National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Canagliflozin in combination therapy for treating type 2 diabetes [ID554]

You are asked to check the ERG report from **Southampton Health Technology Assessment Centre, University of Southampton** to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **9th January 2014** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Consideration of add-on to insulin data for canagliflozin as out of NICE scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the DIA3008 trial does not match the NICE scope for canagliflozin (Table 2) as approximately one third of patients recruited into DIA3008 had no background therapy apart from insulin. In addition, the DIA30008 trial was excluded from consideration by the ERG as not being relevant to the Decision Problem as there was no active comparator (ERG Report Table 2). In addition, Janssen believes that the DIA3008 trial is	It is requested that the text of the ERG report be amended to reflect that the DIA3008 trial and the add-on to insulin therapy data for canagliflozin can be considered within scope.	Janssen considers the cost-effectiveness of canagliflozin as an add-on therapy to insulin to be an important part of the canagliflozin STA, and this population of patients is likely to be in particular need of additional innovative therapies. The 'Populations' section of the same document states: *"Add-on therapy to insulin*	Strictly speaking this trial was not wholly relevant to the scope, due to the lack of active comparator and the fact that a third of patients in the comparator group did not receive one or more oral anti-diabetic agents (in combination with insulin). However, the ERG report does acknowledge the inclusion of this trial in the NMA and the economic evaluation on page 34, sentence starting *"Finally, although the ERG deemed the three placebo-controlled trials DIA 3002, DIA3012, and DIA3008 as relevant to this report…"* (NB. there was a typo in this

still within the final canagliflozin NICE scope, and that the canagliflozin is consistent with the scope, STA and FAD for dapagliflozin.		*Adults with type 2 diabetes that are inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents."* Although the confusion has perhaps arisen from where it is stated in the 'Comparators' section of the canagliflozin NICE final scope: *"Add-on therapy to insulin* *• One or more oral anti-diabetic agents (in combination with insulin)."* Janssen therefore suggests that it is incorrect to exclude the analysis using the DIA3008 data, as we believe this is fully in accordance with the NICE scope. For the assessment of dapagliflozin in Type 2 diabetes mellitus (T2DM) by NICE, the dapagliflozin final NICE scope was identical to the canagliflozin NICE scope in the wording of both the 'Comparators' and 'Population' section. The dapagliflozin trials included patients receiving insulin monotherapy. In the assessment of dapagliflozin by NICE, this line of therapy was considered within scope and dapagliflozin received a positive recommendation in this line of therapy from NICE.	sentence, which should have read 'irrelevant').

Issue 2 Consideration of canagliflozin trials without direct comparators as out of NICE scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 11 of the ERG report it is stated that: *"The ERG considered that only trials with active comparator arms were relevant to the NICE scope*", and on page 30-31: *"The six studies identified for inclusion by the manufacturer meet the inclusion criteria, but three are not relevant to the decision problem or final scope, as we detail below…three of the included RCTs (DIA3002, DIA3012, and the DIA3008 insulin sub-study) were not relevant, for the reasons detailed in Table 2 – namely the absence of active comparators."* It is the view of Janssen that lack of an active comparator is not sufficient grounds to exclude a trial from the decision problem. Many Phase 3 trial programmes are carried out with placebo-controlled trials and no direct comparative data; the existence of direct comparative data should not reduce the relevance of placebo-controlled RCT data. As is common in economic evaluations, data from a well-constructed NMA were used to populate the analyses.	It is requested that the text within the ERG report stating these trials as irrelevant is amended to describe these trials as being relevant and informative to the decision problem.	Although the placebo-controlled trials DIA3002, DIA3012 and DIA3008 do not include an active comparator, the data gathered within these trials can be considered as informative to the assessment of canagliflozin in T2DM. The DIA3002 trial provides additional data on the efficacy of canagliflozin in triple therapy with Met+SU, DIA3012 important data on the efficacy in triple therapy with Met+Pioglitazone, and DIA3008 shows the efficacy of canagliflozin in add-on to insulin therapy..	Strictly speaking the three placebo-controlled trials were not of direct relevance to the scope, due to the lack of active comparators. For this reason, and to keep the ERG report succinct, we did not focus on them. However, the report does acknowledge their contribution to the NMA and the economic evaluation on page 34, sentence starting "*Finally, although the ERG deemed the three placebo-controlled trials DIA 3002, DIA3012, and DIA3008 as relevant to this report…"* (NB. there was a typo in this sentence, which should have read 'irrelevant'). The results of the placebo-controlled trials are reflected in the ERG report in section 3.3.8 (adverse events) whereby we report pooled rates of AEs for canagflilozin and non-canagliflozin (including placebo) arms of the trials. No further action necessary.

