Boehringer Ingelheim's response to clarification questions (sent 19/05/2014)

Please note that some questions have been reordered into groups since they address the same area.

Section A: Clarification on effectiveness data

A1. PRIORITY. *The four key trials (counting EMPA-REG 1245-23 as two trials, one in dual therapy, one in triple, with the other two being EMPA-REG BASAL and EMPA-REG MD) report mean change in HbA1c. Please provide for each of the four trials, the proportions of patients achieving the following HbA1c targets: 6.5% or less (the NICE CG 87 target); 7.0% or less (to cater for a situation wherein NICE relax the current target during the current guideline revision): and 7.5% or less (based on the NICE "switching point").*

Response: Please see appendix 1 for the complete set of results for each treatment in each trial.

A2. *For convenience and clarity in the NMA diagrams, please identify trials for each line, rather than just number of RCTs – using name of first author. For example, in figure 28, replace "5" in the line connecting sitagliptin with metformin with the names of first authors of the five RCTs.*
&
A9. ***PRIORITY****. It is difficult to relate the individual studies listed in Table 29 to the 5 NMA diagrams in Figures 28 to 32. Please provide separate tables for the studies included in each of the NMAs illustrated in Figure 28 and in Figure 29.*

Response: Please see appendix two for the revised diagrams and tables.

A3. *Since the NMAs have been done to inform the cost effectiveness model, and since the MS specifies the cost effectiveness is done to compare sitagliptin v. canagliflozin, v dapagliflozin v empagliflozin, please clarify why studies of additional gliptins (linagliptin, saxagliptin, alogliptin) have been included in the NMA shown in Figures 28 etc. We note that vildagliptin studies appear in the NMA shown in Figures 28, but are missing from the NMA in figure 29.*

Response: Inclusion of other gliptins has two functions. First, inclusion of other gliptins in the network meta-analysis allows for a supplementary validity check since gliptins largely exhibit a class effect, and thus, consistency is expected. Efficacy across gliptins was highly consistent, thus adding to the validity of the sitagliptin estimate. Second, the inclusion of additional trials of similar designs investigating other gliptins adds data points for the estimation of between-trial heterogeneity (for the 2nd line NMA where enough trials were available to estimate heterogeneity). Since the reliability of 95% credibility partly depends on the reliability of the heterogeneity estimate, this addition thus adds validity to the produce results.

For vildagliptin it would appear that while it does have a marketing authorisation for this indication the study has either not been published or has only been recently available.

A4. PRIORITY. *The NMA diagram in Figure 28 has a single study comparing Met versus Met + SU; please confirm that this is Charpentier et al 2001 (ref 56). Please comment on why this particular study was chosen, from amongst the many studies of Met vs Met + SU.*
&
A5. PRIORITY. *We note that the figures given for the Charpentier study in Table 29 of the manufacturer's submission (MS) are not the same as those in the paper by Charpentier et al. Please check and correct the figures. We have not yet checked data from any of the other trials in the NMA, so we don't know if there are other errors.*

Response: The Charpentier study was included inappropriately and we have therefore, removed it from the network. The results of the revised network are presented with the revised results in appendix 2. There does not appear to have been any significant changes due to its removal. However, we have re-run the model to explore if this has an impact on the results of the metformin network.

We have also checked all the baseline characteristics and there are a few transcription errors which are noted below. These changes have been made in the revised results section.

2nd line:

- BI GMBH 1245.28 2013
- Gallwitz et al. 2012
- Charbonnel et al. 2006
- Scott et al. 2008
- Janssen (DIA3009) 2013
- Janssen (DIA3006) 2013
- Bailey et al. 2010
- Nauck et al. 2011

3rd line:

- Hermansen et al. 2007
- Moses et al. 2013
- Janssen (DIA3015) 2013

A6. *For completeness. The intervention "Placebo" does not appear in any of the NMA diagrams (Figs 28 to 32). Please confirm that the trials where only one drug is mentioned, they are used in combination with metformin.*

Response: We can confirm that all treatments in the figures are given in combination with the background treatment stated. In addition, this is referred to under question A11.

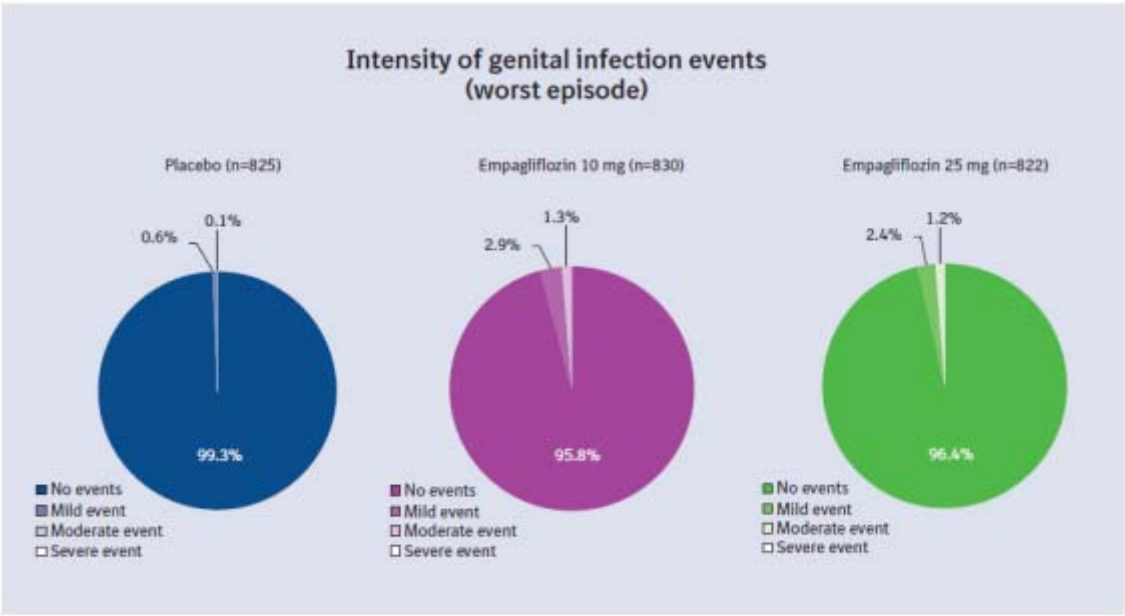
A7. *LOCF. The MS has no information regarding the amount of missing data; in particular please specify separately for each of the two sub-studies of 1245.23, the proportion of observations at week 24 that were carried forward from week 18 for HbA1c in each of the intervention groups (i.e. placebo, Empa10 and Empa25), and similarly for other outcomes listed in tables 17 and 18 of MS.*

Response: Due to strict time windows for this endpoint, a substantial proportion of patients had measurements excluded from the analyses. As a consequence many patients did not have baseline values for MDG and were excluded from the analyses; explaining the lower number of analysed patients as compared to other endpoints. In addition, many patients had only a baseline value; these values were carried forward and included in the LOCF analysis. Therefore, in the LOCF analysis a smaller treatment effect was to be expected. The results based on FAS (observed cases - OC) and FAS (observed cases including values after rescue medication - OC-IR) including only valid on-treatment data may reflect more accurately the treatment effect of empagliflozin on MDG.

A8. *The value of the EXTEND study (1245.31, monotherapy) is for safety data. However Table 20 provides no information on adverse events, in particular for UTI or GTI. Across studies considered in section 6.92 there appears to be a consistent excess of AEs belonging to BICMO "genital infection" category in empagliflozin interventions relative to all others. Section 6.10.1 acknowledges this excess but states "these were generally of mild or moderate intensity". Please provide any data supporting this.*

Response: The following data is from a pooled analysis of trials EMPA-REG MONO, EMPA-REG MET, EMPA-REG METSU and EMPA-REG PIO that will be presented at ADA 2014 by Kim et al 2014. The analysis included a total of 2477 patients with 825 patients on placebo, 830 patients on empagliflozin10 mg and 822 patients on empagliflozin 25 mg. For genital infections the results are presented in Figure 1 demonstrating that in total only 3 patients discontinued treatment due to genital infections.

Figure 1 Results for GTIs from pooled analysis



- Events consistent with genital infection did not lead to dose reduction or discontinuation in most patients. Events led to discontinuation in only one patient (0.1%) on empagliflozin 10 mg and two patients (0.2%) on empagliflozin 25 mg

A10. *Table 31 appears to present only comparative results from the NMAs. Please present absolute results for each intervention, as some appear to have been used in*

the economic model. Please clarify which sets of NMA results derive from which NMAs shown in Figures 28 and 29.

Response: The model used the absolute baseline change in the model (which are presented below in). The RR and baseline changes were then applied to this to calculate the changes in the model. These remain unchanged with the removal of the Charpentier study.

Table 1:Pooled placebo group response and risk estimates from the performed Bayesian network meta-analyses

Outcome	MET Failure (2nd line)	MET+SU Failure (3rd line)	Met+TZD failure	Insulin failure
Mean change from baseline				
HbA1c	-0.051 (-0.095, -0.009)	-0.135 (-0.238, -0.029)	-0.262 (-0.354 to -0.1729)	-0.191 (-0.255 to -0.133)
Weight	-0.879 (-1.110, -0.662)	-0.490 (-0.797, -0.171)	0.907 (0.527 to 1.287)	0.323 (0.121 to 0.514)
Systolic blood pressure	-2.194 (-3.09, -1.271)	-0.540 (-1.493, 0.411)	0.943 (-1.137 to 2.966)	-1.901 (-2.830 to -0.982)
Proportion of events				
Hypoglycaemic events				
Overall	0.0174 (0.0124, 0.0241)	0.065 (0.041, 0.099)	0.010 (0.005 to 0.027)	0.229 (0.201 to 0.257)
Non-Severe	0.0177 (0.0129, 0.0261)	0.083 (0.057, 0.114)	0.006 (0.002 to 0.014)	0.241 (0.206 to 0.279)
Severe	0.00	0.00	0.00	0.0096 (0.0051 to 0.0169)
UTI	0.031 (0.022, 0.042)	0.062 (0.043, 0.083)	0.0216 (0.007 to 0.049)	--
GTI	0.00	0.00	0.008 (0.0002 to 0.0441)	--

Abbreviations: MET (Metformin); SU (Sulfonylurea); Thiazolidinedione (TZD); UTI (Urinary tract infection); GTI (Genital infection)

A11. *The intervention "Placebo" does not appear in any of the NMA diagrams (Figs 28 to 32) in any form. The large NMA depicted in Figure 28 therefore appears to have assumed equivalence of the following treatments: [a] Met = Met +Placebo; [b] Met + SU = Met + SU + Placebo. Please clarify and justify this assumption. The identification of intervention and comparator in the list of studies in Table 29 is inconsistent with regard to the inclusion of "placebo". For example: ERG are familiar with the study of Bolinder in which Met was administered with placebo but in Table 29 it appears the comparator was only Met. Please supply full details of intervention and comparator for all studies in Table 29.*

Response: The rationale for assuming that Met = Met + placebo and Met + Su = Met + SU + Placebo was that it has been accepted in previous reviews by both CADTH and NICE (Canagliflozin STA) and therefore, was considered appropriate here as well.

