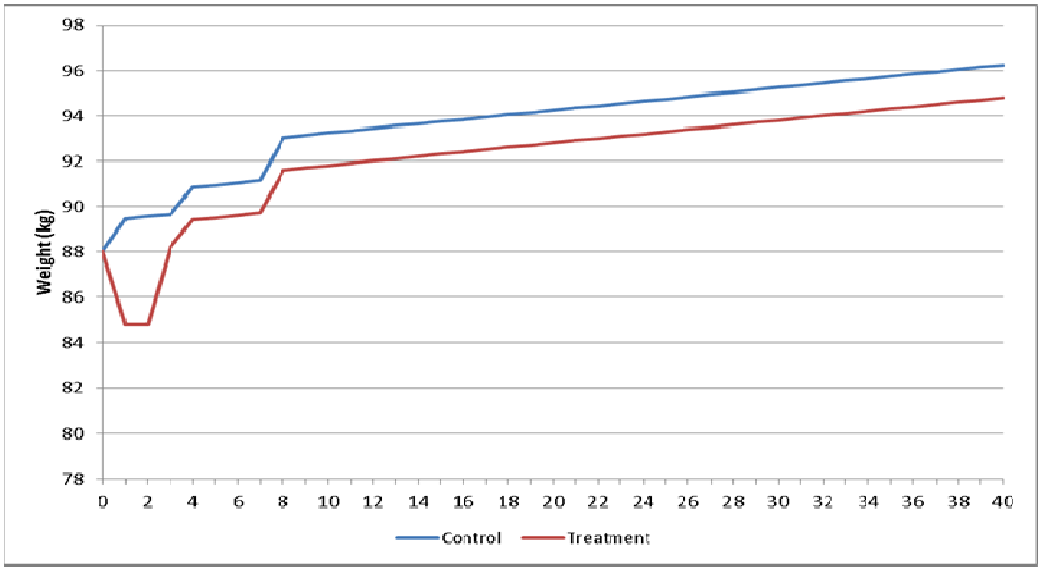
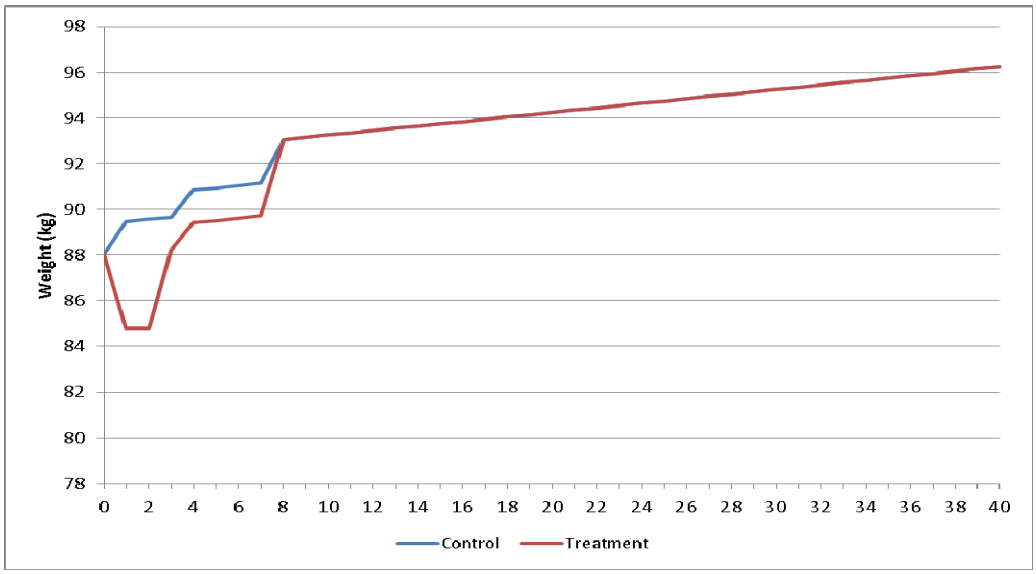


Figure 3.1.2.5 Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Scenario analysis of converging body weight profiles after switch to 3rd line.



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 3.1.2.6 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.

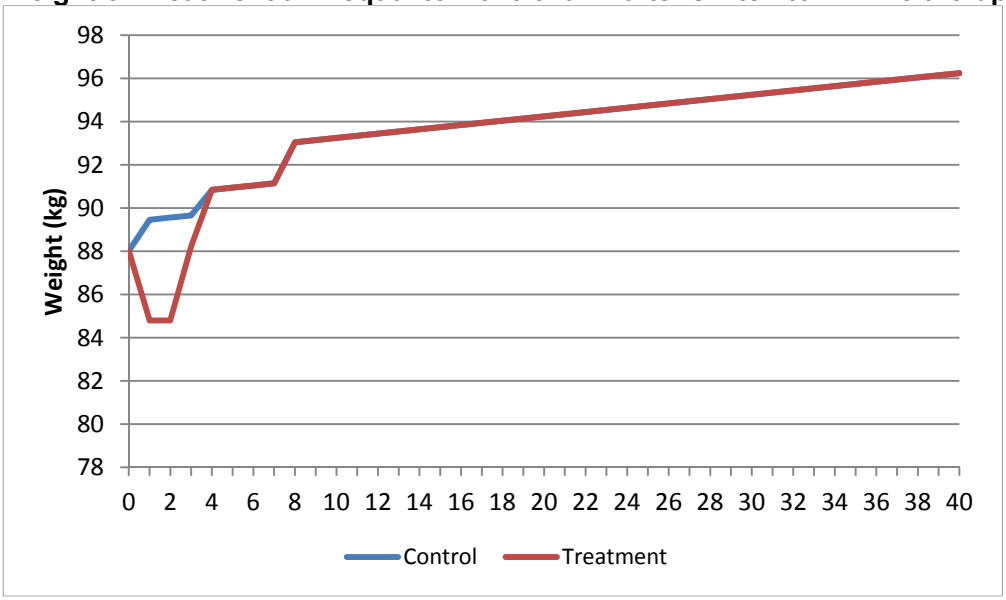
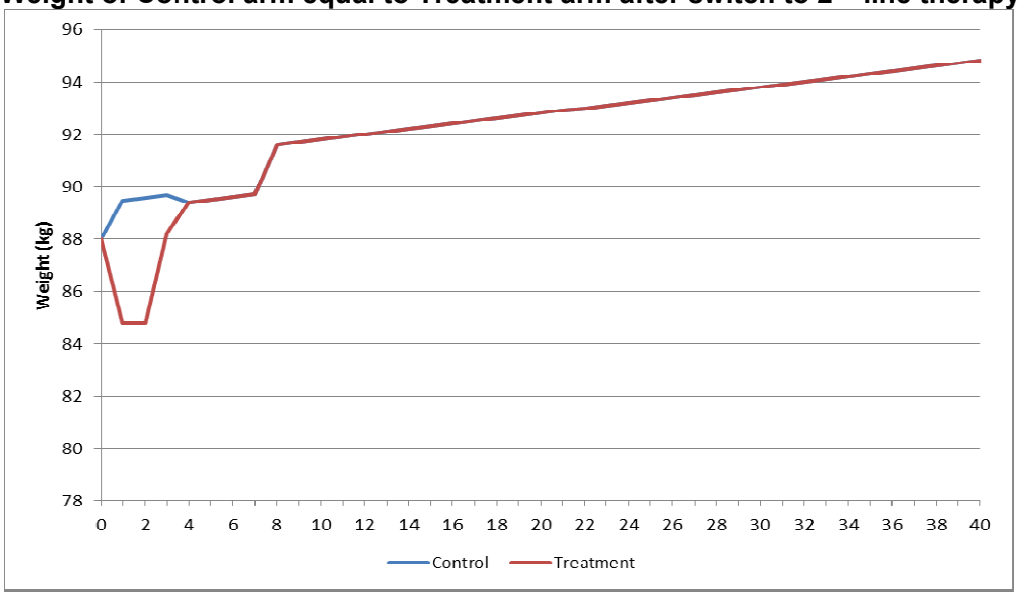


Figure 3.1.2.7 Predicted progression of weight over time; MET+dapagliflozin vs MET+SU Weight of Control arm equal to Treatment arm after switch to 2nd line therapy.



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 published data on body weight beyond two years of treatment with dapagliflozin. The four year results are disclosed here showing that weight loss achieved at 1 year is at least maintained at 4 years. While clinical data supports that weight loss is maintained throughout the whole duration of dapagliflozin treatment, a much more conservative approach has been followed in the cost-effectiveness analyses by assuming that the weight-lowering effect decreases with time on dapagliflozin treatment, although such a loss of effect while on study drug has not been witnessed in any of our phase 3 trials. In fact, in the add on to insulin study, where insulin requirements increased over time in the placebo arm, with a linear and progressive gain in weight, the dapagliflozin achieved weight loss as well as a stabilisation of insulin requirements, further belying the conservative approach taken in modelling where weight is assumed to go up.. 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 (Fig 3.1.2.8).

Fig 3.1.2.8 "Effectiveness and AE" sheet in the model,

(Met+SGLT2 24wk) MTC1

Efficacy Profile

HbA1c			
Reduction in Yr1	-0.58		
Months benefit in Yr 1	12.00		
Delay in creep (Yrs)	0.00		
Slope (per year)	0.759	Drift	0.000
CV Risk Factors			
SBP	-4.5		
Total-C (mmol/L)	0.0		
HDL-C	0.0		
Weight	-2.79	Natural Annual Wt Gain (kg)	0.1
Years of maintained weight loss	2.0	Years to loss of weight effect	2.0

Adverse events		P(event)	Event Cost	Utility Decrement
Hypoglycaemia				
Number Symptomatic events		0.08	£0	0.00
Number Nocturnal events		0.00	£0	0.00
Probability Severe		0.00	£390	0.00
Renal monitoring	1	1.00	£39	0.000
UTI		0.067	£36	0.00283
GI		0.089	£36	0.00283
AE4		0.00	£0	0.00
Other		0.00	£0	0.00

Discontinuation			
P(discontinuation in first 6 months)	0.022	£36	0.00
Annual Treatment	£ 500.38		

Parameters related to treatment effect on body weight, and progression over time.

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 before. 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 3.1.2.3 below.

Table 3.1.2.4: 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 again that for treatments associated with weight gain (Met+TZD, Met+SU, Insulin+DPP4i, 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.

Dapagliflozin has been shown in the phase 3 clinical trials to be associated with significant weight loss, in particular from the add-on to metformin study where the primary endpoint consisted of change in patient body weight (Bolinder et al 2012), but also from the other phase 3 studies reported NMA reports. In the dapagliflozin arm, weight reduction is assumed to be maintained in year 2 based on 2-year extension data from the phase 3 study vs. SU (glipizide) (Del Prato et al 2011).). Interim analysis of the extension phase of phase 3 study of dapagliflozin vs SU (glipizide) shows that weight loss in the dapagliflozin arm is maintained over 4 years as shown below (Figure 3.1.2.9). Our approach that weight is maintained over only 2 years is therefore a conservative assumption.

[redacted]

Interim analysis of extension phase 3 study vs SU (glipizide) shows that weight is maintained over 4 years on dapa+met. Weight continues to increase for patients on SU+met after the first 52 weeks.

