NHS
National Institute for
Health and Clinical Excellence

NICE
Level 1A
City Tower
Piccadilly Plaza
Manchester
M1 4BT

[redacted]

[redacted]

Dear [redacted]

Re: Single Technology Appraisal – Dapagliflozin for the treatment of type 2 diabetes

The Evidence Review Group (Health Economics Research Unit and Health Services Research Unit, University of Aberdeen) and the technical team at NICE have now had an opportunity to take a look at submission received on the 17 July 2012 by Bristol Myers Squibb and AstraZeneca. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00 on 01 November 2012**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] Any procedural

questions should be addressed to [redacted] in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

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

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

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

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

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

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

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

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

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

clarify the rationale for assuming a treatment duration of 14.7 years for GLP-1.

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

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

Section B: Clarification on cost-effectiveness data

General

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

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

C++ programming code

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

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

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

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

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

- These files should be the exact versions used to generate the DLLs provided in the submission.
- If a specific compiler is required, please provide details of this compiler and supply a temporary product license covering the anticipated timeframe of the appraisal. This compiler should allow step by step debugging.

- It should be possible to compile these DLLs from the files provided without errors or significant warnings.

Clinical effectiveness and baseline characteristics

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

Model structure

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

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

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

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

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

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

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

B16. In regard to the model therapy target values in cells Q29:Q31 of the *Demographics* worksheet, please clarify whether a change of therapy occurs if any of the 3 target values are met, only if all the 3 values are met or something else? Further please clarify what happens if these cells are empty? And how do the targets of these cells differ from the threshold HbA1c of cells L29 and L31 in the same worksheet? Do 3 lines of therapy always have to be specified even if only second to last or last line is being considered?

Model validation

B17. **Priority Question:** Please outline which studies within table 1 of the Cardiff (DCEM) model validation report are drawn from Mt Hood challenges. To what extent do the values reported in table 1 comprehensively report the disaggregated and aggregated event rates modelled in each of the Mt Hood challenges? Has the Cardiff (DCEM) model changed between the Mt Hood challenges?

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

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

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

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

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

Modelling submitted

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

Health-related quality of life

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

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

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

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

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

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

Hypoglycaemia fear score and utility equations

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

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

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

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

Costs

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