Section B: Clarification on cost-effectiveness data

B1. *The MS considers models submitted to NICE for canagliflozin and dapagliflozin as well as the submitted empagliflozin model. While the relative differences between different treatments are consistent across these models there are large differences in the lifetime accumulated QALYs for interventions according to model. Thus the*

Empagliflozin model generates QALYs in the range 6.9 to 7.5, whereas the Canagliflozin model generates QALYs in the range 8.9 to 9, and the Dapagliflozin model QALYs in the range 11.2 to 12.6.These differences have not been commented upon in the MS. Please clarify.

Response: These models present very different designs and assumptions. Moreover, as it was mentioned as part of the submission, when the results of the empagliflozin model were compared to those of the CORE model, higher absolute values in terms of QALYs and costs were obtained with the CORE model; one of the main reasons for this was due to differences in the baseline utility used between both models: given the number of additional health states within the CORE model, if the baseline utility used in the empagliflozin cost-effectiveness model was used, it could result in negative utility values and therefore produce counter intuitive results. The baseline utility values used for validation in the IMS CORE model and those of the empagliflozin model used in the base case analyses are reported in Table 2 below.

Table 2. Comparison of baseline utility values used in the empagliflozin model vs. the IMS CORE model used for validation purposes

Health state	Utility value (mean)	95% CI	Reference
Type 2 no complications IMS CORE model	0.8140		IMS CDM Default
Type 2 no complications empagliflozin model	0.77	0.76, 0.78	Clarke 2002[1]

Other significant differences between the models include the use of age-related utilities, the way complications are modelled, the relative impact of BMI and weight changes.

B2a. PRIORITY. *Please clarify table 59, page 253, reproduced below, for hypoglycaemia, non-severe (dual therapy) and how this relates to model inputs? Where does the figure of 0.018 come from, and is it a rate rather than a probability? Is that the rate per annum on metformin alone?*

Response:

For the section of the table referring to 'Hypoglycaemia –non severe (prob.):

The value 0.018 reflects the proportion of patients experiencing at least 1 non-severe hypoglycaemia in the placebo/reference treatment group (i.e. metformin+placebo). The data used reflects the proportion of patients experiencing severe hypoglycaemias over a period of one cycle, since it was estimated from the network meta-analysis (NMA), which considered 26-week data as part of the main analyses. Since this value reflects a proportion of patients, it is a probability rather than a rate.

The figures for the treatments other than placebo (i.e. for which 'baseline risk' corresponds to) are relative risks (RRs) that were estimated from the NMA. All these values are presented also as part of the worksheet 'Default' in the model, where all calculations based on the NMA values or other sources have been presented for transparency purposes.

Revised headings for table 59 are presented below in Table 3

Table 3 Revised table 59 from submission for probability of experiencing a non-severe hypoglycaemia

'Hypoglycaemia - non severe (probability of experiencing at least one event for placebo/reference treatment and RRs for other treatment combinations when compared to placebo/reference treatment*)		
Reference treatment: metformin+placebo	0.018	NMA canagliflozin 100mg and 30mg assumed to be equivalent to dapagliflozin 5mg and 10mg
Met + Sitagliptin*	0.5	
Met + Empagliflozin 10mg*	4.17	
Met + Empagliflozin 25mg*	2.87	
Met + Canagliflozin 100mg*	2.27	
Met + Canagliflozin 300mg*	1.38	
Met + Dapagliflozin*	1.38	

B2b *In the second half of the table [below], the figures look like relative risks – have the tables been labelled the wrong way round? Please explain how the RR of 3.33 was derived, and why the figures for the comparators are all 1.5.*

Response:

For the section of the table referring to 'Hypoglycaemia –non severe (number):

In this part of the table, the average number of hypoglycaemias experienced by each of the patients who had experienced at least one hypoglycaemia is presented. These numbers were obtained from the empagliflozin trials.

There was an outlier patient in the empagliflozin 10 mg arm that resulted in a higher average number of hypoglycaemias experienced per patient (i.e. 3.33 events), and therefore, given that no number of hypoglycaemias was available for the comparators, the value from the empagliflozin 25 mg treatment arm (i.e. 1.5 events) was assumed for these other comparators for conservative purposes.

The information from the NMA and the corresponding links to the default values can be found in worksheet 'Default' (Module 'Documentation', tab 'Default values and data sources'), on the right hand side. To see this information, under the worksheet 'Default', in cell E14, click 'Select all' under 'Inputs' to show all the input parameters that the global model could consider. Please keep in mind some of these inputs may not be used in the model, as it has been identified under column U: 'Sources'. By identifying the cell for the parameter for which you want to know how it was estimated on the basis of the network meta-analysis, you can click on the corresponding formula and see how this is linked to the NMA data, reported on the right hand side of the worksheet (in range AK180:CY2509).

The heading of this subsection within Table 59 should be changed as presented in Table 4:

Table 4 Revised headings for table 59 number of non severe hypoglycaemias events

Hypoglycaemias - non severe (number of events experienced per patient experiencing at least one non-severe hypoglycaemia)		
Met + Sitagliptin	1.5	Clinical study report 1245-0023 Met ; page 1160 – for empa 25mg (1.5) and for empa 10 (3.33)
Met + Empagliflozin 10mg	3.33	
Met + Empagliflozin 25mg	1.5	
Met + Canagliflozin 100mg	1.5	
Met + Canagliflozin 300mg	1.5	
Met + Dapagliflozin	1.5	

B3. PRIORITY. *Earlier in Table 59, a baseline figure for HbA1c change of a reduction of 0.05% is given. Where does that come from? Is it the reduction on metformin and placebo? It appears that in the model, the baseline figure has been added to the reductions on active drugs, whereas a placebo-adjusted figure would subtract the reduction on placebo, as done in para 2 of page 113. This appears to happen with most baseline figures in the modelling, which will exaggerate the effects. For example, if a reduction in HbA1c is 0.05% on placebo, and 0.6% on empagliflozin, adding the former gives an empagliflozin value of 0.65% where correctly subtracting it gives a value of 0.55%. Please check and re-run the model with correct effect sizes.*

Response: The value 0.05 reflects the full treatment effect of metformin + placebo, while 0.60 reflects the relative effect of empagliflozin 10 mg vs. metformin+placebo. Therefore, the absolute effect for met+ empagliflozin 10 mg will be 0.05+0.60 = 0.65.

With the clarifications presented for Table 59 in question B2 (see above) it is hoped that it is now clear that the treatment effect related to baseline appears as an absolute effect, and the treatment effects of all other treatments appear as relative effects vs. baseline/placebo.

It should be noted that in the submission, the values reported for the clinical efficacy estimates reflected the results of the NMA in terms of the absolute value for the placebo/reference treatment and the relative value of the other treatments vs. the placebo/reference treatment. In the model, the efficacy estimates for the empagliflozin treatment combination reflected an absolute treatment effect, and the treatment effects of all other treatments were inputted as relative effects vs. the absolute effect from the empagliflozin combinations. As an example, a clarification is presented in Table 5 for the submissions Table 59, specifically related to the clinical efficacy estimates of the reduction from baseline in HbA1c for second line therapies, where it can be seen the corresponding absolute responses associated to empagliflozin combinations, and the relative responses of all other treatment combinations when compared to either empagliflozin 10 mg treatment combinations or empagliflozin 25 mg treatment combinations. The clinical efficacy estimates included in the model were presented in the worksheet 'Treatment efficacy' and whether each of the treatment effects referred to an absolute or a relative effect was presented in columns S:T for HbA1c estimates, columns AL:AM for SBP estimates and in columns BX:BY for weight change estimates.

Table 5: Revision to table 59 from submission for estimates for HbA1c

Clinical efficacy estimates for the decrease from baseline in HbA1c		
Absolute response		
Met + Empagliflozin 10 mg	0.65	NMA
Met + Empagliflozin 25 mg	0.75	
Relative response vs. Met + Empagliflozin 10 mg		
Met + Sitagliptin 100 mg	0.19	
Met + Canagliflozin 100mg	0.06	
Met + Canagliflozin 300mg	0.19	
Met + Dapagliflozin 10 mg	-0.04	
Relative response vs. Met + Empagliflozin 25 mg		
Met + Sitagliptin 100 mg	0.09	
Met + Canagliflozin 100mg	-0.04	
Met + Canagliflozin 300mg	0.09	
Met + Dapagliflozin 10 mg	-0.14	

However, to explore the impact of this alternative method of calculation, additional analyses were run considering placebo-adjusted effects. The results of these analyses are presented in Table 6 to Table 9 below. Although absolute values in terms of health benefits were smaller than those for the analyses presented in the submission (considering non-placebo adjusted effects) and the corresponding costs higher because of higher incidence of long term complications, the incremental values and ICERs obtained under both scenarios are rather similar (see Table 1 and Table 2 below). The ICER that became more favourable compared to the initial analyses run for the NICE submission was that corresponding to insulin+canagliflozin 300 mg when compared to insulin+dapagliflozin 10 mg (which was reduced from £74,075 to £260), which was due to a higher incremental number of QALYs when compared to dapagliflozin 10 mg after the placebo-adjusted estimates were considered.