The approach described here for weight control effects of dapagliflozin should be considered conservative as they reflect the availability of clinical trial data alone, whereas, the anticipated effects of dapagliflozin are likely to continue beyond the period of data collection as long as patients continue to be treated with dapagliflozin. In a real world setting an effect on weight control is likely to continue beyond 4 years, i.e. the years of weight control for dapagliflozin is likely to extend further than that depicted by the years of maintained weight loss for dapagliflozin and will depend on the duration of dapagliflozin treatment rather than a pre-specified study endpoint.

Figures 3.1.2.10 and 3.1.2.11 below illustrate the weight profile for Dapa+met vs DPP4i, TZD and Insulin add on. Weight loss is maintained for 2 years but regained before switch to the next therapy. In the scenarios below switch occur at different points in time which makes the gradient of weight regain different. The first Figure illustrates the scenario comparing Met+Dapa vs Met+DPP4i and it can be seen from the weight profiles that switch from met+dapa to next therapy occur just before met+DPP4i. Due to the conservative approach to weight benefit used in the model weight loss on met+dapa is regained before

met+DPP4i. This is entirely a result of the conservative assumption that all weight loss is regained after 2 years on dapa treatment.

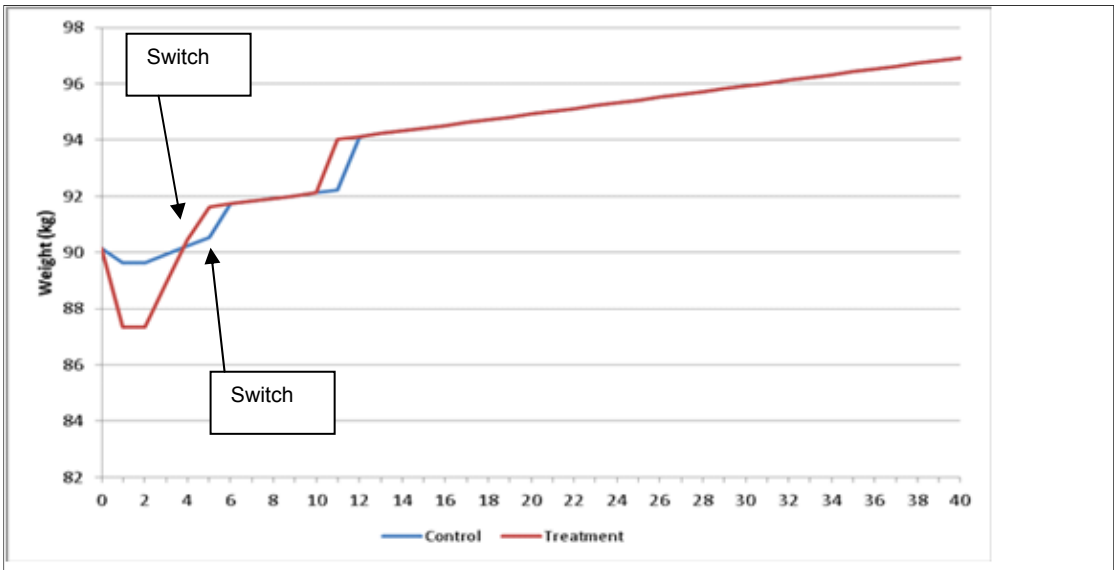


Figure 1. Predicted progression of weight over time; MET+dapagliflozin vs MET+DPP4

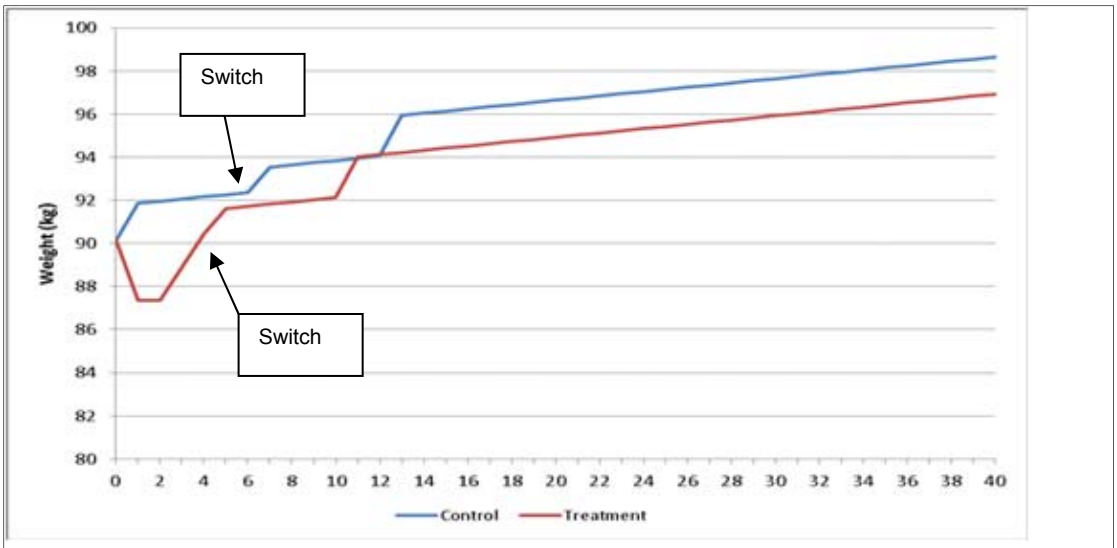


Figure 1. Predicted progression of weight over time; MET+dapagliflozin vs MET+TZD

Figures 3.1.2.10 and 3.1.2.11

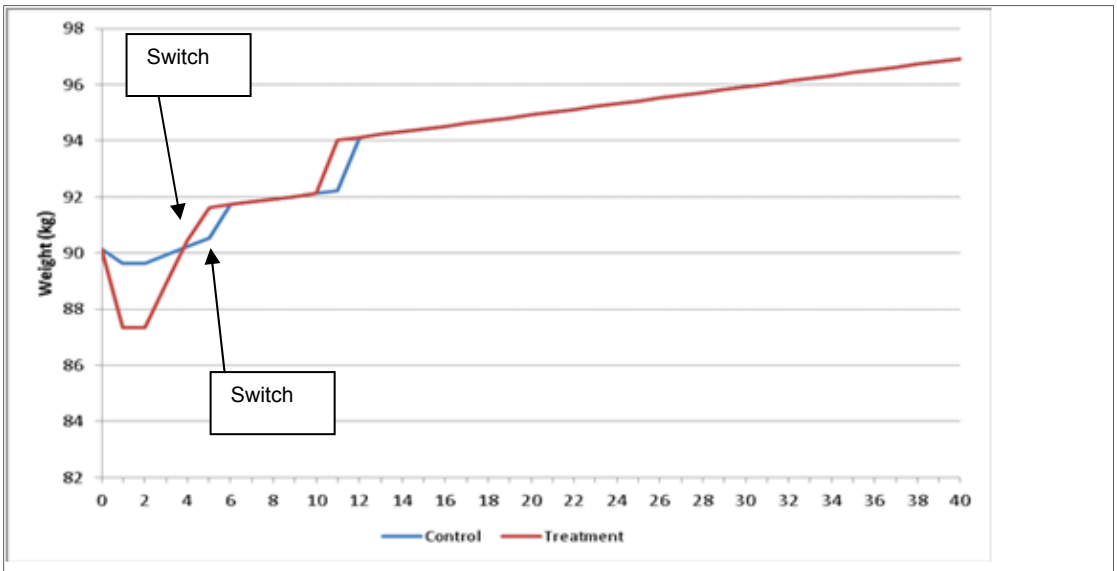


Figure 1. Predicted progression of weight over time; MET+dapagliflozin vs MET+DPP4

Figure 3.1.2.12

3.1.3 Clarification request 3 (ACD Section 1.2, bullet 3): *Further clarification of the sources of the treatment-related adverse events and discontinuation rates included in the economic model*.

We provide further clarification on the sources used for AEs and discontinuation rates for the A) add-on to metformin and B) add-on to insulin economic analyses in our response below. Only AEs particularly related to dapagliflozin and its mechanism of action have been modelled, UTIs and GIs, as they are most likely to be relevant to the comparisons made.

A. Add-on to metformin analysis

1. Comparison of MET+dapagliflozin versus MET+SU (based on study 4)

The comparison of MET+dapagliflozin versus MET+SU is taken from study 4, and hence values for rates of UTI, GI and discontinuation were retrieved from Nauck et al., as presented in the table 3.1.3.1

Table 3.1.3.1 Overall summary of adverse events reported (Nauck et al, 2011)

Table 1—Overall summary of numbers of patients with an AE, numbers of AEs with frequency ≥3% in any group, and numbers of patients with AEs of special interest during the 52-week double-blind treatment period using the safety analysis set

	Dapagliflozin + metformin $n = 406$	Glipizide + metformin $n = 408$
Overall summary of patients with an AE		
Patients with AE		
≥1	318 (78.3)	318 (77.9)
≥1 related to study treatment	110 (27.1)	110 (27.0)
Leading to discontinuation*	37 (9.1)	24 (5.9)
Patients with SAE		
≥1	35 (8.6)	46 (11.3)
≥1 related to study treatment	6 (1.5)	4 (1.0)
Leading to discontinuation	9 (2.2)	8 (2.0)
Deaths	0	3 (0.7)
Patients with AE with frequency ≥3% in any group†		
Nasopharyngitis	43 (10.6)	61 (15.0)
Hypertension	30 (7.4)	35 (8.6)
Influenza	30 (7.4)	30 (7.4)
UTI†	30 (7.4)	17 (4.2)
Upper respiratory tract infection	24 (5.9)	31 (7.6)
Headache	21 (5.2)	17 (4.2)
Back pain	19 (4.7)	20 (4.9)
Bronchitis	19 (4.7)	14 (3.4)
Diarrhea	19 (4.7)	26 (6.4)
Calculated creatinine renal clearance decreased*	17 (4.2)	7 (1.7)
Cough	15 (3.7)	20 (4.9)
Dizziness	15 (3.7)	37 (9.1)
Gastroenteritis	14 (3.4)	14 (3.4)
Nausea	14 (3.4)	15 (3.7)
Vulvovaginal candidiasis†	14 (3.4)	2 (0.5)
Arthralgia	11 (2.7)	21 (5.1)
Patients with special interest AE		
Hypoglycemic events‡		
Total	14 (3.4)§	162 (39.7)§
Major episode	0	3 (0.7)
Minor episode	7 (1.7)	147 (36.0)
Other episode	7 (1.7)	40 (9.8)
Leading to study discontinuation	0	6 (1.5)
Classified as a SAE	0	3 (0.7)
Signs and symptoms suggestive of genital infections‖		
Total	50/406 (12.3)	11/408 (2.7)
Male	12/226 (5.3)	1/223 (0.4)
1 event	7 (3.1)	1 (0.4)
2 or 3 events	4 (1.8)	0
>3 events	1 (0.4)	0
Classified as a SAE	0	0
Signs and symptoms suggestive of UTI‖		
Total	44/406 (10.8)¶	26/408 (6.4)
Male	18/226 (8.0)¶	9/223 (4.0)

Hence, the exact data that were applied in the model are as follows:

Comparison	Compared to MET+SU	
	study 4	
Comparators	MET+SU	MET+Dapa
Urinary tract infection- UTI	0.064	0.108
Genital infection- GI	0.027	0.123
Discontinuation rate (due to adverse events)	0.059	0.091

2. Comparison of MET+dapagliflozin versus MET+DPP4i and versus MET+TZD

Data on discontinuation rates, and the incidence of urinary tract infection (UTI) and genital infection (GI), were extracted from 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.