Issue 3 Modelling with second order uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG questioned the use of second order uncertainty in both the base case and the DSA. For example, • *It is unclear why second order uncertainty was not switched off in DSA as this means that results are confounded to some extent by stochasticity in other parameters. (p. 124)* • *The MS indicates the model was run with 500 patient cohorts and 1000 patients in each cohort in scenario analysis (Table 53). Second order uncertainty was not switched off in scenario analysis (i.e. by specifying only one patient cohort) which means that results are to some extent confounded with parameter stochasticity. (p. 124)* The ERG additionally implies that use of second order uncertainty in the base case and the DSA are unusual. Janssen argues that lack of second order uncertainty in models previously assessed is a failing of those economic analyses, not a virtue. With second order uncertainty inactivated, the results will naturally vary as diabetes models are inherently non-linear with respect to the uncertain inputs. A statement on page 92 of the ERG report captures the nature of the potential bias (albeit in the context of microsimulation vs. cohort modeling): ”This can mean that the average of risks is not same as the risk for the patient with ‘average’ characteristics, and consequently a patient-level simulation is preferred to a cohort model.” For the same reason, removing parameter uncertainty by inactivating second order uncertainty will make the estimate of cost-effectiveness more precise but less accurate, as the non-linearity of relationships will be lost. Inclusion of second order uncertainty best reflects our current understanding of the treatment of T2DM with canagliflozin, and thus Janssen would argue that the basecase and	It is requested that the criticism of the approach to model with second order uncertainty activated be reduced, and that questions into the robustness of the basecase ICERs are amended.	Inclusion of second order uncertainty in the basecase does not invalidate the ICERs calculated and Janssen would argue that the ICERs including second order uncertainty are more accurate, both because they include a greater number of patients and because they capture natural non-linearities in the disease associated with our limited understanding of a complex disease. The potential loss of accuracy is perhaps best illustrated with a simple example from queuing theory: If people arrive at a service machine with exponential inter-arrival times of one minute and it takes the machine 0.99 minutes on average (exponentially distributed) to service each person, then if we run a simulation model using mean input values only there would never be a queue - because the service rate is shorter than the arrival rate. However the true average delay is 98 minutes and this would be accurately reproduced in a simulation model sampling input values	The ERG is not questioning the use of second order uncertainty in the base case and DSA, rather pointing out that the MS does not justify its use. Given that second order uncertainty is used, base case and DSA results will be to some extent confounded with parameter stochasticity. Not a factual inaccuracy. The ERG report states that ‘in the ERG’s experience base case analyses do not usually reflect PSA’ (p96). Not a factual inaccuracy.