Table 6. Comparison of ICERs from analyses including vs. excluding the placebo effect for 2nd line therapy comparisons

Treatment combination	QALYs	Δ QALYs		Δ Costs	ICER
Base case analysis presented to NICE (considering placebo effect)					
Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	£133	Dominated by sitagliptin 100 mg
Met + Canagliflozin 100 mg	7.415	-0.01	£32,300	£255	Dominated by sitagliptin 100 mg

Met + Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
Met + Empagliflozin 10 mg	7.424	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Met + Canagliflozin 300 mg	7.418	-0.015	£32,737	£384	Dominated by empagliflozin 25 mg
New analysis removing placebo effect					
Met + Sitagliptin 100 mg	7.409	-	£32,258	-	-
Met + Dapagliflozin 10 mg	7.385	-0.024	£32,471	£214	Dominated by sitagliptin 100 mg
Met + Canagliflozin 100 mg	7.397	-0.012	£32,513	£255	Dominated by sitagliptin 100 mg
Met + Empagliflozin 25 mg	7.417	0.008	£32,540	£282	£35,263
Met + Empagliflozin 10 mg	7.406	-0.011	£32,833	£293	Dominated by empagliflozin 25 mg
Met + Canagliflozin 300 mg	7.406	-0.011	£32,959	£420	Dominated by empagliflozin 25 mg

Table 7. Comparison of ICERs from analyses including vs. excluding the placebo effect for 3rd line therapy comparisons with metformin+SU background

Treatment combination	QALYs	Δ QALYs		Δ Costs	ICER
Base case analysis presented to NICE (considering placebo effect)					
Met+SU+ Canagliflozin 100 mg	6.98	-	£31,217	-	-
Met+SU+ Sitagliptin 100 mg	6.959	-0.021	£31,365	£148	Dominated by canagliflozin 100 mg
Met+SU+ Empagliflozin 10 mg	6.991	0.011	£31,409	£192	£17,445
Met+SU+ Empagliflozin 25 mg	6.978	-0.013	£31,557	£148	Dominated by empagliflozin 10 mg
Met+SU+ Canagliflozin 300 mg	6.976	-0.015	£32,087	£679	Dominated by empagliflozin 10 mg
New analysis removing placebo effect					
Met+SU+ Canagliflozin 100 mg	6.974	-	£31,539	-	-
Met+SU+ Sitagliptin 100 mg	6.945	-0.029	£31,622	£82	Dominated by canagliflozin 100 mg
Met+SU+ Empagliflozin 10 mg	6.979	0.005	£31,640	£101	£20,200
Met+SU+ Empagliflozin 25 mg	6.963	-0.016	£31,820	£180	Dominated by empagliflozin 10 mg
Met+SU+ Canagliflozin 300 mg	6.97	-0.009	£32,244	£604	Dominated by empagliflozin 10 mg

Table 8. Comparison of ICERs from analyses including vs. excluding the placebo effect for 3rd line therapy comparisons with metformin+TZD background

Treatment combination	QALYs	Δ QALYs		Δ Costs	ICER
Base case analysis presented to NICE (considering placebo effect)					

Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-
Met + TZD + Canagliflozin 100 mg	6.983	0.016	£31,329	£26	£1,644
Met + TZD + Empagliflozin 25 mg	6.999	0.016	£31,486	£157	£9,806
Met + TZD + Canagliflozin 300 mg	6.978	-0.021	£31,866	£380	Dominated by empagliflozin 25 mg
Met + TZD + Empagliflozin 10 mg	6.996	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg
New analysis removing placebo effect					
Met + TZD + Sitagliptin 100 mg	6.956	-	£31,627	-	-
Met + TZD + Canagliflozin 100 mg	6.974	0.018	£31,721	£93	£5,183
Met + TZD + Empagliflozin 25 mg	6.979	0.005	£31,815	£94	£18,780
Met + TZD + Canagliflozin 300 mg	6.975	-0.004	£32,240	£425	Dominated by empagliflozin 25 mg
Met + TZD + Empagliflozin 10 mg	6.970	-0.009	£32,301	£486	Dominated by empagliflozin 25 mg

Table 9. Comparison of ICERs from analyses including vs. excluding the placebo effect for insulin background comparisons

Treatment combination	QALYs	Δ QALYs		Δ Costs	ICER
Base case analysis presented to NICE (considering placebo effect)					
Insulin + Canagliflozin 100 mg	6.944	-	£30,418	-	-
Insulin + Dapagliflozin 10 mg	6.953	0.009	£30,545	£128	£14,178
Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Insulin + Canagliflozin 300 mg	6.957	0.004	£30,842	£296	£74,075
New analysis removing placebo effect					
Insulin + Canagliflozin 100 mg	6.918	-	£30,746	-	-
Insulin + Empagliflozin 10 mg	6.916	-0.002	£30,861	£115	Dominated by canagliflozin 100 mg
Insulin + Dapagliflozin 10 mg	6.924	0.006	£30,870	£124	£20,700
Insulin + Sitagliptin 100 mg	6.896	-0.028	£30,923	£52	Dominated by dapagliflozin 10 mg

Insulin + Empagliflozin 25 mg	6.916	-0.008	£30,925	£55	Dominated by dapagliflozin 10 mg
Insulin + Canagliflozin 300 mg	6.933	0.009	£31,131	£261	£260

B4. PRIORITY. *Please explain table 59 for dual therapy UTIs and how this relates to model inputs? Again, the figures in the top half of the section below, described as RRs, look more like absolute values (rates per time period) and the figures in the bottom half, though described as numbers, look more like relative risks. Please clarify, and explain why the figures for empagliflozin 25 and both canagliflozin doses are 1. Why should the RR be higher for the lower dose of empagliflozin?*

Response: As an example, the value 0.03 reflects the proportion of patients experiencing UTIs in the placebo/reference treatment group (i.e. metformin+placebo). Therefore, it does not reflect an RR but the baseline probability of experiencing at least 1 UTI among patients treated with met+placebo. The data used to populate the model reflects one cycle, since it was estimated, whenever available, from the NMA, which considered 26-week data as part of the main analyses. Since it reflects a proportion of patients, it is a probability rather than a rate. For the other treatments, values reflect the RRs vs. the placebo/reference treatment, again in terms of the proportion of patients experiencing at least 1 UTI.

The values for cana and empa 25 are equal to 1 because from the empagliflozin trial 23 the average number of UTIs experienced among patients experiencing at least 1 UTI was 1. Since no data specific for canagliflozin was available, it was conservatively assumed that patients with canagliflozin that experienced at least 1 UTI event would experience only 1 (as for empa 25 mg).

The value for the average number of UTIs experienced per patient experiencing at least one event is higher in the case empagliflozin 10 mg due to one outlier patient that had experienced between 3 and 4 UTIs in the 26-week follow-up period considered, which increased up to 1.41 the average number of events experienced among patients treated with empa 10 mg that had at least 1 UTI.

B5. PRIORITY. *Please explain the figures in table 59 for non-severe hypoglycaemia and how they relate to model inputs? The figures in the model appear different.*

Response: For Met+SU(+placebo) the figure reflects the proportion of patients experiencing at least one non-severe hypo. The same applies to Met+Pio(+placebo). For the other treatments, the values reflect RRs vs. the reference treatment (either met+SU+placebo or met+pio+placebo).

The values for the treatments with metformin and pioglitazone as background treatment presented in the submission seemed to be a typo. The actual values obtained from the NMA and used in the model are presented in Table 10 below.

Table 10. Proportion of patients experiencing at least one event (for reference treatment)* or RR vs. reference treatment**

Treatment	Values reported in the table presented in the submission	Correct values from the network meta-analysis used in the model
Met + Pio*	0.01	0.006
Met + Pioglitazone + Sitagliptin**	2.29	2.46
Met + Pioglitazone + Empagliflozin 10mg**	0.62	0.47
Met + Pioglitazone + Empagliflozin 25mg**	1.49	1.5
Met + Pioglitazone + Canagliflozin 100mg**	0.1	0.08
Met + Pioglitazone + Canagliflozin 300mg**	0.11	0.08

*It reflects the proportion of patients experiencing at least one non-severe hypoglycaemia in the treatment reference arm, as considered in the NMA

**Values reflect the relative risks of patients in each of these treatments experiencing at least one non-severe hypoglycaemia when the treatment was compared to the reference treatment used in the NMA (i.e. Met+pio).

B6. PRIORITY. *Please explain why the figures in table 59 for Triple therapy BMI/weight change differ from those in the model.*

Response: 'Baseline [..]' reflects absolute treatment effect of the reference treatment (i.e. met+SU+placebo or met+TZD+placebo), while the values for the other treatments reflect the relative treatment effect vs. the reference treatment. Therefore, the absolute effect for sitagliptin, for example, would be the absolute effect for the reference treatment met+SU+placebo plus the relative effect of sitagliptin vs. placebo, i.e. -0.49+0.907 = 0.417. It should be noted that in the model the relative effect of sitagliptin is presented vs. empagliflozin acting as the reference treatment, since this is the treatment used as reference in the pairwise comparison used in the model, and the values to populate the model were also obtained from the comparisons that used empagliflozin as the reference treatment in the network meta-analysis. In this case, we use the relative effect of sitagliptin when compared to empaglifozin in terms of change from baseline, as it was estimated from the network meta-analysis. This can be checked further in the model by clicking under the worksheet 'Default', in cell E14, 'Select all' under 'Inputs', and then checking the corresponding formulas to see how they are linked to the NMA data, reported on the right hand side of the worksheet. From here it can be seen that the relative treatment effect of sitagliptin vs. empagliflozin 25 mg, for example, was 2.97 kg increase in weight relative to empa 25 mg, and this is the value used in the model as relative treatment effect.

The headings/text in table 59 should actually read as follows in Table 11:

Table 11 revision to table 59 from submission for BMI/Weight change

BMI/weight change (change from baseline) kg		
Absolute effect for Met+SU background		
Met+SU+empagliflozin 10 mg	-2.26	NMA

Met+SU+empagliflozin 25 mg	-2.49
Relative effect for Met+SU background when treatments are compared vs. Met+SU+empagliflozin 10 mg	
Met + SU + Sitagliptin	2.74
Met + SU + Canagliflozin 100mg	0.51
Met + SU + Canagliflozin 300mg	0.07
Relative effect for Met+SU background when treatments are compared vs. Met+SU+empagliflozin 25 mg	
Met + SU + Sitagliptin	2.97
Met + SU + Canagliflozin 100mg	0.74
Met + SU + Canagliflozin 300mg	0.31
Absolute effect for Met+TZD background	
Met+pioglitazone+empagliflozin 10 mg	-1.233
Met+ pioglitazone +empagliflozin 25 mg	-1.073
Relative effect for Met+TZD background when treatments are compared vs. Met+pioglitazone+empagliflozin 10 mg	
Met + Pioglitazone + Sitagliptin	2.33
Met + Pioglitazone + Canagliflozin 100mg	-0.41
Met + Pioglitazone + Canagliflozin 300mg	-1.35
Relative effect for Met+TZD background when treatments are compared vs. Met+pioglitazone+empagliflozin 25 mg	
Met + Pioglitazone + Sitagliptin	2.18
Met + Pioglitazone + Canagliflozin 100mg	-0.57
Met + Pioglitazone + Canagliflozin 300mg	-1.51

B7. PRIORITY. *Please check the values in table 59, insulin combination – BMI/ weight change, and the values in the model? For example, we think the 0.21 for insulin + sitagliptin may be wrong.*

Response: Similarly to what was explained in the answers to questions B3 and B6 (above), the baseline risk is actually referring to the absolute treatment effect, in terms of changes from baseline in weight, associated with insulin. The other values refer to relative effects vs. insulin (since insulin was the reference treatment used in the NMA). This value is used when estimating the absolute weight change from empa, which would be the absolute for the reference treatment plus the relative treatment effect of empa vs. the reference treatment.