2.1 Incidence of urinary tract infection (UTI) and genital infection (GI) adverse events

Data on the incidence of UTI and GI were not subject to meta-analysis. This was primarily due to reporting bias associated with safety outcomes. In the dapagliflozin trial programme, in addition to spontaneous reporting of adverse events, a specific UTI/GTI questionnaire was used to elicit these signs and symptoms, thereby resulting in a much higher actual reported rate than in other trial programmes. These outcomes in non-dapagliflozin trials were deemed to be

1) not well-established safety outcomes associated with all drug classes (and therefore not routinely pre-specified in study protocols);
2) infrequently reported;
3) inconsistently defined.

Therefore, rather than conducting a meta-analysis, safety outcomes were summarized in a tabular format. Given the need for a 'best estimate' value of relative safety for the cost effectiveness model, one trial was identified for each comparator that was most similar to the dapagliflozin trial in the same indication in terms of

- titration and dosing regimen;
- enrolled patient population;
- duration of follow-up;
- definition of safety outcome; and
- method of monitoring adverse events.

For the add-on to metformin NMA, the extracted safety outcomes of the selected trials are listed in *Appendix 8* of the NMA report. A copy of the tables with the extracted outcomes is presented below. The discontinuation rates that served as input to the cost-effectiveness model for the comparison of dapagliflozin vs DPP4i and vs TZD (as reported in *Table 58* of the STA) are highlighted with a yellow box. No estimate of UTI or GI could be extracted for TZD, and therefore a value of zero was assumed.

Appendix 8 Metformin-add-on: safety outcomes

Appendix Table 8-1 Extracted safety fields from select active treatment arms of 24 week randomized clinical trials involving subjects with type 2 diabetes inadequately controlled on metformin monotherapy

Adverse Event	DAPA Bailey (2010) 24 Weeks - n/N (%)	TZDs Pio @ 30mg Kaku (2009) 24 Weeks - n/N (%)	DPP-4 inhibitors Saxagliptin 5mg DeFronzo (2009) 24 Weeks - n/N (%)	GLP-1 analogues Exenatide 10/20ug Liraglutide 1.2/1.8mg DeFronzo (2005) (exenatide) Nauck (2009) (liraglutide) 24 Weeks - n/N (%)
Gastrointestinal				
Nausea			4/191 (2.1)	40/110 (36%) 5ug exen 51/113 (45%) 10ug exen 16% 1.2 mg lira 19% 1.8 mg lira
Diarrhea	10/135 (7.4)		11/191 (5.8)	13/110 (12%) 5ug exen 18/113 (16%) 10ug exen 8% 1.2mg lira 15% 1.8 mg lira
Vomiting			6/191 (3.1)	12/110 (11%) 5ug exen 13/113 (12%) 10ug exen 5-7% 1.2mg lira 5-7% 1.8mg lira
Dyspepsia			10/191 (5.2)	
Constipation		<2%	4/191 (2.1)	
Other		2/83 (2.4)[a] 1/83 (1.2)[b]	All: 40/191 (20.9)[c]	
Respiratory/Sinus[d]				
Upper RTI	3/137 (2.2)		9/191 (4.7)	15/110 (14%) 5ug exen 11/113 (10%) 10ug exen
Sinusitus			4/191 (2.1)	5/110 (5%) 5ug exen 7/113 (6%) 10ug exen
Pharyngitis			0/191 (0)	
Nasopharyngitis	8/137 (5.8)		13/191 (6.8)	
Other				
Headache	11/135 (8.1)		11/191 (5.8)	
Dizziness			4/191 (2.1)	10/110 (9%) 5ug exen 5/113 (4%) 10ug exen
Influenza	8/137 (5.8)		13/191 (6.8)[g]	
UTI	9/135 (6.7)		10/191 (5.2)	
UTI[f]	11/135 (8.1)			
GI[f]	12/135 (8.9)		1/191 (0.5)	
Back pain	10/135 (7.4)		5/191 (2.6)	3/110 (3%) 5ug exen 7/113 (6%) 10ug exen
Myalgia			5/191 (2.6)	
Hypertension	5/137 (3.6)		4/191 (2.1)	
Edema		3/83 (3.6)	0/191 (0)	
Peripheral edema		2/83 (2.4)	5/191 (2.6)	
Cancer			0/191 (0)[e]	

*[a]Upper abdominal pain; [b]Infectious enteritis (serious adverse event); [c]Other preferred terms reported; [d]Includes 12 cases of influenza and one case of an influenza like illness; [e]Benign, malignant, or unspecified neoplasms; [f]Events suggestive of a UTI or Genital infection (GI). Indicates that the infection was not confirmed. Includes vulvovaginal candidiasis, vulvovaginal mycotic infection, genital candidiasis, balanitis candida, genital infection fungal, genital infection, penile infection, vaginal infection, vaginitis bacterial, vulvitis, vulvovaginitis. Full list available upon request; [g]No other adverse respiratory or sinus events were reported; **DPP-4** =Dipeptidyl peptidase-4 inhibitors; **GI** = Genital infection; **GLP-1** =Glucagon-like peptide-1 analogues; **RTI** = Respiratory tract infection; **TZD** = Thiazolidinediones; **UTI** = Urinary tract infection*

Bailey et al. 2010 study: Dapagliflozin add on regimen (24 weeks)

"Table 3.1.3.2 (below) provides a summary of adverse events. There were no deaths during the study. Adverse events leading to discontinuation were less frequent in the dapagliflozin groups than in the placebo group. Symptoms of hypoglycaemia occurred infrequently, were mild, and occurred in similar proportions of patients in the placebo and dapagliflozin groups. There were no major events of hypoglycaemia, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behavior, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration".

Table 3.1.3.2 Summary of adverse events (Bailey et al, 2010)

	Placebo group (n=137)	Dapagliflozin 2·5 mg group (n=137)	Dapagliflozin 5 mg group (n=137)	Dapagliflozin 10 mg group (n=135)
One or more adverse event	88 (64%)	89 (65%)	95 (69%)	98 (73%)
One or more drug-related adverse event*	22 (16%)	22 (16%)	25 (18%)	31 (23%)
Adverse event leading to discontinuation	5 (4%)	3 (2%)	3 (2%)	4 (3%)
One or more serious adverse event†	5 (4%)	4 (3%)	4 (3%)	4 (3%)
Deaths	0	0	0	0
Adverse events with frequency ≥5% in any group (by preferred term)				
Headache	6 (4%)	4 (3%)	10 (7%)	11 (8%)
Back pain	7 (5%)	5 (4%)	3 (2%)	10 (7%)
Diarrhoea	7 (5%)	3 (2%)	5 (4%)	10 (7%)
Urinary tract infection	7 (5%)	4 (3%)	7 (5%)	9 (7%)
Influenza	10 (7%)	13 (9%)	13 (9%)	8 (6%)
Nasopharyngitis	11 (8%)	12 (9%)	4 (3%)	8 (6%)
Hypertension	6 (4%)	9 (7%)	4 (3%)	5 (4%)
Upper respiratory tract infection	10 (7%)	5 (4%)	4 (3%)	3 (2%)
Cough	7 (5%)	4 (3%)	4 (3%)	1 (<1%)
Special interest categories				
Hypoglycaemia‡§	4 (3%)	3 (2%)	5 (4%)	5 (4%)
Events suggestive of urinary tract infection¶	11 (8%)	6 (4%)	10 (7%)	11 (8%)
Events suggestive of genital infection‡‖	7 (5%)	11 (8%)	18 (13%)	12 (9%)
Hypotension or syncope‡	1 (<1%)	0	2 (1%)	0

Data are number of patients (%), and include data after rescue. *Events with a certain, probable, possible, or unknown relation to study drug were deemed to be drug-related adverse events. †Each patient had only one report of a serious adverse event. ‡None led to discontinuation from study. §None was a major event, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration. ¶Reports of urinary tract infection (UTI) were based on 20 preferred terms for upper UTI events, and 44 preferred terms for non-upper UTI events. These events included signs, symptoms, and other reports suggestive of UTI, as well as definitive terms for UTI. ‖Reports of genital infection were based on 49 preferred terms, including bacterial and mycotic infections. These events included signs, symptoms, and other reports suggestive of genital infection, as well as definitive terms for genital infection.

Table 3: **Adverse events**

DeFronzo et al. 2009 study: DPP4i add on regimen (24 weeks)

Table 3.1.3.3 (below) presents the safety profile of saxagliptin add on to metformin including the number of patients who discontinued due to adverse events.

Table 3.1.3.3: Safety profile of saxagliptin add on to metformin (De Fronzo et al, 2009)

Table 2—*Adverse events in double-blind treatment period: total, serious, deaths, discontinuations, most frequent (≥5%), reported hypoglycemia, confirmed hypoglycemia, and exposure to study medication*

	PBO + MET	2.5 mg SAXA + MET	5 mg SAXA + MET	10 mg SAXA + MET	Total SAXA + MET
n	179	192	191	181	564
Adverse event	116 (64.8)	153 (79.7)	134 (70.2)	132 (72.9)	419 (74.3)
Serious adverse event	5 (2.8)	5 (2.6)	8 (4.2)	5 (2.8)	18 (3.2)
Deaths*	1 (0.6)	0	0	0	0
Discontinuation due to adverse event	2 (1.1)	5 (2.6)	6 (3.1)	5 (2.8)	16 (2.8)
Adverse events ≥5%†					
Nasopharyngitis	14 (7.8)	18 (9.4)	13 (6.8)	18 (9.9)	49 (8.7)
Headache	13 (7.3)	18 (9.4)	11 (5.8)	16 (8.8)	45 (8.0)
Diarrhea	20 (11.2)	19 (9.9)	11 (5.8)	10 (5.5)	40 (7.1)
URI	9 (5.0)	13 (6.8)	9 (4.7)	15 (8.3)	37 (6.6)
Influenza	13 (7.3)	12 (6.3)	12 (6.3)	10 (5.5)	34 (6.0)
UTI	8 (4.5)	10 (5.2)	10 (5.2)	9 (5.0)	29 (5.1)
Arthralgia	5 (2.8)	8 (4.2)	8 (4.2)	9 (5.0)	25 (4.4)
Back pain	12 (6.7)	11 (5.7)	5 (2.6)	8 (4.4)	24 (4.3)
Hypertension	6 (3.4)	11 (5.7)	4 (2.1)	5 (2.8)	20 (3.5)
Cough	6 (3.4)	10 (5.2)	6 (3.1)	3 (1.7)	19 (3.4)
Dyspepsia	6 (3.4)	4 (2.1)	10 (5.2)	4 (2.2)	18 (3.2)
Pain in extremity	10 (5.6)	5 (2.6)	4 (2.1)	8 (4.4)	17 (3.0)
Reported hypoglycemia	9 (5.0)	15 (7.8)	10 (5.2)	7 (3.9)	32 (5.7)
Confirmed hypoglycemia	1 (0.6)	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)
Exposure (days)	134 ± 54.4	152 ± 42.8	150 ± 44.3	151 ± 40.2	

Data are *n* (%) or means ± SD. Treated patients dataset. An adverse event was defined as any new or worsening illness, sign, symptom, or clinically significant laboratory test abnormality as noted by the investigator during the course of the study, regardless of the investigator's attribution of the event to study treatment. Confirmed hypoglycemia is defined by symptoms of hypoglycemia in the setting of a fingerstick blood glucose value ≤50 mg/dl. Extent of exposure is defined as the time from the first day to the last day, inclusive, that a patient took double-blind study medication during the 24-week short-term treatment period. *Death from cardiogenic shock. †Hypoglycemia events excluded. MET, metformin; PBO, placebo; SAXA, saxagliptin; URI, upper respiratory tract infection; UTI, urinary tract infection.