other comparisons should include second order uncertainty. The NICE Briefing paper for methods review (1), moreover, echoes this with the statement that exploring uncertainty in non-linear decision models, probabilistic methods provide the only reliable means of estimating mean costs and outcomes (Section 5.8 of the Briefing paper).		appropriately.	
The ERG report states on pages 16, 97 and 128 that the original submission ran comparisons using 1000 patients, whereas the ERG comparisons were run with 100,000 patients. The inference is made by the ERG on page 16 that the manufacturer comparisons contained less information and are thus less robust than the ERG comparisons. In fact, the original submission was run using 1000 cohorts of 1000 patients each, thus generating 1 million unique patients, an order of magnitude greater than the ERG comparisons run (and the reason why simulation run times are 15 hours and 1.5 hours, respectively). Janssen believes that the simulations with 1 cohort and 100,000 replicates contains substantially less information and the results may not be robust. Janssen has replicated the ERG simulations with both 100,000 and 500,000 replicates and found that the results differed (in particular, the big increase seen in the ICER in the ERG simulation in DUAL vs. DPP-4 disappeared; see Table 3 below).	It is requested that it is acknowledged that 1000 cohorts of 1000 patients were run, rather than just 1000 patients, on pages 16, 97 and 128.	To state only that 1000 patients were run understates the level of rigour of the manufacturer basecase comparisons and the amount of data within these datasets.	The ERG report uses the term '1000 patients' as shorthand for '1000 patients per cohort'. We recognise that the full meaning of this shorthand may not be clear in all contexts in the ERG report and the requested amendments have been made to pages 16, 97 and 128.
The ERG states that the deterministic sensitivity analyses (DSA) are confounded with PSA (page 121 and 124). The ERG also states (page 124) that the scenario analysis results are confounded by the second order uncertainty not being switched off. As noted above, inactivating second order uncertainty actually fundamentally changes the disease model, but a more useful description may be instead that results can be confounded by inactivation of second order uncertainty (rather than the opposite). Additionally, versus the base case which we argue should definitely include second order uncertainty, inactivation of second order uncertainty for the scenario analyses divides the source of changes into the changes within that scenario and the inactivation of second order uncertainty, making it difficult to interpret.	While there is added 'noise' around some of the DSA analyses as a result of the second order uncertainty being active, Janssen does not consider that the DSA are confounded but that they remain valid. The ERG's assertion of confounding might therefore be reduced/rewritten.	The exploration of uncertainty around single parameters with DSA and second order uncertainty are separate issues; the DSA estimates the impact on the ICER of varying a single parameter, while second order uncertainty shows the variability around that estimate. Janssen believes that the results of the DSA in the original submission remain valid and that the uncertainty of the parameters has been explored.	Given the small incremental costs and benefits associated with many of the treatments it is possible for ICERs to be greatly changed by use of an alternative parameter set (for example compare ERG report Table 67 and Table 69). The ERG considers that these differences do amount to confounding since the key outcome (ICER) is in some cases substantially affected by incorporation of the PSA. Not a factual inaccuracy.

Issue 4 Fully incremental analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
By expanding the information set to the complete set of comparators simultaneously, the fully incremental cost-effectiveness analysis performed by the ERG (Tables 72 and 74) has the potential to be informative. Janssen considers the replication sizes to be too small to be robust, however. Even small differences in the distribution of initial baseline characteristics, while not greatly affecting the absolute values of the outcomes, can affect the relatively smaller Δ values when combining results from different simulation runs. Some variability, indeed, is evident when comparing the results of Tables 72 and 74 that can impact the results directionally: If the ERG is correct in their assertion that 100,000 replicates (with second order uncertainty inactivated) is sufficient to inform fully incremental analysis, then the canagliflozin 100mg results from Table 72 are equally valid if inserted into Table 74 (and vice versa for canagliflozin 300mg): **Table 1. ERG Table 74, with Cana 100 data inserted from ERG Table 72.** Comparator | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER compared to next cheapest option SU | £25,773 | 8.797 | | | Dapagliflozin | £26,121 | 8.965 | £348 | 0.168 | £2,071 DPP-4-i | £26,225 | 8.972 | £104 | 0.007 | £14,857 **Cana 100 | £26,234 | 8.977 | £9 | 0.005 | £1,800** Cana 300 | £26,809 | 9.004 | £575 | 0.027 | £21,296 GLP-1-a | £28,702 | 9.008 | £2,468 | 0.031 | £79,613 Rather than generating the high ICER for canagliflozin 100mg vs. DPP-4-I, the ICER is quite low and canagliflozin (both doses) can be interpreted as cost-effective in dual therapy. The adjusted Table 74 above, moreover, is no less valid than Table 72. While increasing the number of replications to reduce this variability is warranted a more robust analysis would use averages of the results for the comparators (from Tables 72	While the usefulness of the ERG's analysis is recognised, it is requested that the text of the ERG report acknowledges the remaining uncertainty in the analysis using a single cohort of 100,000 patients, and that the conclusion that canagliflozin 100mg has an ICER of £84,800 changes if a more robust analysis using the average results from the comparisons is applied.	Janssen considers the emphasis placed on the ICER of £84,800 to be undue (mentioned on pages 16, 136 and 140) considering that it is not a robust estimate and, under other analyses, the fully incremental cost-effectiveness estimate for canagliflozin 100mg is considerably lower.	Not a factual inaccuracy, no action required. The ERG report does not assert that 100,000 replicates (patients per cohort) are sufficient to inform fully incremental analysis. The ERG welcomes the further illustration here of the differences in the model results which can arise when the model is re-run with both the same and altered settings.