Then, because the model uses empagliflozin as the reference treatment for pairwise comparisons, for the estimation of the parameters for the comparators, the relative treatment effect of the comparators vs. empa are considered in the model, as estimated from the NMA. These values depend on whether comparisons are against empa 10 mg or empa 25 mg. This information is reported on the right hand side of the 'Default' worksheet, and can be clearly identified following the appropriate links in the formulas inserted for default values. To unhide all the relevant calculations, please go the worksheet 'Default', and in cell E14 click 'Select all' (under the heading 'Inputs'). Then you will be able to see all the relevant rows unhidden, and to check the corresponding formulas to see how they are linked to the NMA data, reported on the right hand side of the worksheet, by following the links of the formulas included as part of the identified default values.

It should be noted that in the submission, the values reported for the weight change estimates reflected the results of the NMA in terms of the absolute value for the placebo/reference treatment and the relative value of the other treatments vs. the placebo/reference treatment. Based on the previous explanations, this section of Table 59 should read as follows (Table 12) to reflect the parameters in the way they were inputted in the model:

Table 12 Revision to table 59 from submission to reflect the method values were inputted into the model for weight change

Weight change from baseline (in kgs)		
Absolute effect for insulin background		
Insulin + Empagliflozin 10mg	-1.037	
Insulin + Empagliflozin 25mg	-1.457	
Relative effect for insulin background when treatments are compared vs. insulin + Empagliflozin 10 mg		
Insulin + Sitagliptin 100mg	2.07	
Insulin + Canagliflozin 100mg	-0.49	
Insulin + Canagliflozin 300mg	-0.97	
Insulin + Dapagliflozin 10mg	-0.67	
Relative effect for insulin background when treatments are compared vs. insulin + Empagliflozin 25 mg		
Insulin + Sitagliptin 100mg	2.49	
Insulin + Canagliflozin 100mg	-0.06	
Insulin + Canagliflozin 300mg	-0.55	
Insulin + Dapagliflozin 10mg	-0.26	
Insulin add-on **(absolute effect)**	0.5	Khunti K et al 2013 (99)

As identified by the ERG, the value reported in the table for 'Insulin + Sitagliptin 100mg' a typographical error, and should be instead 0.71. This value represents the relative effect of sitagliptin vs. insulin(+placebo). However, in the model the

appropriate value (i.e. 0.71) was used to run the analysis, so there was no need to re-run additional analyses because of the comment raised in this question.

For further clarification, the value reported for 'Insulin add-on' represents the absolute treatment effect on weight rather than a relative value.

B8. PRIORITY. *Please explain how the figures in table 59 for insulin combination and non-severe hypoglycaemia are derived, and how they relate to model inputs?*

Response: The baseline risk value (i.e. insulin) actually reflects a probability, since it is the proportion of patients experiencing at least one non-severe hypoglycaemia. For the other treatments, the values reflect RRs vs. the reference treatment (which in this case is insulin).

The values were derived from the NMA. In the model, for combinations of insulin with an oral agent, the probability of experiencing at least one severe hypoglycaemia from insulin+placebo is used in combination with (i.e. multiplied by) the relative risk for the treatment in question vs. the reference treatment (e.g. empagliflozin+insulin) to estimate the probability of experiencing at least 1 non-severe hypo for each of the different treatment combinations.

B9. PRIORITY. *We are puzzled by some of the effects of changing the relative inputs. For example, changing the absolute inputs for HbA1c level for Met + Empag from 0.65 to 0.10,changes the mean QALY from 7.424 to 7.343. Should we not expect a bigger change? Also, changing HbA1c level for Met + Empag from 0.65 to 0.45 did not change the mean QALY. Why does such a big change in absolute effect not affect the mean QALYS?*

Response: There are several possible reasons for the treatment effect not having a huge impact on QALYs, including, for example, the fact that the empagliflozin cost-effectiveness model used lower baseline utilities compared to other models (such as the CORE model, used for validation; see answer to question B1), with a potential to accumulate less QALYs over a lifetime, and there were no utility adjustments considered for weight loss (only disutilities related to treatment-related weight gain), since the aim was to have a model as conservative as possible for interventions resulting in weight loss, as is the case with empagliflozin.

We have run the model for second line, comparing met+empagliflozin 10 mg vs met+canagliflozin 100 mg, changing the parameter for HbA1c(Met+empagliflozin) from 0.65 to 0.45 as suggested by the ERG (cell N22 under the worksheet 'Treatment efficacy'). The results for the empagliflozin arm from the base case analysis presented in the submission and those of this new analysis, with the corresponding confidence intervals, are presented in Table 3.

As it can be seen from these results, there was a reduction in the number of QALYs obtained with met+empa 10 mg when the decrease from baseline of HbA1c was reduced to 0.45, which was due to the occurrence of a higher average number of complications due to poorer HbA1c control over time. This seemed to be in line with the expectations of the ERG regarding the impact of HbA1c changes on the number of QALYs obtained.

We have also run the analysis considering HbA1c for met+empa 10 mg = 0.1 (and considering a confidence interval –CI- between 0 and 0.2, for consistency of the parameter values; otherwise, the mean value would be lower than the values of the CI). The results obtained are also presented in Table 3. There is a consistent trend between a decrease in the HbA1c effect (i.e. a lower reduction in the HbA1c levels from baseline) and an increase in the number of complications, resulting in lower life years and QALYs associated with the lower impact on HbA1c, as observed from Table 13. Additionally, the lower the control of HbA1c, the higher the likelihood of patients to die from a diabetes-related reason (compared to other causes), as it would be expected as well.

Table 13. Health benefits obtained with the base case analysis presented in the NICE submission (HbA1c estimate for met+empa 10 mg = 0.65) vs. additional analysis considering HbA1c estimate for met+empa 10 mg = 0.45

Effects	Met + Empagliflozin with HbA1c estimate = 0.65 (same CI)			Met + Empagliflozin with HbA1c estimate = 0.45 (same CI)			Met + Empagliflozin with HbA1c estimate = 0.1 (CI: 0 to 0.2)		
	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound
QALY	7.424	1.455	11.449	7.401	1.454	11.448	7.347	1.452	11.387
Life Years	9.952	1.92	15.339	9.929	1.92	15.401	9.869	1.915	15.301
LTCs: Total number of events	0.704	0	2.307	0.714	0	2.348	0.728	0.000	2.357
IHDs	0.09	0	0.915	0.09	0	0.915	0.091	0.000	0.915
MIs	0.222	0	0.945	0.224	0	0.945	0.226	0.000	0.940
CHFs	0.076	0	0.85	0.077	0	0.86	0.077	0.000	0.865
Strokes	0.174	0	0.97	0.178	0	0.97	0.184	0.000	0.970
Amputations	0.082	0	0.671	0.084	0	0.691	0.087	0.000	0.691
Blindness in one eye	0.041	0	0.732	0.041	0	0.732	0.042	0.000	0.742
Renal failures	0.019	0	0.221	0.019	0	0.225	0.019	0.000	0.235
Total deaths	1	1	1	1	1	1	1.000	1.000	1.000
Diabetes-related deaths	0.27	0	0.99	0.274	0	0.99	0.282	0.000	0.995
Other deaths	0.73	0.01	1	0.726	0.01	1	0.718	0.005	1.000

B10. *With regard to the model inputs, where have the covariances within the variance covariance matrices of the risk equations been drawn from; e.g. cell BP49 of the Baseline_Parameters worksheet?*

Response: The co-variances were estimated from the standard errors for the coefficients stated in Clarke et al 2004.

B11. PRIORITY *With regard to the model structure, it is not immediately clear how many treatment changes, in terms of moving onto the next line of therapy due to treatment failure (rather than switching treatment at the same line of therapy), occur within the model. Please outline:*
- *For 2nd line therapies what a typical sequence of treatments would be as the patient changes treatment due to hitting the HBA1c threshold.*
- *For 3rd line therapies what a typical sequence of treatments would be as the patient changes treatment due to hitting the HBA1c threshold.*

Response: If patients start in second line therapy and HbA1c is out of control, insulin will be added to the treatment combination they were on while in second line. Once on insulin, patients remain in that treatment combination.

If patients start on third treatment line and HbA1c is out of control, again insulin will be added to whatever combination they were taking, and once on insulin, patients will remain in that treatment combination.

In the case of the assessment of insulin combinations, once HbA1c is out of control, patients would move to rescue insulin.

This was the most common pathway followed by patients, representing also NICE recommendations from clinical guidelines, as discussed with the clinical expert consulted.

B12. PRIORITY "*The frequency of events was based on the methods used in the UKPDS Outcomes Model." Please outline how this is aligned with the values of cells BT24:BW28 of the Model_Scope worksheet, what the function of these cells is and where this appears in the VBA of the model.*

Response: The UKPDS68 risk equations were used to estimate long-term complications and death, and the input values for these are presented under the worksheet 'Baseline parameters', tab 'Risk equations'.

The frequency of adverse events was estimated on the basis of the results from the NMA mainly, empagliflozin RCTs and submissions or SmPCs for other treatments. The information reported under the worksheet 'Model scope', tab 'Specifications AEs' refers to how each of the AEs is assumed to happen in the model:

- For hypoglycaemic events (non-severe and severe), these can happen in any cycle. This was discussed and validated with the consulted clinical experts.

- For UTIs and genital infections, these were assumed to happen only during the first cycle after treatment initiation, the reason for this being that these AEs are more

likely to occur in the first months after treatment initiation and they are not very likely to happen afterwards. In clinical practice some patients may experience recurrent events over time, but the number seems to be very limited based on the discussions with the clinical experts, so it was considered to be close to reality to assume they would happen only during the first 6 months.

The cells that are hidden (e.g. BT23:BW28) are settings of AEs that were not finally considered in the model. The global model allowed consideration of a higher number of AEs, however, only the ones presented in the NICE submission were finally considered relevant for the analyses of the type of treatment combinations presented.

The setting of these AEs was identified in the VBA code as part of an array named 'MatAE_All_Spec', which contained in total 15 potential AEs, although at the end only 4 AEs were considered in the model submitted to NICE (i.e. non-severe and severe hypoglycaemias, UTIs and genital infections). The location of these 4 AEs as part of the array were elements 1 and 2 for non-severe hypoglycaemias and for severe hypoglycaemias, respectively (i.e. corresponding to MatAE_All_Spec(1) and MatAE_All_Spec(2) in the code), and elements 7 and 8 of the array for UTIs and genital infections, respectively (corresponding to MatAE_All_Spec(7) and MatAE_All_Spec(8)).