2.2 Discontinuation rates

Likewise, discontinuation rates were not meta-analyzed due to the heterogeneity in the definitions used by study authors for reporting discontinuation, and the different criteria applied in the study design to warrant discontinuation. To obtain a 'best estimate' for discontinuation rate for the cost-effectiveness model, one trial was identified for each comparator that was most similar to the dapagliflozin trial in the same indication in terms of

1) study design;
2) enrolled patient population;
3) duration of follow-up; and
4) criteria for study discontinuation.

The extracted discontinuation rates were listed in *Appendix 9* of the NMA report (Oxford Outcomes, 2011). A copy of the tables with the extracted outcomes is presented below. The discontinuation rates that served as input to the cost-effectiveness model for the comparison of dapagliflozin vs DPP4i and vs TZD (as reported in *Table 58* of the STA) are highlighted with a yellow box. No estimate of UTI or GI could be extracted for TZD, and therefore a value of zero was assumed.

Appendix 9 Metformin-add-on: discontinuations

Appendix Table 9-1 Discontinuations from select active treatment arms of 24 week randomized clinical trials involving subjects with type 2 diabetes inadequately controlled on metformin monotherapy

DAPA Bailey (2010) 24 Weeks - n/N (%)	TZDs Pio @ 30mg Kaku (2009) 24 Weeks - n/N (%)	DPP-4 inhibitors Saxagliptin 5mg DeFronzo (2009) 24 Weeks - n/N (%)	GLP-1 analogues Exenatide 10/20ug Liraglutide 1.2/1.8mg DeFronzo (2005) (exenatide) Nauck (2009) (liraglutide) 24 Weeks - n/N (%)
Total Discontinuations			
14/135 (10.4%)	9/83 (10.8%)	48/191 (25.1)	20/110 (18.2%) exen 5ug 20/113 (17.7%) exen10ug 44/241 (18%) lira 1.2mg 51/242 (21%) lira 1.8mg
Criteria for Discontinuation			
Lack of efficacy (0)	Lack of efficacy (3)	Lack of efficacy (22)	(5ug exen; 10ug exen)
Adverse events (3)	Adverse events (5)	Adverse events (6)	Withdrew consent (6; 4)
Withdrew consent (2)	Withdrew consent (1)	Withdrew consent (13)	Adverse events (4; 8)
Lost to follow-up (5)		Lost to followup (4)	Investigator Decision (0; 0)
Did not meet study criteria (2)		Did not meet study criteria (2)	Protocol violation (2; 3)
Administrative (1)		Poor/noncompliance (1)	Lost to follow-up (3; 4)
Other (1)			Administrative (0; 0)
			Lack of efficacy (5; 1)

DPP-4 =Dipeptidyl peptidase-4 inhibitors; GLP-1 =Glucagon-like peptide-1 analogues; TZD =Thiazolidinediones

Kaku et al. 2009 study: TZD add on regimen

In the results section of the publication, it is stated:

"In total, 236 subjects were screened and following a 12 week observation period, 169 qualifying patients were randomized to receive pioglitazone (nÖ83) or placebo (nÖ86) in combination with metformin. This represented the FAS population, which is the main focus of this report. A per-protocol analysis produced comparable clinical and statistical findings. 16 patients withdrew during the study (nine from the combination group and seven from the metformin group). Reasons for non-completion were: lack of efficacy (3 vs. 5), adverse events (5 vs. 2) and withdrawal of consent (1 vs. 0)."

Bailey et al. 2010 study: Dapagliflozin add on regimen

"Table 3.1.3.2 provides a summary of adverse events. There were no deaths during the study. Adverse events leading to discontinuation were less frequent in the dapagliflozin groups than in the placebo group. Symptoms of hypoglycaemia occurred infrequently, were mild, and occurred in similar proportions of patients in the placebo and dapagliflozin groups. There were no major events of hypoglycaemia, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behavior, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration".

DeFronzo et al. 2009 study :DPP4i add on regimen

Table 3.1.3.3 presents the safety profile of saxagliptin add on to metformin including the number of patients who discontinued due to adverse events.

B. Add-on to Insulin analysis

1. Comparison of INS+dapagliflozin versus INS+DPP4i

For the comparison of dapagliflozin vs DPP4i as add-on to insulin in the cost-effectiveness model, the UTI and GI rate inputs as reported in *Table 58* of the STA were sourced from Study 6 (24 week data) (Wilding et al, 2012)for dapagliflozin and from a saxagliptin study by Barnett et al. (2012) for DPP4i. All data were data on file provided by BMS/AZ.

Comparison	**Compared to DPP4**	
	24 week MTC data	
Comparators	INS+DPP4	INS+Dapa
Urinary tract infection- UTI	0.063	0.056
Genital infection- GI	0.003	0.092
Discontinuation rate	0.0197	0.0306

3.1.4 Clarification request 4 (ACD Section 1.2, bullet 4): *Further clarification of how the effect of treatment on risk factors (including HbA1c, systolic blood pressure and body mass index [BMI]) evolves in the economic model and the impact of this on how long these effects are maintained in the model.*

Strict interpretation of UKPDS equations 11,12,13 requires knowledge of HbA1c, SBP and TC:HDL following diagnosis of diabetes. This is generally unknown in practical applications of modelling type 2 diabetes; consequently, the original DCEM model assumed post-treatment HbA1c, SBP and TC:HDL levels to initialize these equations. This approach was also adopted by the CORE diabetes model but has been recently modified in version 8.5 of the CORE model consistent with the ERG and DSU suggestion that pre-treatment baseline risk factor values should be used. Figure 3.1.4.1 illustrates the impact of this modification on HbA1c progression and Figure 3.1.4.2 shows how this modification can impact therapy progression; Figures 3.1.4.3 and 3.1.4.4 illustrate the implications for SBP and TC:HDL respectively.

.**Figure 3.1.4.1: UKPDS HbA1c trajectory [points] and DCEM HbA1c trajectory [dotted line] in the original model [A] and revised model [B]**

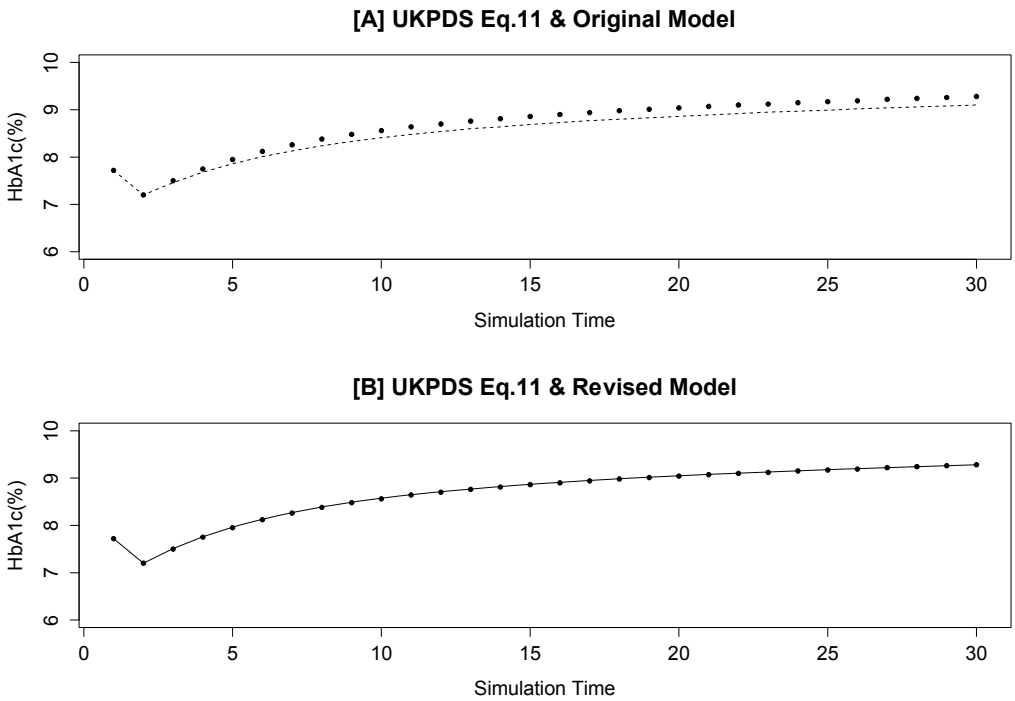


Figure 3.1.4.2: HbA1c trajectory when modelling metformin + SU versus metformin + SGLT2 in 2nd line (using study 4 data) using the previous HbA1c progression equation [dotted line] and the revised equation [solid line]. The slight increase in the gradient of HbA1c associated with the revised equation combined with an HbA1c therapy escalation

threshold set to 7.5% results in a more rapid escalation to next treatment line (at year 3).