and 74) since the comparators were run versus both doses. Using averages by comparator from Tables 72 and 74 gives the following results:

Table 2. Fully incremental analysis using averages of comparator costs and QALYs from Tables 72 and 74.

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER compared to next cheapest option
SU	£25,857	8.794			
DPP-4-i	£26,107	8.973	£250	0.179	£1,390
Dapagliflozin	£26,111	8.961	£4	-0.012	Dominated
Cana 100	**£26,234**	**8.977**	**£128**	**0.004**	**£31,875**
Cana 300	**£26,809**	**9.004**	**£575**	**0.027**	**£21,296**
GLP-1-a	£28,639	9.012	£1,830	0.008	£228,750

Janssen has replicated the ERG comparisons with both 100,000 and 500,000 replicates and found that the results differed (in particular, the large increase seen in the ICER in the ERG comparison for canagliflozin 100mg in dual therapy vs. DPP-4-i disappeared. Note that due to lack of detail in the ERG report, we were unable to run these comparisons using the ERG basecase, but would be happy to do so if these data were supplied.

Table 3. Fully incremental cost-effectiveness analysis with 500,000 patients and no parameter uncertainty

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER compared to next cheapest option
SU	£25,996	8.787			
DPP-4-i	£26,160	8.966	£164	0.178	£919
Dapagliflozin	£26,204	8.973	£44	0.008	£5,865
Cana 100	£26,247	8.977	£43	0.004	£11,932
GLP-1-a	£28,668	9.010	£2,421	0.033	£73,670

* Data for Canagliflozin 100mg averaged across the four pairwise comparisons

Issue 5 Comparators modelled in triple therapy; comparisons vs. insulin were modelled

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Modelling comparisons against insulin in triple therapy are not consistently acknowledged the ERG report. On page 23, the ERG report states "*For the assessment of triple therapy with a combination of canagliflozin, metformin and a sulfonylurea, the comparators stated in the manufacturer's decision problem are: DPP-4-inhibitors and GLP-1 analogues, both in combination with metformin and a sulfonylurea. The manufacturer has therefore included two of the four comparators stated to be of interest in the final scope*" The inclusion has been noted by the ERG in places (e.g. ERG report Table 55; Page 80, Table 49) but not elsewhere (e.g. Table 51) While the original error was made by Janssen by omitting this comparison from Table 6 of the MS, modelling was conducted against long-acting insulin and was detailed throughout the main body and results sections of the MS. Thus three of the four comparators of interest in the final scope were modelled.	It is requested that the sentences noting the omission of this modelling comparison are amended, as this comparison has been carried out, and is noted in other sections of the ERG report, on pages 23 and Table 51.	This modelling comparison is an additional piece of evidence exploring the cost-effectiveness of canagliflozin in triple therapy. In addition, inclusion of this comparison demonstrates that Janssen has made best efforts to adhere to the NICE scope.	Acknowledged, amendments made to page 23, and page 90 (Table 51).
The sentence on page 100 is unclear: *"Some comparators from the scope were excluded from the decision problem:* *In triple therapy in comparison to insulin (alone or in combination with one or more oral antidiabetic agents, such as a DPP-4-1 or GLP-1-a).* [redacted] As stated above, comparisons against insulin were indeed performed in triple therapy. Comparisons for products in combination with DPP-4-I or GLP-1-a were not performed, for the reasons stated in the report.	It is suggested that the sentence on page 100 is clarified. Possible text is below: In triple therapy comparisons in combination with a DPP-4-1 or GLP-1-a). [redacted]	The current sentence is not clear in which comparisons from the NICE scope were included and which were not, and thus may be confusing to the reader.	Acknowledged, amended page 100.
On Page 23 the ERG state: *"The comparators specified in the scope that have not been considered*	It is suggested that the sentence on page 23 is	Long acting insulin and biphasic insulin were included in the MET+SU network as part of the	Acknowledged, page 23 amended.