When the AE was identified to happen during 'All cycles', the value of the variable was 1 (e.g. MatAE_All_Spec(1) = 1 since non-severe hypoglycaemias could happen in all the cycles). In this case, as part of the subroutine: 'higher_steps_effects_diabetes', non-severe hypoglycaemias were considered to happen not only during the first cycle of any treatment but also in subsequent cycles, as it can be seen in the following bit of code:

```
'-----------------------------------------------------

'Adverse events and weight change

'-----------------------------------------------------

If MatTx_Current(index_cycle + 1) <> MatTx_Current(index_cycle) Then

    'Adverse events are just taken to be the sampled parameter values and not
the occurence of an adverse event.

    'They are not related to long term complications until now.

    'Initially division by cycle length was performed at the summary of the events
program, although this has

    'been modified to adjust for probabilities that reflect a 6-month period instead
of an annual probability

    MatAE_Hypo_prob(index_cycle + 1) =
MatHypo_events_prob(identifier_treatment)
```

```
MatAE_Hypo_no(index_cycle + 1) =
MatHypo_events_no(identifier_treatment)
```

The code above refers to the situation where treatment has changed (i.e. MatTx_Current(index_cycle + 1) <> MatTx_Current(index_cycle) meaning that the treatment in this cycle is different from the treatment in the previous cycle). In this case, all AEs relevant for the model would apply (since at least during the first cycle AEs could happen).

Then, for the situation where treatment remains the same as in the previous cycle, i.e.:

```
Else

'AE only in first cycle, or more?

MatAE_Hypo_prob(index_cycle + 1) =
MatHypo_events_prob(identifier_treatment) * MatAE_All_Spec(1) 'Non-severe hypo

MatAE_Hypo_no(index_cycle + 1) =
MatHypo_events_no(identifier_treatment) * MatAE_All_Spec(1)
```

as seen in the code above, whenever the user selected to apply to AE to all cycles, then the value of the variable associated to that AE will be 1 (e.g. MatAE_All_Spec(1) = 1) meaning that the AE could happen also in subsequent cycles, not only during the first cycle after initiation of a new treatment.

B13. *Please clarify if the QALY decrements associated with UKPDS68 events are assumed to be cumulative; i.e. a patient having experienced two events has the sum of their disutilities applied?*

Response: For a patient who experienced multiple complications, it was assumed that multiple complications had an additive effect on utility. Therefore, for a patient experiencing two events the disutility of the two events would be estimated as the sum of each of the events' disutilities.

B14. *Please clarify if the disutility for weight gain only applies to weight gain. Or does it also apply to weight loss when it would result in a QALY gain?*

Response: When considering the QALY-adjustments related to weight changes, it was assumed that weight loss did not have an impact on utilities while weight gain would result in a decrease of utility. This disutility was applied whenever the weight gain was higher than the baseline weight of the patient as a result of a treatment-related weight gain. The reason for this adjustment was to avoid considering disutilities related to medications associated with a weight loss for which patients later on regained the lost weight through time. Moreover, weight-related disutilities were applied only to treatment-related weight increases, not to natural increase of weight.

B15. PRIORITY *Please outline how to run the model deterministically; i.e. without any 2nd order sampling. When cell H22 of the Run_Model worksheet reads "No" does this reliably indicate when the model is being run deterministically?*

Response: To run the model deterministically the user needs to set the analysis under the worksheet 'Model scope', tab 'Specification model'. Here, under the 'Probabilistic sensitivity analysis setting' the user needs to select 'No' under all the sets of parameters identified in that section (i.e. cells AJ28, AJ21, AJ34, AJ37, AJ40, AJ42, AJ45 and AJ48 should be set as 'No').

The user should not modify the cell H22 under the worksheet 'Run Model' since this cell only indicates whether at least some of the parameters have been selected to be run probabilistically. If all sets of parameters have been set to run 'deterministically', i.e. selected as 'No' under the 'Model scope' worksheet, then the cell H22 under the 'Run Model' worksheet will read 'No' (for the 'PSA conducted?' question).

Also, when running the model deterministically, it is important to keep in mind the model should allow for heterogeneity of patients (see answer to question B17) so that patients with different baseline characteristics are allowed to enter the model, allowing, therefore, for all types of complications to happen in the long term.

B16. PRIORITY *It appears that the model results reported in the submission are all based upon probabilistic modelling; i.e. sampling of 2nd order uncertainty of parameter values. How do these results compare with running the model "deterministically"; i.e. without sampling of 2nd order uncertainty of parameter values?*

Response: When second order uncertainty was removed from the analysis, allowing for patients' heterogeneity (i.e. when under the worksheet 'Model scope', the cells AJ28, AJ31, AJ34, AJ37, AJ40, AJ42 and AJ45 were set to 'No', and cell AJ48 remained as 'Yes'), the results obtained between the 'deterministic' and the 'probabilistic' analyses (i.e. the latter having all the aforementioned cells set up to 'Yes') were rather similar in terms of life years gained and QALYs (see Table 14).

In the case of the probabilistic analysis, on average patients experienced a higher number of complications, and this resulted in higher average costs. This could have been the result of extreme values resulting from the 'probabilistic' analyses, given the consideration of uncertainty of second order, would result in higher number of complications in the long term. This higher number of complications also resulted in average life years and QALYs that were slightly lower in the 'probabilistic' analysis compared to the 'deterministic' analysis. The fact that under the 'probabilistic' analysis the average number of AEs was slightly lower than for the 'deterministic analysis seems to be the result of bounding the probabilities of experiencing an AE between 0 and 1. In some cases, the high relative risks associated to some treatments may have resulted in probabilities exceeding 1, and this was adjusted to 1 to keep the consistency of the parameter values used in the analysis. Additionally the narrower percentile confidence intervals estimated from the 'deterministic' analysis compared to those obtained from the 'probabilistic' analyses, as it would be expected due to the exclusion of 2nd order uncertainty as part of the 'deterministic' analyses.

Table 14. Comparisons of the results for deterministic vs. probabilistic sensitivity analyses when 3rd line therapies with Met+SU background were compared

	DETERMINISTIC						PROBABILISTIC					
Effects	**Met + SU + Empagliflozin 10 mg**			**Met + SU + Canagliflozin 100 mg**			**Met + SU + Empagliflozin 10 mg**			**Met + SU + Canagliflozin 100 mg**		
	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound
QALY	7.037	1.974	11.169	7.031	1.973	11.155	6.991	1.466	10.793	6.98	1.465	10.773
Life Years	9.36	2.639	14.67	9.363	2.639	14.674	9.369	1.965	14.373	9.362	1.965	14.373
LTCs: Total number of events	0.557	0.005	1.467	0.554	0.005	1.461	0.722	0	2.221	0.721	0	2.221
AEs: Total number of events	23.994	3.367	44.211	30.714	4.308	59.118	23.03	2.495	48.134	28.719	2.745	56.943
Total costs NHS perspective	£27,296.10	£4,448.30	£78,933.20	£27,157.10	£4,428.80	£78,117.10	£31,408.50	£3,737.40	£94,559.70	£31,216.60	£3,674.40	£94,797.30
Effects	**Met + SU + Empagliflozin 10 mg**			**Met + SU + Sitagliptin 100 mg**			**Met + SU + Empagliflozin 10 mg**			**Met + SU + Sitagliptin 100 mg**		
	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound
QALY	7.037	1.974	11.169	7.004	1.968	11.154	6.991	1.466	10.793	6.959	1.465	10.775
Life Years	9.36	2.639	14.67	9.321	2.639	14.67	9.369	1.965	14.373	9.343	1.946	14.364
LTCs: Total number of events	0.557	0.005	1.467	0.569	0.005	1.491	0.722	0	2.221	0.732	0	2.221
AEs: Total number of events	23.994	3.367	44.211	21.367	2.456	40.039	23.03	2.495	48.134	27.233	1.764	83.715
Total costs NHS perspective	£27,296.10	£4,448.30	£78,933.20	£27,224.80	£4,332.80	£80,445.50	£31,408.50	£3,737.40	£94,559.70	£31,364.60	£3,797.70	£93,588.40
Effects	**Met + SU + Empagliflozin 25 mg**			**Met + SU + Canagliflozin 300 mg**			**Met + SU + Empagliflozin 25 mg**			**Met + SU + Canagliflozin 300 mg**		
	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound
QALY	7.029	1.972	11.158	7.04	1.972	11.147	6.978	1.466	10.789	6.976	1.465	10.802
Life Years	9.356	2.639	14.67	9.378	2.639	14.693	9.36	1.965	14.373	9.364	1.963	14.452

LTCs: Total number of events	0.559	0.005	1.474	0.552	0.003	1.461	0.728	0	2.255	0.725	0	2.241
AEs: Total number of events	27.006	4.009	50.977	33.731	5.301	66.544	25.748	2.37	54.076	31.738	3.194	62.931
Total costs NHS perspective	£27,294.50	£4,459.40	£79,610.90	£27,904.30	£4,682.60	£79,744.00	£31,556.70	£3,837.70	£95,633.50	£32,087.10	£3,927.10	£93,692.40

B17. PRIORITY *The model can be set to run with cells AJ28, AJ31, AJ34, AJ37, AJ40,AJ42, AJ45 and AJ48 of the Model_Scope worksheet being "No", cell BA15:BB15 of the Model_Scope worksheet being 1 and the number of patients in cell BA14:BB14 of the Model_Scope worksheet being 10,000. Further setting the comparison to 3rd line empagliflozin 10mg versus canagliflozin 100mg and running the model, the results for the 10,000 patients simulated can be outputted to the Graph_CE worksheet. Within this, it appears that columns N:Q contain the total costs and QALYs by arm, this interpretation cross checking with the net values reported in columns C:F. The means of the values in columns C:F also cross check with the values reported in cells O13 and O53 of the Results worksheet. Concentrating upon the values reported in columns N:Q of the Graph_CE worksheet it can be noted that of the 10,000 patients simulated:*

- *In column N there are 40 distinct values for empagliflozin QALYs, with 1,886/10,000 accruing less than 1.8 QALYs*
- *In column O there are 30 distinct values for empagliflozin £s, with 1,886/10,000 having £0*
- *In column P there are 40 distinct values for canagliflozin QALYs, with 1,886/10,000 accruing less than 1.8 QALYs*
- *In column Q there are 30 distinct values for canagliflozin £s, with 1,886/10,000 having £0*

Please provide:

- *An explanation of why there are so few distinct values for the total QALYs and total Costs for each arm reported in columns N:Q of the Graph_CE worksheet.*
- *An account of what interpretation should be placed upon the 1,886 patients who appear to be simulated as accruing less than 1.8 QALYs within column N and column P of the Graph_CE worksheet.*
- *An account of what interpretation should be placed upon the 1,886 patients who appear to be simulated as having £0 total costs within column O and column Q of the Graph_CE worksheet.*

Response: If all parameters are run deterministically, including patients' baseline characteristics and disease history, patients initiating the model will systematically have or not some specific characteristics with no variation around these characteristics. Given this, only some events will be likely happen in the long term, but not others. Moreover, given that all patients have similar characteristics, it is more likely to obtain extreme results around these characteristics that were allocated at the beginning of the simulations. Therefore, the extreme values obtained. It seems more appropriate when testing how the model runs deterministically to allow heterogeneity across patients (i.e. to keep cell AJ48 under the worksheet 'Model scope') set to 'Yes'. In this way, patients can be allocated all different baseline characteristics and potential disease history, without limiting these to average values.