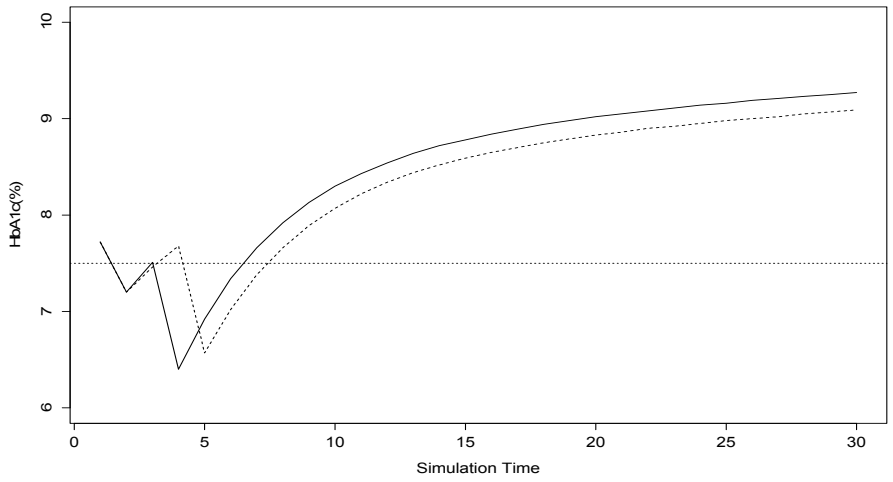


Figure 3.1.4.3: UKPDS SBP trajectory [points] and DCEM SBP trajectory [dotted line] in the original model [A] and revised model [B]. Also shown is the SBP trajectory for metformin + SU versus metformin + SGLT2 2nd line comparison in original model [C] and revised model [D]

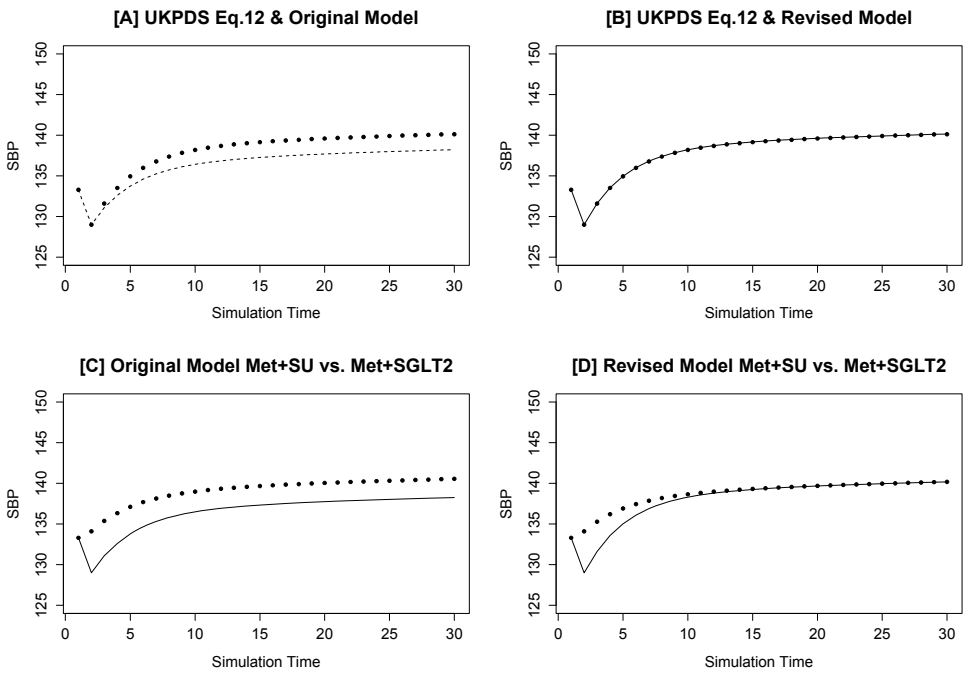
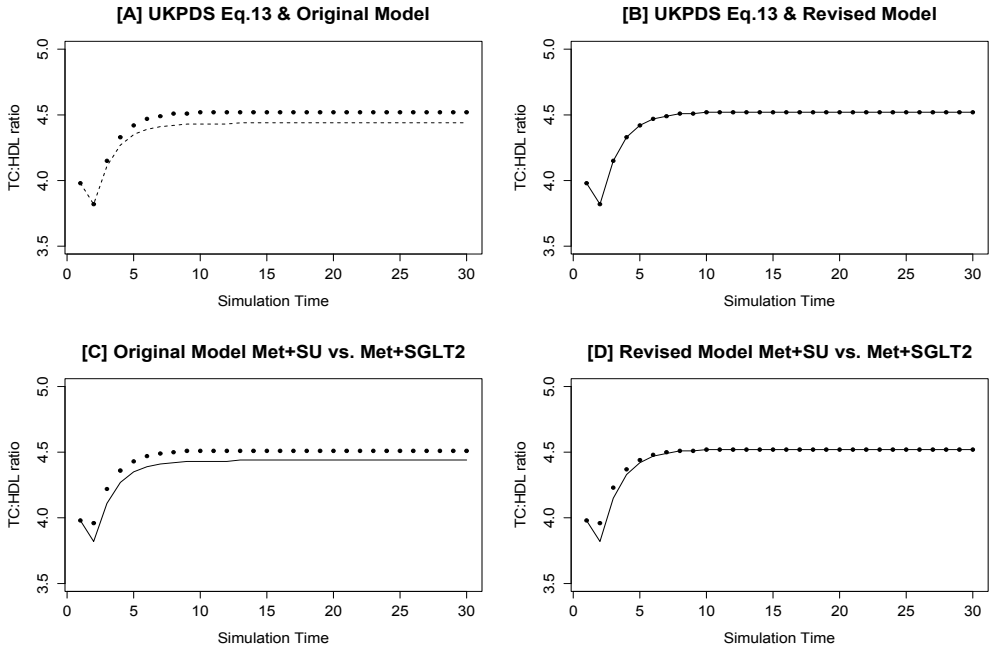


Figure 3.1.4.4: UKPDS TC:HDL ratio trajectory [points] and DCEM TC:HDL ratio

trajectory [dotted line] in the original model [A] and revised model [B]. Also shown is the TC:HDL ratio trajectory for metformin + SU versus metformin + SGLT2 in 2nd line comparison in original model [C] and revised model [D]



3.1.5 Clarification request 5 (ACD Section 1.2, bullet 5): *Further explanation of why variations in baseline characteristics and risk factors of simulated patients were not accounted for in the model.*

The DCEM does account for variations in baseline characteristics and risk factors for simulated individuals. The model runs in two modes; mean values and PSA. In mean value mode there is no parameter sampling in the model - just stochastic variability (1st order uncertainty). Increasing the cohort size modelled minimizes this 1st order uncertainty. When run in 'mean' mode, the DCEM operates in a similar manner to a Markov cohort model that provides deterministic results. It is designed to explore scenarios and subgroups with model variability minimized. When running in PSA mode, all baseline characteristics and risk factors (plus costs, utilities and risk factor coefficients) are subject to sampling (as selected by the user) - in order to quantify 2nd order uncertainty. Consequently, when running the model in 'PSA' mode results variations in baseline characteristics and risk factors are accounted for

3.1.6 Clarification request 6 (ACD Section 1.2): *A review of utility values associated with urinary tract and genital infections, with further justification for the values chosen..*

The clinical program for dapagliflozin included an integrated analysis of adverse events. Rates of events suggestive of UTI and more definitive events of diagnosed UTI were similar to placebo with Dapa 2.5 mg and higher with 5 mg and 10 mg. The majority of events were mild to moderate and few patients discontinued or interrupted treatment as a result. The manufacturer performed a study (Lane et al) to add to the limited research on health utilities in UTI and GTI and develop health states specific to unintended effects of dapagliflozin. The health states of diabetes base case plus UTI and diabetes base case plus genital tract infections had the lowest utility scores across the public and patient populations in the Lane study. In the DCEM however, the Barry et al utility decrement was adopted for the UTI value, as it was perceived to provide a more conservative approach. In order to address the question regarding the choice of utility values in the DCEM for utility estimates for urinary tract infections and genital infections we performed a search of the literature (using PubMed) and identified the following five publications reporting utility values for UTI's, which included a recently published systematic review which was funded by NICE No additional publications were identified for health utility in genital tract infections.

1: Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. BJU Int. 2012 Dec;110(11 Pt C):E830-6. doi: 10.1111/j.1464-410X.2012.11337.x. Epub 2012 Jul 20. PubMed PMID: 22816657.

2: Wiwanitkit V, Udomsantisuk N, Boonchalermvichian C. Diagnostic value and cost utility analysis for urine Gram stain and urine microscopic examination as screening tests for urinary tract infection. Urol Res. 2005 Jun;33(3):220-2. Epub 2005 Feb 25. PubMed PMID: 15731899.

3: Schaefer SE. Cost-utility analysis for UTIs. J Fam Pract. 1997 Apr;44(4):329. PubMed PMID: 9108820.

4: Barry HC, Ebell MH, Hickner J. Evaluation of suspected urinary tract infection in ambulatory women: a cost-utility analysis of office-based strategies. J Fam Pract. 1997 Jan;44(1):49-60. PubMed PMID: 9010371.

5: Ganiats TG, Humphrey JB, Taras HL, Kaplan RM. Routine neonatal circumcision: a cost-utility analysis. Med Decis Making. 1991 Oct-Dec;11(4):282-93. PubMed PMID: 1766331.

3.2 Additional analysis requests (ACD Section 1.3)

3.2.1 Additional Analysis request 1 (ACD Section 1.3, bullet 1): Revised network meta-analyses for dual therapy and add-on to insulin therapy. This should include the programme code used for each analysis, and the individual trial data used for each comparison in each analysis.

1. Requests to re-run the network meta-analyses (using the DSU recommended code)

In section 4.9 of the ACD the Committee concluded that there was significant uncertainty about the validity of the results of the network meta-analyses, and requested that the manufacturers were asked to provide a revised analysis.

The models were re-run using DSU-recommended code and results compared to those using the original code in the submission. This validation exercise consisted of:

- Data checks and quality assurance, i.e. checking any manipulation of data from published papers for use in the analyses, e.g. calculation of variance in those studies where the standard deviations are not reported
- NMA re-analysis using the code recommended by the NICE DSU (Evidence Synthesis, Technical Support Document 2 and calculation of absolute differences and rates for the cost-effectiveness model using the methodology recommended by the NICE DSU (Evidence Synthesis, Technical Support Document 5.

The NMA analyses, presented in the submission, were successfully replicated. Overall the results from the re-analysis are similar to the results from the original analysis, and provides a validation of the original code used. As the differences are small the impact on the economic model results are minimal (see Section 3.2.9)[3]. Summary of the results are presented in the tables below:

- Add-on to metformin, 24 week analyses, Tables 3.2.1.1-3.2.1.4
- Add-on to metformin, 52 week analyses, Tables 3.2.1.5-3.2.1.7
- Add-on to insulin, 24 week analyses, Tables 3.2.1.8-3.2.1.11

Along with this response document, the following materials are provided:

- Two reports on the validation exercise, for add-on to metformin analysis (Orme M, 2013a) and for the add-on to insulin analysis (Orme M, 2013b) in Appendix 4

[3] The NMA re-analysis results used in the cost-effectiveness analyses are presented in section 3 of the respective reports.