*by the manufacturer are: thiazolidinediones (although, again, the scope more specifically states 'pioglitazone') and insulin, both combined with metformin and a sulfonylurea. The manufacturer states that these comparators have not been included as "insufficient clinical data were found to populate the NMA [network meta-analysis]"(*MS p. 41)." Long acting insulin and biphasic insulin were included in the MET+SU network as part of the NMA.	amended. Possible text is below: "The comparator specified in the scope that has not been considered by the manufacturer for use in triple therapy, combined with metformin and a sulfonylurea, is: thiazolidinediones (although, again, the scope more specifically states 'pioglitazone').The manufacturer states that this comparator has not been included as "insufficient clinical data were found to populate the NMA [network meta-analysis]" (MS p. 41)."	NMA and are a relevant additional piece of evidence for the assessment of the efficacy of canagliflozin in triple therapy.	

Issue 6 Quality checking of extraction of data for the clinical systematic literature review and NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 39, the ERG state: *"Critical appraisal of included studies appears to have been conducted by one reviewer"* On page 43: *"The ERG considers that the data extraction of all of the publications should have been checked, rather than just 20% of them."* With apologies for the error in our original submission, we have checked with the agency that performed the data extraction and they have confirmed that the data extracted for inclusion in the NMA was 100% quality checked by a	It is requested that the sentences that highlight this issue are amended accordingly, on pages 39, 40 (Table 4) and 43.	Checking of 100% by a second reviewer is appropriate methodology, endorsed by NICE and the DSU. While Janssen acknowledges its error in the original report, stating that this step of the NMA was correctly performed reduces uncertainty in the quality of the NMA.	Acknowledged, amended on page 39, page 40 (Table 4), and page 43.

second reviewer.			

Issue 7 Minor corrections

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following paragraph on Page 12 of the ERG report: *"In both the dual therapy trials canagliflozin 300mg and 100mg were associated with statistically significant greater weight loss at 52 weeks than sulfonylurea glimepiride or the DPP-4-i sitagliptin"* omits the fact that treatment with a SU causes weight gain and DPP-4-i is weight-neutral, whereas CANA is associated with weight loss.	It is requested that this paragraph is amended to reflect that treatment with an SU leads to weight gain, and with DPP-4i is for the most part weight-neutral (as stated in the ADA/EASD position statement, original submission reference 45.	While this may appear a minor wording issue, weight gain with an SU is of concern to patients and is a considered as a disadvantage of treatment with an SU.	Not a factual inaccuracy, no further action necessary.
The sentence on page 128 of the ERG report: "*The standard errors used for the HbA1c % treatment effect parameters are too small*." is not clear. The standard errors have been taken directly from the NMA data and there is no option to take alternative data.	It is suggested that this sentence is deleted.	This sentence is unclear in its meaning and incorrectly suggests inaccuracy in the data inputs.	This sentence refers to ERG report p104 where it is stated that 'the standard error of the drift assumption is not reflected in the standard error for the combined first year change in HbA1c and drift estimate, which as specified in the model is simply the standard error associated with the NMA estimate of the first year change in the HbA1c %'. This has now been clarified on ERG report p128.
On page 88, the ERG report states: "*These revised base cases are based on assumptions about BMI change rather than actual BMI changes which were observed in the key trials".*	It is requested that the sentence is expanded to include the fact that this amendment in the clarification letter was to allow a like-for-like comparison which should reduce the	The current ERG sentence implies deliberate bias by Janssen to improve the ICER and does not note the scientific validity of the amendment.	Not a factual inaccuracy, no action required.