Additional analyses were run and are here presented to show that when the model considers heterogeneity across patients and only one sample of patients, with 10,000 patients, is run (for consistency with the analysis run by the ERG and presented in this question), the results show the expected pattern. Figure 2 to Figure 5 below present histograms of the number of patients (among the 10,000 patients run as part of one large sample) that attained different numbers of QALYs. Rather than obtaining extreme values (as it is the case when no heterogeneity across patients is allowed in

the deterministic run of the model), the histograms present a consistent pattern in terms of the number of patients achieving different number of QALYs over time.

Figure 2. Empagliflozin 10 mg QALY histogram

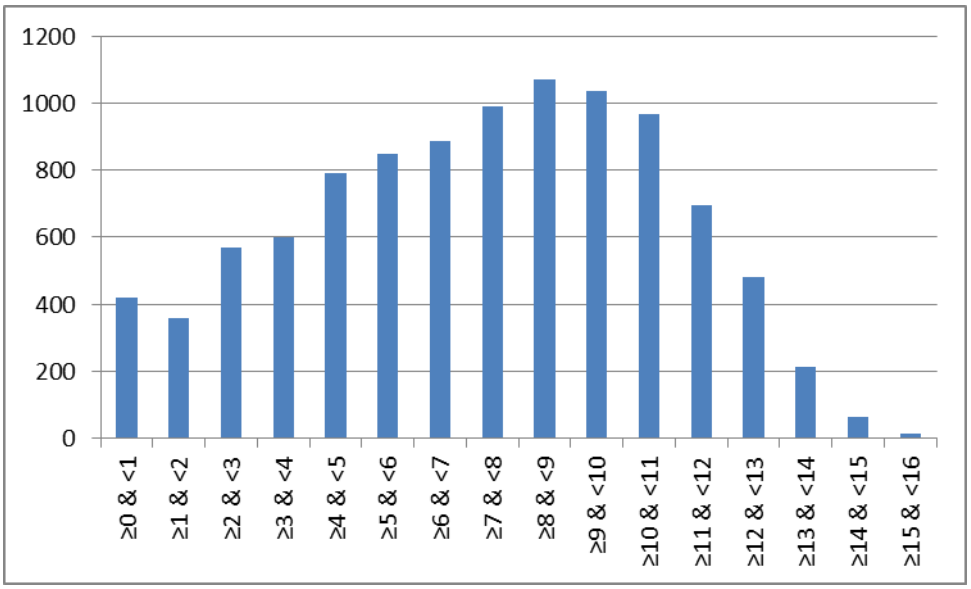


Figure 3. Empagliflozin 10 mg cost (in £) histogram

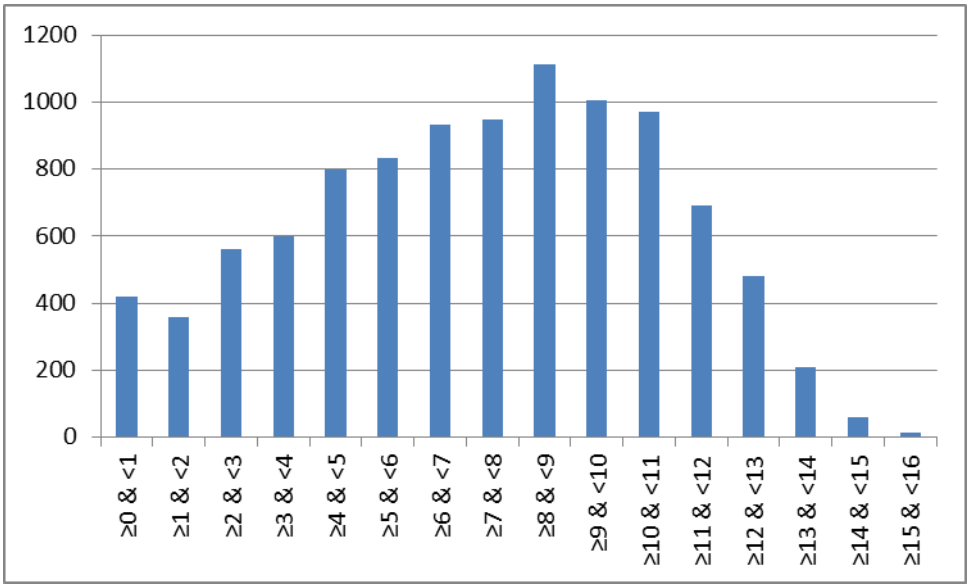


Figure 4. Canagliflozin 100 mg QALY histogram

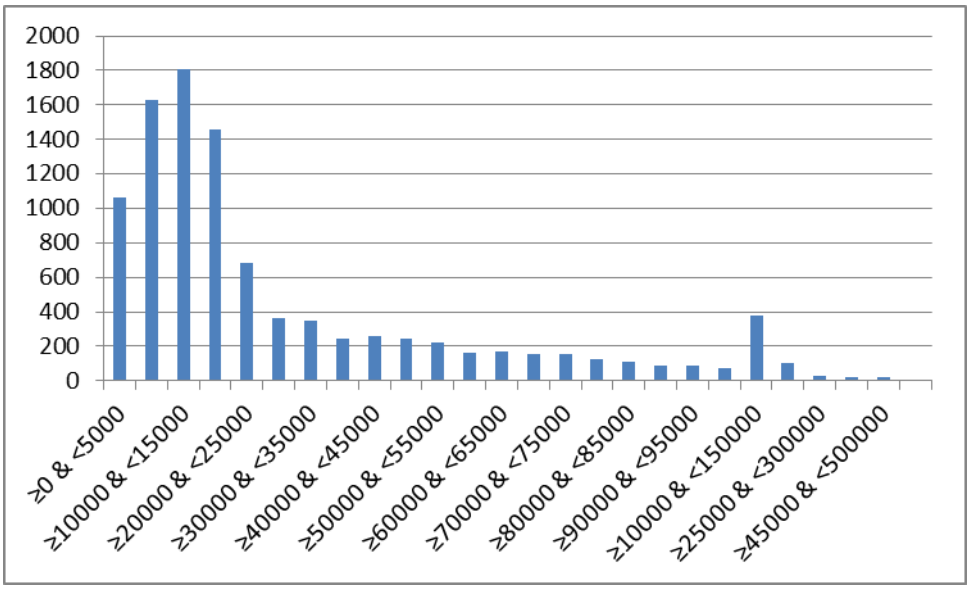
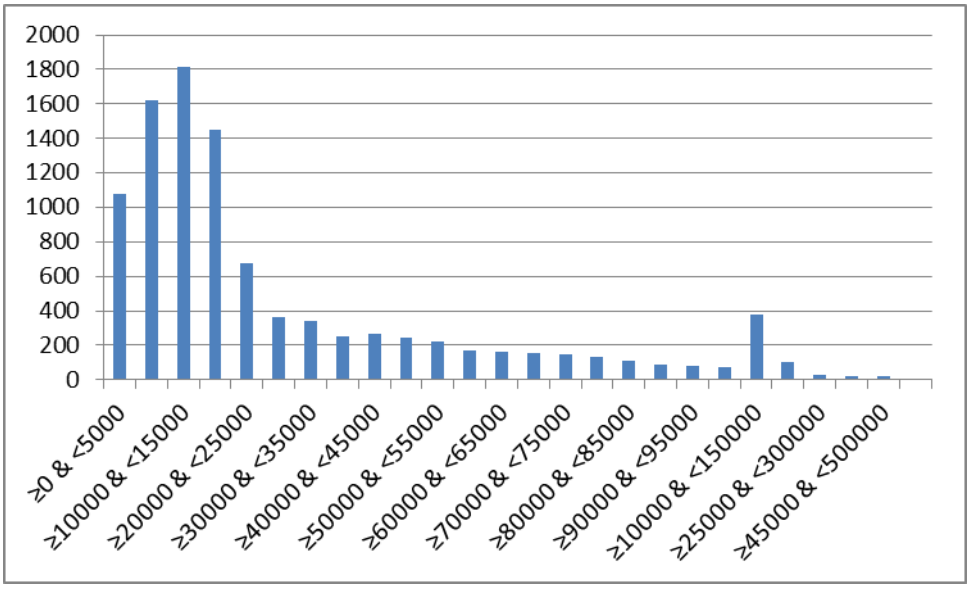


Figure 5. Canagliflozin 10 mg cost (in £) histogram



B18. *The submission notes that "In total, 60,000 simulations were conducted, considering a sample of 30,000 patients per treatment arm (300 samples of 100 patients each). These values were chosen as this was the maximum number of simulations Excel can manage."*
The maximum number of patients of 30,000 was apparently the limiting factor.
- *How should the 300 samples be interpreted. Is this the number of PSA loops undertaken for the assessment of 2nd order uncertainty?*
- *How should the 100 patients be interpreted. Is this the number of patients with different patient characteristics at baseline due to the sampling of patient characteristics? And is each patient only run once through the model for a given arm (two arms being compared) and PSA iteration?*

Response: The 300 samples represent loops of 2nd order uncertainty; each sample will have a specific set of efficacy, safety, discontinuation, costs and utility values that will apply across the full sample of patients. In each sample, 100 patients are simulated, each of them with different baseline characteristics, to reflect patients' heterogeneity. Each patient within a sample will have therefore different baseline characteristics and disease history, but will be subject to the same efficacy, safety, cost, etc. values within the same sample. Moreover, the same patient will be run through each of the treatments compared at analysis (i.e. intervention and comparator) so that a replicate of patients is run through each treatment arm.

Once all the 100 patients within a sample have been simulated, the model draws another set of efficacy, safety, discontinuation, etc. values for the next sample of patients, and applies them for each of the 100 new patients simulated within that sample. Again, each of the new patients simulated within the new sample will have different baseline characteristics and will run through each of the interventions compared in the analysis.

Therefore, each patient is run only once through the model for a given arm (two arms being compared) and PSA iteration (interpreting the PSA iteration as the simulation within the same sample of patients).