[redacted]

Table 3.2.1.5: Metformin add-on: HbA1c at week 52

		Original NMA estimate†		Re-analysis NMA estimate†	
Comparison (mean difference)	**Model type**	**Fixed Effect**	**Random Effects**	**Fixed Effect**	**Random Effects**
DPP4i vs SU	Unadjusted	0.08 (0.04, 0.13)	0.08 (-0.01, 0.16)	0.08(0.04, 0.13)	0.08(-0.01, 0.15)
	Adjusted	0.07 (-0.02, 0.16)	0.07 (-0.06, 0.21)	0.07(-0.01, 0.15)	0.08(-0.07, 0.24)
TZD vs SU	Unadjusted	0.02 (-0.09, 0.13)	0.02 (-0.15, 0.18)	0.02(-0.09, 0.13)	0.02(-0.15, 0.19)
	Adjusted	0.03 (-0.10, 0.17)	0.03 (-0.23, 0.29)	0.03(-0.11, 0.17)	0.01(-0.32, 0.30)
Dapa vs SU	Unadjusted	0.00 (-0.11, 0.11)	0.00 (-0.16, 0.16)	0.00(-0.11, 0.11)	0.00(-0.17, 0.17)
	Adjusted	-0.01 (-0.13, 0.11)	0.00 (-0.22, 0.26)	-0.01(-0.12, 0.11)	0.00(-0.25, 0.30)
SU vs baseline	Unadjusted	-0.69		-0.92(-1.03, -0.80)	-0.92(-1.03, -0.80)
	Adjusted			-0.92(-1.03, -0.80)	-0.92(-1.04, -0.80)

Notes: *† results based on 7 studies included in the basecase (30-36). The somewhat greater difference between the original analysis and the re-analysis for SU v baseline may be explained by a difference in the method used to calculate baseline risk (average risk versus average weighted using random effect weights)*

Table 3.2.1.6: Metformin add-on: Weight at week 52

		Original NMA estimate†		Re-analysis NMA estimate†	
Comparison (mean difference)	**Model type**	**Fixed Effect**	**Random Effects**	**Fixed Effect**	**Random Effects**
DPP4i vs SU	Unadjusted	-1.81 (-2.03, -1.59)	-1.92 (-3.12, -0.80)	-1.81(-2.03, -1.60)	-1.92(-3.10, -0.80)
Dapa vs SU	Unadjusted	-4.66 (-5.16, -4.17)	-4.67 (-7.03, -2.35)	-4.66(-5.16, -4.16)	-4.66(-6.99, -2.32)
SU vs baseline	Unadjusted	-	1.31	0.11(-0.10, 0.32)	0.11(-0.10, 0.32)

Notes: *† results based on 7 studies included in the basecase (30-36). The somewhat greater difference between the original analysis and the re-analysis for SU v baseline may be explained by a difference in the method used to calculate baseline risk (average risk versus average weighted using random effect weights)*

There was no SBP data recorded for the metformin add-on indication at week 52.

Table 3.2.1.7: Metformin add-on: Hypoglycaemia at week 52

		Original NMA estimate†		Re-analysis NMA estimate†	
Comparison (mean difference)	**Model type**	**Fixed Effect**	**Random Effects**	**Fixed Effect**	**Random Effects**
DPP4i vs SU	Unadjusted	0.09 (0.06, 0.11)	0.09 (0.04, 0.15)	0.09(0.06, 0.11)	0.09(0.03, 0.21)
TZD vs SU	Unadjusted	0.10 (0.03, 0.24)	0.12 (0.02, 0.37)	0.11(0.03, 0.25)	0.17(0.01, 0.60)
Dapa vs SU	Unadjusted	0.05 (0.03, 0.09)	0.06(0.02. 0.17)	0.06(0.03, 0.09)	0.08(0.01, 0.28)
Placebo: mean odds	Unadjusted	-	0.33	0.34(0.19, 0.60)	0.34(0.19, 0.60)
probability		-	0.25	0.26(0.16, 0.38)	0.26(0.16, 0.38)

Notes: *† results based on data from 5 studies (31, 33-36); 2 studies did not report incidence of hypoglycaemia (30, 32).*

3.2.2 Additional Analysis request 2 (ACD Section 1.3): *For the dual therapy cost-effectiveness analyses, the same baseline characteristics and risk factors should be used for each analysis.*

In section 4.17 of the ACD the Appraisal Committee noted that two different sources of data were used for the baseline characteristics and clinical effectiveness of dapagliflozin vs comparators in dual therapy as an add-on to metformin, hence the request for additional analysis using the same data source.

We have re-run the analysis using the same baseline characteristics and risk factors for each analysis, as requested. In the original submission, data were taken from the head-to-head RCT for the comparison versus SU, and from the NMA for all other comparators, resulting in two sets of baseline characteristics and risk factors. To use only one set of baseline characteristics and risk factors, we must obtain estimates of treatment effect versus all comparators from one source. Hence, this has been achieved by using data from the 52 week NMA, which has the added benefit of providing the longest follow-up.

3.2.3 Additional Analysis request 3 (ACD Section 1.3): *For all cost-effectiveness analyses, the model should apply the same baseline risk factors for both treatment groups rather than the baseline value minus the treatment-specific effect.*

In section 4.20 of the ACD the Appraisal Committee noted that the baseline risk factors implemented in the model were the trial baseline values minus the treatment specific effect and so baseline risk factors differed between treatment groups. The Committee considered this resulted in risk factor curves for both treatment groups that did not converge over time, which may not be clinically plausible, hence the above request.

The metformin add on scenarios comparing Forxiga vs SU, DPP4i and TZD now uses the same baseline characteristics. The analysis is now based on the 52 week network meta analysis which includes all comparators.

3.2.4 Additional Analysis request 4 (ACD Section 1.3): *For all cost-effectiveness analyses, the decision to switch or intensify treatment in the model should be based on HbA1c levels that are currently recommended in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87) rather than from the clinical trials included in the submission.*

In section 4.18 of the ACD the Appraisal Committee noted that the HbA_{1c} threshold levels for switching treatment in the dual therapy and triple therapy analyses were above those

recommended in NICE clinical guideline 87 and therefore may not reflect UK clinical practice. Hence, it was requested to use the threshold values in the clinical guideline (of 7.5%) in the base case (see Part 3.2.9 for results).

AstraZeneca/Bristol Myers Squibb used higher HbA1c thresholds in the Manufacturer Submission to reflect the clinical practice in the UK and have used the trial/NMA based values in order to be consistent with the source used for treatment efficacy in the model. While CG87 recommends to use the HbA1c threshold level of 7.5% when switching treatment in the dual therapy and triple therapy analyses, in practice as patients with type 2 diabetes are reviewed once or twice a year, many are likely to have exceeded the targets at the time of review. Indeed, as per CG87, patients just below the target will less likely have their treatment intensified. This is evident is cross sectional studies showing that a significant proportion of patients are not achieving and maintaining these targets represents a significant challenge for the majority of UK type 2 diabetic patients with a prevalence of inadequate glycaemic control of approximately 60% regardless of the number of medications they are on. (Fox et al, 2006; Calvert MJ et al, 2007, de Pablos-Velasco P. et al, 2012)

In a retrospective analysis of General Practice Research Database (GPRD) records, physicians were observed waiting several months after patients' first post-sulfonylurea HbA1c test result which were greater than or equal to 8.0% before prescribing a new agent, with most therapy changes occurring only after HbA1c was well above 9.0% (Cook et al, 2005). The Warwick Diabetes Care Intensive Management of Type 2 Diabetes programme established that the mean HbA1c baseline before initiation of insulin was 9.6% (Dale et al, 2008) and this was supported by a retrospective cohort study using the DIN-LINK database which demonstrated the mean HbA1c before therapy was 9.07% and mean HbA1c before initiation of insulin was 9.85% (Calvert MJ et al, 2007).

In a recent unpublished retrospective cohort study conducted in the Health Improvement Network (THIN), the mean HbA1c prior to addition was [redacted] for metformin and sulfonylurea , [redacted] for sulfonylurea and metformin, and [redacted] for metformin and thiazolidinedione (Gordon J et al, 2011)

The NICE clinical guidelines HbA1c thresholds have always been communicated to the NHS as best practice and therefore aspirational. This is clearly demonstrated by the literature which demonstrates that UK clinical practice clearly uses different HbA1c thresholds when initiating or switching therapies to those identified within the NICE clinical guidelines.

Moreover, the 'treat to failure concept for improving glycaemic control stems from oral anti-diabetic drugs available until recently that to a large extent relied on beta cell function for their efficacy. This gives rise to the well described "sawtooth" appearance of HbA1c over time as the efficacy of such insulin dependent drugs wane. It therefore made sense in existing guidelines to recommend reviewing such agents when more stringent control with insulin treatment due to progressive beta cell dysfunction was required. Dapagliflozin has an insulin independent mechanism of action proven to work with other therapies including insulin, by retaining its glucose lowering ability and even avoiding the additional weight gain from an insulin regimen. This unique mode of action (MOA) along with the long term durability data of up to four years provides strong clinical rationale to not discontinue dapagliflozin when more glycaemic control with insulin treatment or other agents is required.

In response to the specific request made in the ACD, we have included the analyses using a threshold of 7.5%. However, these results must be interpreted with caution as they do not accurately reflect UK clinical practice, nor does the underlying concept of switching treatments do justice to the clinical utility of dapagliflozin with its unique insulin independent MOA.

3.2.5 Additional Analysis request 5 (ACD Section 1.3): *For the triple therapy cost-effectiveness analyses, the sequence of treatments should be revised so that the starting treatment is triple therapy rather than dual therapy.*

In section 4.25 of the ACD the Committee noted that the sequencing of treatments in the triple therapy analysis, which assumed that people started treatment with dual therapy before switching to triple therapy, was inconsistent with the approach taken for the dual therapy and add-on to insulin analyses.

We have performed updated analyses for triple therapy in which the sequencing of treatments start with triple therapy according to table 3.2.5.1 below for the comparisons performed.

Table 3.2.5.1 Revised sequencing

	Treatment arm		Control arm		
First line	MET+SU+Dapagliflozin	**vs**	MET+SU+DPP4i	MET+SU+TZD	MET+SU+GLP1
Second line	MET+INS		MET+INS	MET+INS	MET+INS
Third line	INS (intensified)		INS (intensified)	INS (intensified)	INS (intensified)

HbA1c switching threshold	Same as HbA1c baseline (i.e.8.61%) for both switches

The baseline characteristics for this analysis, including baseline HbA1c threshold chosen is based on the systematic review conducted by Canadian Agency for Drugs and Technologies in Health, which reviewed trials of patients failing metformin and sulphonylureas treatments. These characteristics were felt to be more reflective of what patients at this stage of the disease would look like. The baseline characteristics of studies 18/19, which were studies specifically designed to look for patients having already experienced a cardiovascular event or with multiple risk factors, show much worse baseline characteristics, likely to represent a minority of patients. For example, patients from 18/19 were older, more likely to have IHD(82% vs 11%), stroke (18% vs 5%) and other diabetes related complications at baseline

3.2.6 Additional Analysis request 6 (ACD Section 1.3): *The changes proposed by the Evidence Review Group:*

- ***reducing the loss in QALYs associated with hypoglycaemia to −0.012 for a severe event and −0.004 for a symptomatic event.***
- ***reducing the annual cost of pioglitazone to £112.18***
- ***including an annual cost of £483 for people not experiencing diabetic complications and***
- ***using utility values associated with weight change of ±0.0061 per unit of BMI.***

In section 4.26 of the ACD the concerns were expressed that ERG exploratory analyses using alternative utility values associated with weight change, reducing the loss in QALYs associated with hypoglycaemia, reducing the annual cost of pioglitazone, and adding an annual cost for diabetes without complications increased the ICERs (although they were all below £30,000 per QALY gained).

We have therefore performed the requested changes to the economic analyses, applying the above estimates separately and combined. However, in performing these additional analyses we wish to make two further comments:

- Using a lower cost for pioglitazone was only relevant for comparisons with TZD. We would like the Committee to take note that the lower cost for pioglitazone was not available at the time we made our submission, and we used the cost that was available at time of submission.
- The combined analysis includes using the lower cost for pioglitazone (where relevant), the annual cost for diabetes without complications, and the utility of ±0.0061 per unit of BMI. However, it does not include the requested change to handling hypoglycaemia disutility: we believe the ERG has misinterpreted the approach by which hypoglycaemia has been modelled and that the utilities in the model are correct (i.e., the correction proposed is not appropriate). For more detailed explanation, see section 3.1.1. ('response to the report produced by the DSU'), under the heading 'Hypoglycaemia'.