This sentence does not take into account that the original submission compared actual BMI change in the CANA arm with imputed BMI changed (based on kg change and mean UK height) in the dapagliflozin and GLP-1-a treatments arms (based on incomplete data availability). The inconsistency in these cases could be a possible source of bias because of potential mismatch between mean UK and trial height (and their distributions). By taking the weight loss data for both products in this subset of simulations and then applying a conversion to BMI, although the absolute values are vulnerable to the conversion equation applied (as noted by the ERG on page 106 of their report), the comparative effect on patient weight between canagliflozin and the interventions is a more valid measure, i.e. is a like-for-like comparison.	risk of bias, rather than a substitution of trial data for an assumption in order to improve the ICER.		
On page 126, the ERG state "*These results bear out the clinical finding that dapagliflozin is better at controlling BMI than both canagliflozin 100mg and canagliflozin 300mg (MS Table 185,Appendix p299).*" It should be noted that these modelling results used BMI data from the canagliflozin trials against weight loss data from dapagliflozin (as outlined in the row immediately above). A like-for-like comparison of weight loss from the network meta-analysis (Figure 40 of the original submission) shows that dapagliflozin in fact causes less weight loss than both doses of canagliflozin.	The conclusion that dapagliflozin is better at controlling BMI than canagliflozin is too strong once all data is considered and it is requested that the sentence is amended to reflect that this is the conclusion that can be made only on the data used in the model (which Janssen has argued in the response to clarification questions letter and above, that this approach is flawed).	The conclusion that dapagliflozin is better at controlling BMI than canagliflozin is not supported by the data.	Acknowledged, the requested amendment has been made to p126.
On page 34 the ERG describes a study from the UKCRN database that they could not reconcile against the studies described in the original submission. The study description noted in the UKCRN reflects an earlier design of the DIA3002 study (the final design of which is fully described in the submission). The design evolved over time including the removal of the sitagliptin arm (which was incorporated into the	It is suggested that this paragraph is deleted from the report.	Inclusion of this paragraph of a seemingly undeclared canagliflozin trial may be confusing to the reader, and implies that Janssen has not been fully forthcoming in canagliflozin trials conducted.	Thanks for clarifying the status of this study. The ERG considered it possibly relevant in the light of the information available, and erred on the side of inclusion.

DIA3006 trial). The UKCRN website therefore contains a defunct trial design that was never initiated. Sites from both England and Northern Ireland participated in the final DIA3002 study.			
On page 34 the report states "*, although the ERG deemed the three placebo-controlled trials DIA3002, DIA3012, and DIA3008 (insulin sub-study) as relevant to this report*" This statement is inconsistent with the ERG statements detailed in Issue 1 and 2 above. It is assumed that a word has been accidentally omitted from this sentence.	It is suggested that this sentence is revised in line with revisions in Issues 1 and 2 above.	The sentence as it stands is inconsistent with statements elsewhere in the report and potentially confusing to the reader.	Apologies, this should have read *"…as irrelevant to this report"* (as noted above in our response to issue 2). Amended on page 34
On page 36 the ERG report states "These included established generic instruments such as the EQ-5D, SF-36, and Current Health Satisfaction Questionnaire (CHES-Q)…"	Please move CHES-Q to list of disease specific instruments in second half of this sentence which states, "and disease-specific instruments: Impact of Weight on Quality of Life Lite (IWQOL-Lite); Multi-dimensional Diabetes Questionnaire (MDQ); Diabetes Utility Index (DUI); Diabetes Intention, Attitude, and Behavior Questionnaire (DIAB-Q)."	CHES-Q is not an established generic instrument; it was designed by Janssen specifically to capture subject satisfaction with current diabetes-relevant aspects of health. This amendment is a correction of factual information about the type of PRO instruments implemented in the trial program	Acknowledged, amended on page 36
On page 36, Table 58, the ERG report states "These data appear to be for all patients, rather than for just canagliflozin, although this is not clearly stated."	Please change text to, "These data are for all patients, rather than for just canagliflozin."	The methods section in PRO Appendix states, "All treatment arms were pooled, and treatment assignment was investigated as a potential confounder."	Acknowledged (NB. the page number is 112 not 36). Page 112 amended.
It is stated that the model uses efficacy data in comparison vs. placebo on page 101 and page 125. The model uses as a preference change versus baseline, but in comparisons taking efficacy data from the NMA, only chance vs. placebo is available and so this is used. Related to this is the ERG's question on page 125: "*It*	The sentences on pages 101 and 125 should be changed accordingly.	As the design of clinical trials and the patients enrolled is often heterogeneous, it is not technically appropriate to perform modelling comparisons for two drugs by taking the efficacy vs. placebo from two different placebo-	Not a factual inaccuracy. The model as implemented for this STA uses change versus placebo.