B19. PRIORITY *For a given set of parameter values it seems unlikely that the patient level model will have converged after having run only 100 patients through the model. To what extent has this been explored during model development?*

Response: This is one of the acknowledged limitations for the model, as Excel would run out of memory if more than 60,000 simulations were run. The decision on using 300 samples and 100 patients per sample was to introduce as much uncertainty as possible in the model in terms of second order (with the 300 samples) and of patients' variability at the same time in each one of the samples (with 100 patients in each sample), looking for an optimal combination of numbers of samples and patients that would allow us to do so within the total number of simulations possible to run (i.e. 60,000). Variability in terms of the number of patients considered was indeed tested, and some results are presented below.

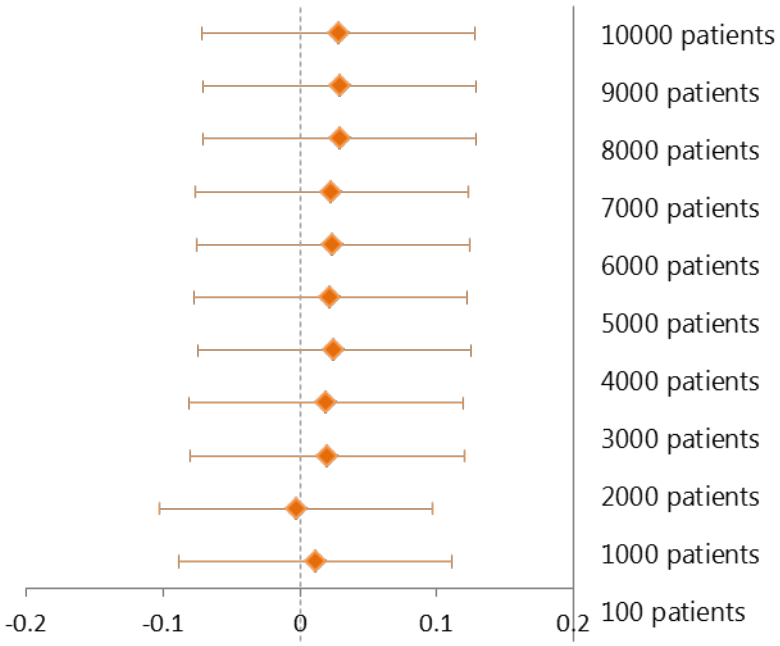
Table 15 below presents, as an example, the results obtained for the comparison Met+SU+empagliflozin 10 mg vs Met+SU+sitagliptin 100 mg. The analyses were run to compare the number of QALYs obtained when the model was run deterministically for second order uncertainty (i.e. only one sample of patients was run, with different numbers of patients each time, and with parameters at the sample level fixed at their average values, so that convergence around patients' characteristics could be investigated).

Table 15. Number of QALYs obtained by patients treated with Met+SU+empagliflozin 10 mg vs. Met+SU+sitagliptin 100 mg, and incremental QALYs when a deterministic analysis was run allowing for patients' heterogeneity and different numbers of patients with only one sample fixed at average values (for efficacy, safety, discontinuation, costs and utility values)

	QALYs Met+SU+empa10	QALYs Met+SU+sita100	Incremental QALYs

Number of patients	Probabilistic Mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound	Probabilistic mean	Lower bound	Upper bound
100	7.271	0.566	12.916	7.26	0.563	12.88	0.011	-0.007	0.006
1000	7.147	0.577	12.864	7.15	0.574	12.867	-0.003	-0.007	0.006
2000	7.262	0.577	13.235	7.242	0.574	13.225	0.02	-0.007	0.006
3000	7.26	0.851	13.22	7.241	0.847	13.146	0.019	-0.007	0.006
4000	7.286	0.909	13.147	7.261	0.895	13.141	0.025	-0.007	0.006
5000	7.292	0.92	13.174	7.271	0.917	13.145	0.022	-0.007	0.006
6000	7.292	0.899	13.164	7.269	0.895	13.142	0.024	-0.007	0.006
7000	7.29	0.909	13.166	7.267	0.895	13.145	0.023	-0.007	0.006
8000	7.284	0.906	13.178	7.255	0.895	13.146	0.029	-0.007	0.006
9000	7.272	0.882	13.164	7.242	0.85	13.146	0.029	-0.007	0.006
10000	7.271	0.848	13.159	7.244	0.814	13.146	0.028	-0.007	0.006

Figure 6. Incremental QALYs for Met+SU+empa 10 mg vs. Met+SU+sita 100 mg when a deterministic analysis was run allowing for patients' heterogeneity and different numbers of patients, with only one sample fixed at average values (for efficacy, safety, discontinuation, costs and utility values)



Although 100 patients per sample did not appear to reach convergence, it was considered to be a conservative approach compared to running more patients per sample. As can be seen in Table 15, the incremental values obtained, for example, in comparisons between empagliflozin 10 mg and sitagliptin 100 mg were smaller for simulations considering higher numbers of patients. Based on the results for larger number of patients, it was still unclear whether the results were converging. Had we had considered larger sample sizes, we would have been able to introduce in the model a lower amount of second order uncertainty (by running less samples) and it would have been expected that the incremental results would have been larger than

what has been presented in the submission. Therefore, the decision to run 300 samples of patients with 100 patients each was considered to be conservative, against the decision to run more patients per sample with a lower number of samples in total.

B20. PRIORITY *Why was it not possible to develop the model along the following lines:*

- *Sample the 2nd order uncertainty to derive parameter values for a PSA iteration*
- *Simulate 10,000 patients for each arm using the parameter values for that PSA iteration as sampled above*
- *Store the resulting mean net cost and mean net QALY for this PSA iteration*
- *Discard the results for the individual 10,000 patients simulated for this PSA iteration*
- *Repeat the above four bullets 5,000 times to yield 5,000 PSA iterations*

Response: The model was built in a way that we could have access to the information of each of the patients simulated under each of the different samples. By running samples of patients and discarding them afterwards the specific information per patient would have been lost, and it was considered relevant to be able to access and export to Excel if necessary that level of detail for transparency purposes. In any case, it is unclear whether by discarding the individual 10,000 patient simulations per PSA and storing the PSA values only for the 5,000 iterations would have solved the memory issue of Excel (i.e. resulting in an 'out of memory' error in Excel).

B21. *Within the VBA the CEM_running value is set equal to 1 in the CEM_Computation_1 module. For the model as submitted is the CEM_running value ever not equal to 1. If so,where does this occur in the VBA and why? What is the distinction between CEM and BIM?*

Response: The model presented to NICE is based on a global model for which a budget impact model (BIM) had been also developed. From the initial code of the global model, CEM_running = 1 whenever the cost-effectiveness model was run, instead of the BIM. All the BIM code has been removed to avoid confusion and the model runs currently only for the CEM (i.e. with the variable CEM_running = 1 always).

B22. *Within the first_steps_effect_diabetes procedure there is the calculation of the HbA1c*
*as: Mat_Current_HbA1c(2) = ((100 *Mat_Current_HbA1c(1)-7.09)+ MatHbA1cStep(1))/100+7.09 / 100*

The ERG is having some difficulty identifying where MatHbA1cStep(1) is calculated or
inputted as a parameter value. It would be much appreciated if this could be clarified.

The code should have read:

Mat_Current_HbA1c(2) = ((100 *Mat_Current_HbA1c(1)-7.09)+ MatHbA1cStep(**2**))/100+7.09 / 100

where MatHbA1cStep(2) had been estimated in the previous lines of code as:

MatHbA1cStep(2) = 0.5 * (MatHbA1cWeigSum(1) - Mat_L1HbA1c(1))

Given that the line of code with the wrong index was not part of the scenarios considered in the model, this error did not affect any of the results presented for the NICE submission. The only situation in which the results could have been affected is if one of the analyses had assumed that the maintenance period (identified in the VBA code as the 'length_stable_period') would have been 0.5 years. The minimum maintenance period considered in the model and used as base case value was 1 year, and this was tested as part of one of the sensitivity analyses by considering a 2-year maintenance period.

B23. *The calculation of the probability of a UKPDS Table 2 event happening within a six month cycle within the first_steps_effects_diabetes procedure seems slightly peculiar. Rather than calculate the cumulative hazard for the start of cycle (e.g. t = 12.0, with the weibull exp(.).t^γ) and the end of cycle (e.g. t=12.5) it appears to calculate the cumulative hazard for the start of cycle (t = 12.0) and the cumulative hazard for one year later (t=13.0) and then average these to get the cumulative hazard for the end of the cycle (t=12.5). Is there any particular reason for adopting the form chosen, given that it is a more convoluted implementation and gives slightly different values?*

Response: The reason for this was the fact that the UKPDS risk equations had been estimated based on annual data on potential risk factors and they estimated, therefore, annual probabilities of experiencing complications or death.[2] Given that the model was developed considering 6-month cycles (so that patients could experience treatment changes as soon as 6 months after treatment initiation, following the feedback from the experts consulted at the initial development stages), the aim was to obtain probabilities that could be applied in each 6-month cycle based on the one-year probability estimation of the UKPDS68 equations, without altering the cumulative, annual probability by using 6-month probabilities, and aiming to be as regular and smooth as possible in the changes. Further information regarding the adjustments conducted to estimate 6-month probabilities based on annual probabilities is presented below, as part of the answers for questions B32 to B34.

B24. *The ERG is also having some difficulty understanding the logic of the following condition that appears repeatedly in the higher_steps_effects_diabetes procedure calculations of the probabilities of a UKPDS Table 2 event:*
*If MatTx_Current(index_cycle + 1) < 10 * MatTx_Current(index_cycle - 1) Then*
Please provide an intuitive account of this condition, the reason for multiplying by 10 and the effect of the condition.

Response: This condition allows identifying whether the treatment in a cycle has changed compared to the treatment administered in the previous cycle. This is important because every time a patient changes treatment line, the corresponding variables affecting the time varying risk factors (i.e. HbA1c, SBP, lipid ratio and smoking status) need to be updated so that the estimation of the risk factors in the next cycle take the efficacy and safety estimates of the new administered treatment, and from there on the variables will be updated once per year so that the annual number of events estimated by the risk equations would be as closely reflected in the model as possible. For this, the variable 'Mat_Update_RiskEqs(index_cycle + 1)' was

used as an indicator of the extremes of the year (see answer to question B33 below for further information).