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3.2.7 Additional Analysis request 7 (ACD Section 1.3): *Changes to the model as a result of responding to the DSU report and the revised network meta-analyses.*

See "Appendix to 3.2.7" for a list of changes made to the model in response to the DSU report

The updated NMA using the DSU recommended code has been used (see 3.2.1), based now on 52 week NMA data for the add-on to metformin comparisons, and the 24 week data for the add-on to insulin comparisons, and a base case switch threshold of 7.5% (see 3.2.4)

3.2.8 Additional Analysis request 8 (ACD Section 1.3): *Analyses using the upper and lower estimates of utility values associated with urinary tract and genital infections identified in the review requested in 1.2.*

Disutility applied in model for UTI and GI event. From study 4 SU H2H trial events were mild to moderate.

Table 3.2.8.1 outline different utility decrements from systematic review published 2012 and includes unpublished data from Oxford Outcomes. The model currently uses data from Barry et al 1997 (also in the 2012 review).

Table 3.2.8.1. Disutility related to UTI and GI. Disutility adjusted to yearly using duration of health state (days) divided by 365.25 days except for Barry et al, 1997 where disutility per month was adjusted to yearly by multiplying with 1/12

Event	Utility decrement	Duration of health state (days)	Disutility per month	Disutility per year	Ref
Pyelonephrities	-0.3732	10	-0.1244	-0.0104	Barry et al 1997
Vaginitis	-0.2894	5	-0.0367	-0.00306*	Barry et al 1997
Persistent dysuria	-0.2894	5	-0.0367	-0.00306*	Barry et al 1997
UTI	**-0.176**	**10****		**-0.00482**	**OxO study**
GI	**-0.170**	**10****		**-0.00464**	**OxO study**
UTI	-0.198 (0.922 no UTI 0.724 with UTI)	10**		-0.00542	Ellis & Verma In Bermingham and Ashe 2012 review

Event	Utility decrement	Duration of health state (days)	Disutility per month	Disutility per year	Ref
UTI	-0.024	10**		-0.000657	Abrahamian In Bermingham and Ashe 2012 review
UTI	-0.049	10**		-0.00134	Vogel In Bermingham and Ashe 2012 review
UTI	-0.1	7		-0.00192	Haran In Bermingham and Ashe 2012 review

*Currently used in model for both UTI and GI. No pyelonephrities recorded for dapagliflozin in study 4

**Assumption

Analyses using the upper and lower estimates of utility values associated with urinary tract and genital infections identified in the review requested in 1.2.

Apply the value of -0.0104 to both UTI and GI as High Value:

Apply the value of -0.000657 to both UTI and GI as Low Value:

The analysis utilizing the upper and lower values from Table 3.2.8.1 demonstrated minimal difference in ICER's as depicted in Table 3.2.8.2 below which supports the original choice of the Barry et al utility, a conservative value, in the DCEM.

Table 3.2.8.2: Different scenarios using high/low disutility for UTI/GI

Analyses	vs Met+SU			vs Met+DPP4			vs Met+TZD			vs Ins+DPP4		
	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER
12. Analyses using the upper and lower estimates of utility values associated with urinary tract and genital infections identified in the review requested in 1.2. Apply the value of -0.0104 to both UTI and GI												
Apply the value of -0.0104 to both UTI and GI	1134	0,754	1503	260	0,373	696	214	0,036	6021	280	0,109	2573
Apply the value of -0.000657 to both UTI and GI	1134	0,758	1496	260	0,378	687	249	0,051	4865	280	0,114	2457

3.2.9 Revised results based on revisions made according to additional analysis requests in section 1.2 of the ACD

In response to this request to use the same baseline characteristics for all dual therapy scenarios, the base-case analyses relied on the data from the 52 week NMA, which was available for all the comparators, i.e. SU, DPP-4, TZD. In addition, the models were run with the data from study 004 to compare the cost-effectiveness of dapagliflozin vs. SU using the data from the H2H trial

As requested, the decision to switch or intensify treatment is now based on HbA1c threshold of 7.5mmol/L as recommended in NICE clinical guideline 87 for the metformin add on scenarios.

As requested, for the triple therapy scenarios the sequence of therapy has been revised so that the starting treatment is triple therapy. The exact comparisons that have been conducted is shown in Table 3.2.9.1:

Table 3.2.9.1: Triple therapy comparisons

	Treatment arm		**Control arm**		
First line	MET+SU+Dapagliflozin	**vs**	MET+SU+DPP4i	MET+SU+TZD	MET+SU+GLP1
Second line	MET+INS		MET+INS	MET+INS	MET+INS
Third line	INS (intensified)		INS (intensified)	INS (intensified)	INS (intensified)

HbA1c switching threshold	Same as HbA1c baseline (i.e. 8.61%) for both switches

The following tables summarise the model inputs used within the analysis regarding triple therapy. As noted, the two sets of data used here have not been formally assessed for comparability and differences between the populations considered will exist. Given the methods applied, it has not been possible to adjust for baseline characteristics.

Figure 3.2.9.1 illustrates the cost effectiveness ratios for the base case scenarios including changes made to the model in response to the DSU report.

Figure 3.2.9.1: Cost effectiveness ratios for base case scenarios

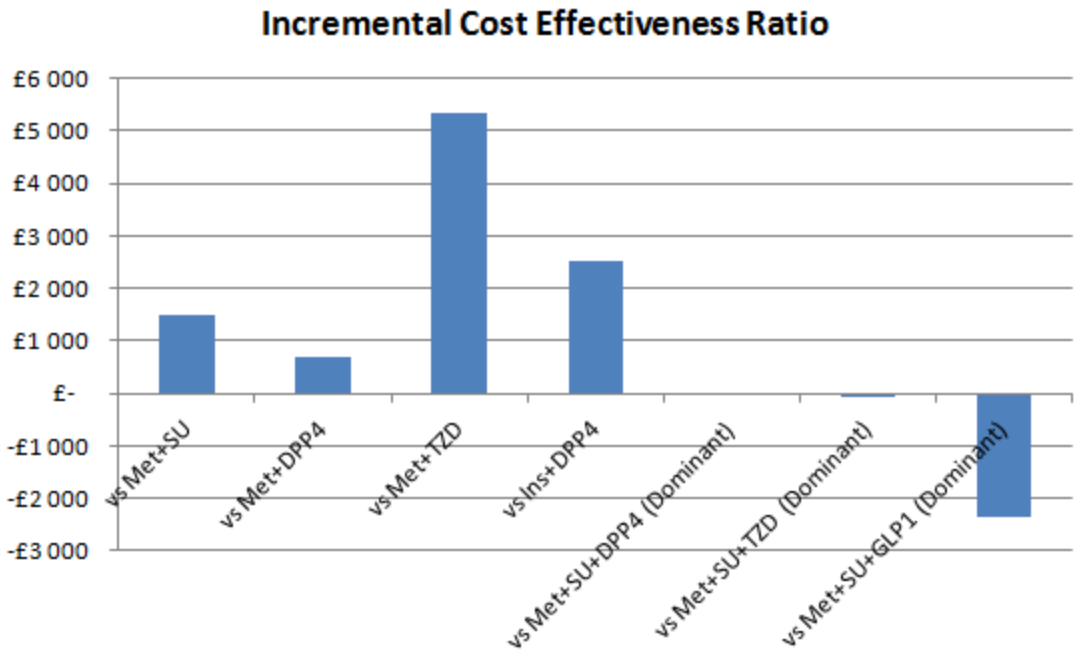


Table 3.2.9.2 shows the results for dual therapy as add-on to metformin and add-on insulin. Dapagliflozin was shown to be a cost-effective treatment as compared with all other treatments administered as add-on to metformin or add-on to insulin, in base-case and all one way sensitivity analyses. Notably, Dapagliflozin remained cost-effective in a multivariate analyses, where all changes proposed by the Evidence review Group were simultaneously applied, vs all comparators, except for the scenario vs met+TZD. It should be noted, that the analyses employed a conservative the assumption on a sustainability of weight loss with dapagliflozin. It was assumed that at the time of escalation to the next treatment line all patients regain weight to their baseline level. Considerations should be given to this conservative approach of modelling weight when interpreting ICER.

Table 3.2.9.2 Results for dual therapy, metformin add on and insulin add on

Analyses	vs Met+SU			vs Met+DPP4			vs Met+TZD			vs Ins+DPP4		
	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER
11. Changes to the model as a result of responding to the DSU report and the revised network meta-analyses. (BASE CASE)	1134	0,757	1498	260	0,377	689	214	0,040	5342	280	0,112	2509
If partial weight regain is assumed instead of full regain *(setting years to loss of weight effect to 4 years)*	1263	0,086	14733							270	0,148	1815
New data regarding weight maintenance *(setting maintenance weight for 4 years)*												
10. The changes proposed by the Evidence Review Group:												
i. reducing the loss in QALYs associated with hypoglycaemia to −0.012 for a severe event and −0.004 for a symptomatic event	1134	0,738	1537	260	0,376	690	214	0,039	5527	280	0,091	3065
ii. reducing the annual cost of pioglitazone to £112.18							1047	0,040	26083			
iii. including an annual cost of £483 for people not experiencing diabetic complications, and	1132	0,757	1495	256	0,377	680	213	0,040	5306	276	0,112	2473
iv. using utility values associated with weight change of ±0.0061 per unit of BMI.	1134	0,146	7748	260	0,077	3378	214	0,013	15919	280	0,049	5717
All together except for scenario I	1132	0,146	7735	256	0,077	3337	1045	0,013	77615	276	0,049	5634
12. Analyses using the upper and lower estimates of utility values associated with urinary tract and genital infections identified in the review requested in 1.2. Apply the value of -0.0104 to both UTI and GI												
Apply the value of -0.0104 to both UTI and GI	1134	0,754	1503	260	0,373	696	214	0,036	6021	280	0,109	2573
Apply the value of -0.000657 to both UTI and GI	1134	0,758	1496	260	0,378	687	249	0,051	4865	280	0,114	2457

Table 3.2.9.3 Results for triple therapy

versus MET+SU+DPP4					versus MET+SU+TZD					versus MET+SU+GLP1				
Summary CE Output					Summary CE Output					Summary CE Output				
		Mean	95% LCL	95% UCL			Mean	95% LCL	95% UCL			Mean	95% LCL	95% UCL
Cost	CI	-£13	(£-98.22,	£71.87)	Cost	CI	-£84	(£-170.03,	£2.14)	Cost	CI	-£2 373	(£-2461.1,	£-2285.09)
Benefit	CI	0,195	(0.186,	0.204)	Benefit	CI	0,593	(0.584,	0.602)	Benefit	CI	0,035	(0.026,	0.044)
ICER	CI	Dominant			ICER	CI	Dominant			ICER	CI	Dominant		

3.3 Additional Analysis request 9 (ACD Section 1.4): *A comparison should also be provided of the results for the analyses requested in 1.3 with the results that would have been obtained from using the CORE model for all relevant comparisons in dual therapy, insulin add-on therapy and triple therapy, and an explanation of any reported differences.*

To compare the cost-effectiveness of dapagliflozin, both the dapagliflozin cost effectiveness model (DCEM) and the CORE diabetes model (CDM) have been populated with base case and scenario analyses (as requested in ACD section 1.3). These analyses have been conducted after making the requested changes to the DCEM.