is not clear why the data used in scenario 16 were restricted to direct trials against active comparators, as the model uses change versus placebo for key biomarkers". If the model could be run robustly using data against placebo from different trials, this would obviate the need for direct comparative trials, indirect comparisons or network meta-analyses.		controlled trials.	
Page 109 of the ERG report states "The systematic review provides summary data of utilities for a range of patient characteristics and complications, however, there is no justification provided in the MS as to why these were not used in the model and why the CODE-2 study was chosen for the source of the majority of utilities." Section 7.4.9 of the original submission and Clarification Question B3 both provide what Janssen believes to be adequate justification for why CODE-2 utilities were used as modelling parameters.	It is requested that the sentence on Page 109 is amended to reflect that justification was provided.	The statement that no justification was provided for this aspect of the modelling exercise undermines the credibility of the analyses conducted and the results obtained.	The ERG comment reflects the fact that no discussion is made in the MS of utilities from the other studies identified by the systematic review, and why these were not used in the model. Not a factual inaccuracy.
On page 61/62 the ERG state *"Canagliflozin 300mg had a probability of reducing weight of 16% compared to exenatide, but had a probability of at least 85% compared to the DPP-4-i sitagliptin, pioglitazone, and the SUs glimepiride and glibenclamide."* The figure of 85% is incorrect, and should in fact be 80%, as stated in the original submission.	It is suggested that this sentence is amended. Suggested wording below: "Canagliflozin 300mg had a probability of reducing weight of 16% compared to exenatide, but had a probability of at least 80% compared to the DPP-4-i sitagliptin, pioglitazone, and the SUs glimepiride and glibenclamide."	Minor typographical correction.	Acknowledged, page 62 amended.
On page 108, the ERG notes a discrepancy in the input value used for change in LDL cholesterol for canagliflozin 100mg at 26 weeks in the 3002 trial vs. a publically available poster on the same trial (a difference of -0.6mg/dL vs. -0.8mg/dL). This slight small difference (0.2 mg/dl) is likely due to the fact that different datasets were used for calculating the numbers in the poster and the model input values. Specifically, the poster was constructed	It is requested that the paragraph be changed such that the statement "whilst the input data spreadsheet uses a value of -0.8 mg/dL attributed to the same source," be amended, as the source of the clinical datasets used to generate data for the poster and the model were different. The model input values were generated from the most recent datasets	Although it is acknowledged that this is not strictly a factual correction, the doubt placed on the validity of the parameter by the ERG report is unjustified, and the modelling using this value of -0.8mg/dL is correct.	Not a factual inaccuracy.

from the 26 week dataset while the model inputs (which were generated after the extension period database was locked) used the 52 week database. In addition, the poster used data on LDL measured in conventional units (e.g. mg/dL) whereas the dataset used for calculating the change in LDL for the model was in SI units (e.g. mmol/L) and applied a conversion factor (0.0259) to the mean difference (2).	available.		

References

1 NICE 'Guide to the methods of technology appraisal 2013', http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case#exploring-uncertainty ; accessed January 2014.

2. Reference: Society for Biomedical Diabetes Research http://www.soc-bdr.org/rds/authors/unit_tables_conversions_and_genetic_dictionaries/e5196/index_en.html ; accessed January 2014