Add-on to metformin and add-on to insulin

Both analyses demonstrated that dapagliflozin is a cost-effective treatment choice for patients with type 2 diabetes as add-on therapy in combination with metformin and in combination with insulin vs other available treatment options (Table 3.1.1). The models produce consistent estimates of the cost-effectiveness of dapagliflozin for most scenarios conducted, with ICERs falling below the accepted thresholds for cost-effectiveness. These results are consistent with those presented in the original submission.

Table 3.1.1 Cost-effectiveness of dapagliflozin in licensed indications: Comparison of the results of the CDM and DCEM[4]

	Incremental cost per QALY	
Base case analyses	CDM	DCEM
1. A combination therapy with metformin		
Met+SU (Study 4 data), 7.5% threshold	£5,747	£3,010
Met+SU (52 wk NMA data) , 7.5% threshold	£8,879	£1,498
Met+DPP4(52 wk NMA data) , 7.5% threshold	£2,014	£689
Met+TZD(52 wk NMA data) , 7.5% threshold	£7,093	£26,083†
2. A combination therapy with insulin		
INS+DPP4	Dapa dominates	£2,509

† Result relates to TZD priced at the £112.18; using TZD price from original submission the ICER decreases to £5,342

[4] See Appendix for the the full IMS CDM modelling report.

Triple therapy

The cost-effectiveness of dapagliflozin in triple therapy is associated with considerable uncertainty, largely resulting from the current lack of reliable clinical evidence reflecting clinical practice in the UK in this setting (Table 3.1.2). The differences in ICERS between the CDM and the DCEM for triple therapy are explained by the following:

Met+SU+DPP4: The magnitude of cost difference in absolute terms is similar between the two but the CDM predicts a slight incremental cost and the DCEM a small incremental saving (see Figure 3.3.1). Consequently the DCEM estimates dominance for dapagliflozin.

Met+SU+TZD: Results are presented for TZD priced full and reduced price. When priced at £112.18 both models estimate dapagliflozin to be cost effective.

Met+SU+GLP1: Both models predict less cost and less benefit; the DCEM predicts a smaller QALY loss and hence larger ICER.

Table 3.1.2 Cost-effectiveness of dapagliflozin in triple therapy: Comparison of the results of the CDM and DCEM[5]

	Incremental cost per QALY	
Base case analyses	CDM	DCEM
Met+SU+DPP4, 7.5% threshold	£53,459	Dapa Dominant
Met+SU+TZD, 7.5% threshold	£13,837	£2,464†
Met+SU+GLP1, 7.5% threshold	£270.49††	Dapa dominant

† Result relates to TZD priced at the £112.18; using TZD price from original submission dapagliflozin dominates

†† Dapagliflozin less costly and less effective in CDM

To explain the differences in results generated by CDM and DCEM when using base-case settings, corresponding lifetime incremental costs and incremental quality adjusted life years (QALY) are presented separately on Figure 3.3.1 and Figure 3.3.2. Notably, both models generate similar estimates of incremental cost (Figure 3.3.1)[6], whereas the DCEM (running with base case settings, blue diamonds) predicts consistently higher incremental QALY gains (Figure 3.3.2). This difference is predominantly driven by BMI utility. When the DCEM weight disutility is set to 0.0061, the DCEM consistently predicts fewer incremental QALYs gained than the CDM.

The influence of BMI utility is further illustrated by the large QALY gains associated with the metformin + sulphonylurea (52 week NMA) and metformin + sulphonylureas + TZD comparators, for which the weight differential modelled is 4.45kg and 4.73kg respectively. When the disutility associated with

[5] See Appendix for the full IMS CDM modelling report.

[6] In this illustration both models have run comparisons with TZDs using the reduced annual therapy cost of £112.18.

weight change is set to 0.0061 (Bagust) the incremental QALY gains for the DCEM aligns closely with the CDM results (as illustrated by the green triangle for Met+SU [52 week]).

It is noteworthy that the incremental QALY gains associated with Met+SU (52 week NMA) results and Met+SU [Study 4] are quite different. This difference is driven by HbA1c reduction, which ultimately controls the timing of duration of therapy. The modelled HbA1c reduction for dapagliflozin is -0.92 using the 52 week NMA data and -0.52 using study 4 data. Consequently simulated patients remain on dapagliflozin longer using the 52 week NMA data and therefore retain more weight loss benefit compared to study 4. This explains why the QALY gains are different in these two evaluations.

Figure 3.3.1: Comparison of the incremental costs obtained from the CORE diabetes model and DCEM for the indicated comparators. Incremental costs for TZD comparisons use £118.12 drug cost.

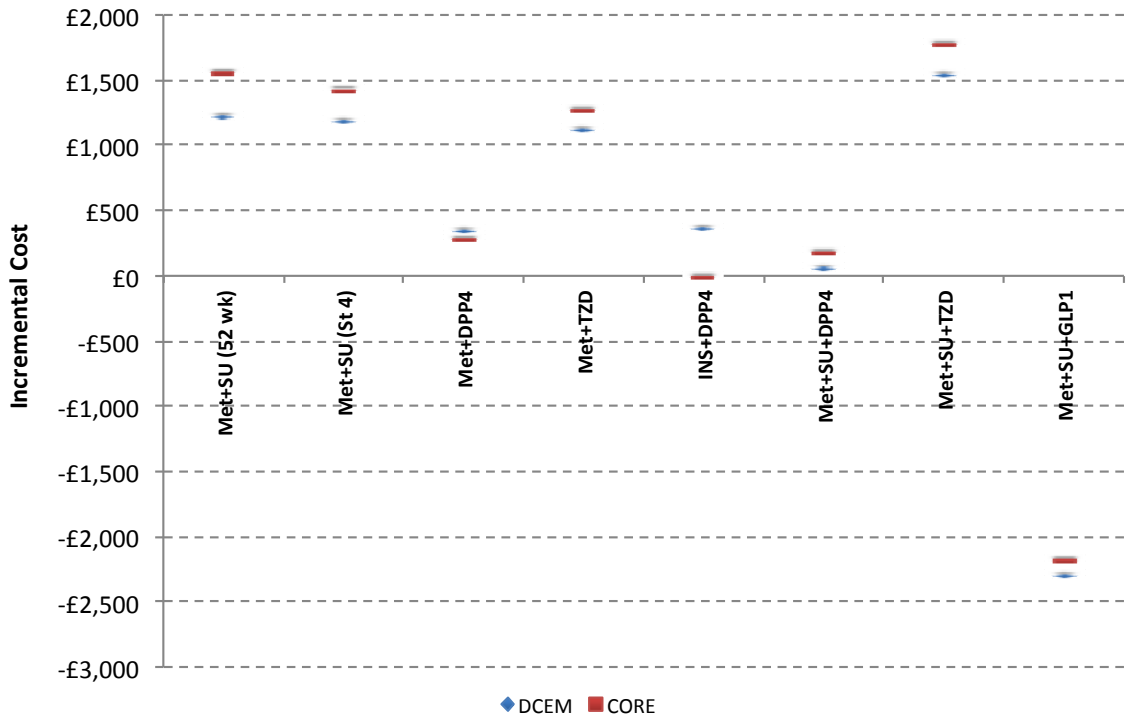
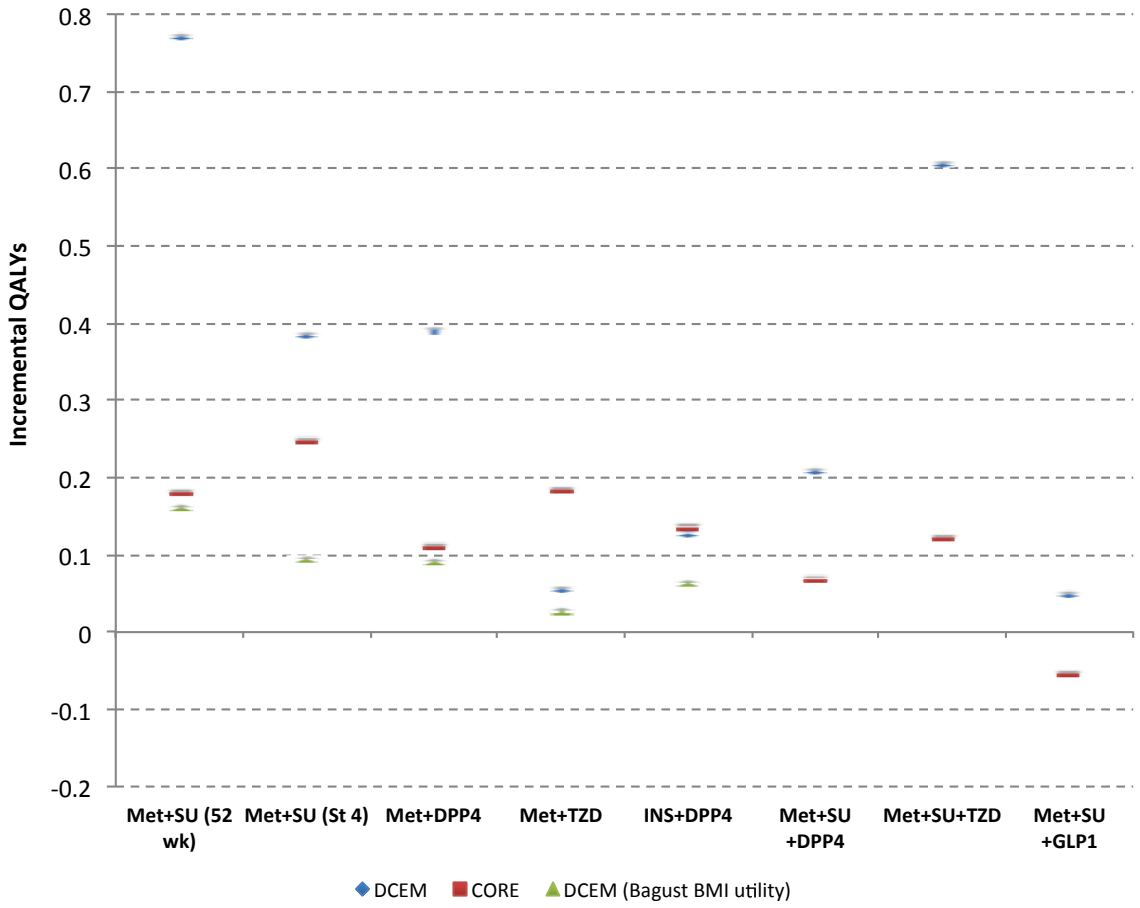


Figure 3.3.2: Comparison of the incremental quality adjusted life years (QALYs) obtained from the CORE diabetes model and DCEM for the indicated comparators.



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