The fact that the model multiplies by 10 reflects the indexes that were allocated to the different treatment combinations to identify the specific treatment combinations and corresponding treatment-specific efficacy, safety and cost parameter values. These indexes can be found in the worksheet 'Txs'.[i] As it can be seen from the worksheet, each of the treatment combinations is allocated an index with as many digits as the treatment line the treatment is included in:

- In column C of the worksheet 'Txs', treatments included under the category of 'dual therapies' or 'second line therapies' are assigned a two digit index, which reflects the treatment corresponds to second line:
    - 16 (in cell C17) refers to Met+ empagliflozin (since metformin is usually identified with the digit '1' and empagliflozin is identified with the digit '6')
    - 13 (in cell C18) refers to Met+ pioglitazone (since metformin is usually identified with the digit '1' and pioglitazone is identified with the digit '3')
    - And so on with the rest of the second line treatment combinations
- In the same worksheet and column, third line therapies (or therapies including a triple combination) are allocated an index with 3 digits, in a similar fashion as explain to second line therapies:
    - 126 (in cell C44) refers to Met+SU+empagliflozin (since metformin is usually identified with the digit '1', SU with the digit '2' and empagliflozin is identified with the digit '6')
    - 123 (in cell C47) refers to Met+SU+pioglitazone (since metformin is usually identified with the digit '1', SU with the digit '2' and pioglitazone is identified with the digit '3')
    - And so on with the rest of the second line treatment combinations

Using this coding system allows to clearly identify whether a change of treatment line has happened between the previous cycle and the current cycle, and differentiate the change between treatment lines from treatment switches within the same treatment line (which may happen whenever a patient experiences AEs leading to discontinuation or primary failure during the first cycle, in which case the patient remains in the same treatment line):

- MatTx_Current(index_cycle + 1) < 10 * MatTx_Current(index_cycle - 1) means that a change of treatment line did not happen between the previous and the current cycle
- Whenever a change of treatment line happens, then: MatTx_Current(index_cycle + 1) > 10 * MatTx_Current(index_cycle - 1) given the coding system used, as explained above.

B25. *Please clarify the modelling of the event fatality of equation 8 of the UKPDS 68 within the first_steps_effects_diabetes procedure and the comment "needs to adjust*

[i] This worksheet can be accessed by scrolling to the right hand side of the worksheets in the document, being 'Txs' the 12th worksheet when counting the right to the left hand side of the Excel document.

for the year the firt (sic) event happened, so for MI and stroke we know whether the event happened the previous year". If an event happened in the previous year equation 8 does not apply as it only applies to the first event of either MI, CHF, stroke, amputation or renal failure. Please provide an account of what these adjustments are and why they are necessary.

Response: Equation 8 of the UKPDS68 risk equations refers to event fatality. According to the authors of the paper, the regression estimates of this equation were estimated based on patients who had experienced one or more of the following complications: MI, CHF, stroke, amputation and renal failure. According to this paper, event fatality (equation 8) deals with the likelihood of immediate death following the occurrence of a first event. Therefore, in order to identify whether the probability of an event-related fatality is to be applied because of the occurrence of a first event we need to identify whether a first event had happened in the previous year or not.

The subroutine 'first_steps_effects_diabetes' simulates what happens with a patient during the first 6 months after treatment initiation. Based on the initial baseline characteristics allocated to the patients, the model is able to identify if the patient started in the model after having previously experienced a first event of the relevant complications. For example:

- MatLTC_IHD(0) > 0 relates to a patient that entered the model having previously experienced his/her first IHD event
- In the case of MI:
    - MatLTC_MI(0) > 0 would reflect a patient that entered the model having previously experienced his/her first MI event. This combined with whether the event had happened in the previous year (i.e. MatPatDbn(13) > 0) or more than one year ago, allows to identify whether the event related death should be applied to the patient in the first cycle or not

It should be noted that the model considers whether a first event of any of the relevant complications happened in the year previous to enter the model to identify whether event fatality is to be taken into account in the first cycle, as identified in the code:

```
If MatLTC_IHD(0) + MatLTC_MI(0) + MatLTC_CHF(0) + MatLTC_STROKE(0) + MatLTC_AMP(0) + MatLTC_RENAL(0) > 0 Then

'The previous line of code identifies whether the patient had experienced any first event complication previous to enter in the model (i.e. if MatLTC_IHD(0) > 0 it would mean she/he had experienced an IHD before entering the model, if MatLTC_MI(0) > 0 it would mean the patient had experienced an MI, and so on)

    If (MatLTC_MI(0) > 0 And MatPatDbn(13) > 0) Or (MatLTC_STROKE(0) > 0 And MatPatDbn(15) > 0) Then

    'The only two events in the model for which we know whether the patient experienced the event in the year previous to enter the model or earlier than that are MI and stroke:

    • MatLTC_MI(0) > 0 means the patient had experienced MI, and MatPatDbn(13) > 0 means the patient had experienced the MI in the year previous to enter the model
    • MatLTC_STROKE(0) > 0 means the patient had previously experienced a stroke And MatPatDbn(15) > 0 means the stroke had happened in the year previous to enter the model

      MatEventDeath_Age_Event(1) = MatPatDbn(1) - 0.5 - 52.59

        'If the previous happened, then we consider that the patient had experienced a first complication in the year previous to enter the model, and therefore the age of event is defined accordingly

    ElseIf (MatLTC_IHD(0) > 0 And MatPatDbn(12) > 0) Or (MatLTC_CHF(0) > 0 And MatPatDbn(17) > 0) Or (MatLTC_AMP(0) > 0 And MatPatDbn(18) > 0) Or _

      (MatLTC_RENAL(0) > 0 And MatPatDbn(20) > 0) Then

      MatEventDeath_Age_Event(1) = MatPatDbn(1) - 1 - 52.59

        'Given that as part of the baseline characteristics the model did not identify when a first event had happened before the patient entered the model for the other complications, since we did not expect to obtain data that would allow us to populate the model for these additional parameters, some additional assumptions were made to identify if the complication had happened in the previous year or not:

    ElseIf (MatLTC_MI(0) > 0 And MatPatDbn(14) > 0) And (MatLTC_STROKE(0) > 0 And MatPatDbn(16) > 0) Then

    'For example, if the MI had happened more than 1 year ago, then it was assumed that it had happened 2 years before entering the model

      MatEventDeath_Age_Event(1) = MatPatDbn(1) - 2 - 52.59

    End If

  Else
```

'If the patient had not experienced a complications previously to enter the model, then the model identified whether the complication had happened in that very first cycle, so that it could update the age of first event to the one the patient had in the first cycle, as identified by the code below:

```
    If MatLTC_IHD(1) + MatLTC_MI(1) + MatLTC_CHF(1) + MatLTC_STROKE(1) +
MatLTC_AMP(1) + MatLTC_RENAL(1) > 0 Then

        MatEventDeath_Age_Event(1) = MatPatDbn(1) + cycle_length - 52.59

    Else
```

'If no event had happened, it allocated a null value to the variable 'age at first event'

```
        MatEventDeath_Age_Event(1) = 0

    End If

  End If
```

B26. *The adjustment MatEventDeath_ln_Age_event(1) = og(MatEventDeath_Age_Event(1) + 52.59) - Log(52.59)This does not appear to be in line with Table 1 of the UKPDS 68. Please provide an explanation for this adjustment.*

Response: There were cases where calculations required a log of a negative number, which is undefined. This in fact had been previously identified as a potential error by the ERG reviewing the dapagliflozin appraisal in relation to a similar adjustment (ln(TC:HDL-5.23)). They suggested to use ln(TC:HDL/5.23) instead. For the empagliflozin CEM, the main author of the UKPDS risk equations study was contacted by email (Prof Clarke, email sent on 14th February 2014) and as a response he provided an Excel document with the type of adjustments recommended for the implementation of the risk equations. In this document we identified ln(TC:HDL/5.23) as being indeed the appropriate adjustment to conduct because there were cases where calculations required a log of a negative number, which is undefined. The same adjustment was applied to log(AGE_EVENT) to avoid logs of negative numbers resulting in errors when running the model.

B27. PRIORITY *It is not immediately clear whether the model treats equations 8, 9 and 10 of the UKPDS as being mutually exclusive; i.e. only one can apply in any one cycle (and any one year). Are these treated as being mutually exclusive, or can more than one apply in a given cycle?*

Response: Equations are treated as mutually exclusive by considering the following:

The model estimates each of the probabilities of dying for different causes (event, diabetes or other causes) in each cycle, compare them with a random value (range: 0-1) sampled from a uniform distribution, to identify whether that type of death could have occurred or not in that cycle according to the probability values obtained.

Death due to events could occur only if patients had experienced an event in the previous year and the probability estimated was higher than the random value simulated from a uniform distribution associated with it. The part of the code identifying this as part of the subroutine: 'first_steps_effect_diabetes' was:

```
event_occured = (MatLTC_IHD(1) - MatLTC_IHD(0)) + (MatLTC_MI(1) - MatLTC_MI(0)) + (MatLTC_CHF(1) - MatLTC_CHF(0)) + (MatLTC_STROKE(1) - MatLTC_STROKE(0)) + _

        (MatLTC_AMP(1) - MatLTC_AMP(0)) + (MatLTC_RENAL(1) - MatLTC_RENAL(0))

If RandMatComplicat(1, 8) < MatEventDeath_Prob(1) And event_occured > 0 Then

    evp_d = 1

End If
```

Then, depending on the values simulated for the corresponding probabilities of death (by type) and the random values associated to each of them, if death occurred in a cycle, the model would allocate the death to the type of death associated to the highest probabilities of dying based on the simulated random values. The part of the code identifying this as part of the subroutine: 'first_steps_effect_diabetes' was:

```
If evp_d + dip_d + odp_d + AE_d > 0 Then

    evp_d2 = (evp_d + AE_d) / (evp_d + dip_d + odp_d + AE_d) 'RAI: Although initially not included in the original model, AE proportion now included to consider the prop of deaths due to AEs

    dip_d2 = dip_d / (evp_d + dip_d + odp_d + AE_d)

    odp_d2 = odp_d / (evp_d + dip_d + odp_d + AE_d)


    a = RandMatSeqIdentifier(1, 8)

    If a < evp_d2 Then

        MatDeath_Event(1) = 1

        MatDeath_Diab(1) = 0

        MatDeath_Other(1) = 0

    Else

        If a > evp_d2 And a < evp_d2 + dip_d2 Then

            MatDeath_Event(1) = 0

            MatDeath_Diab(1) = 1

            MatDeath_Other(1) = 0

        Else

            MatDeath_Event(1) = 0

            MatDeath_Diab(1) = 0

            MatDeath_Other(1) = 1

        End If

    End If

Else
```

```
        MatDeath_Event(1) = 0

        MatDeath_Diab(1) = 0

        MatDeath_Other(1) = 0

    End If
```

It should be noted that the variable 'AE_d' was related to CV deaths due to AEs, which were **not** considered in the model and therefore the corresponding value would be null and would not influence the results of the model (see answer to question B31 provided below).

B28. PRIORITY *Please clarify how the model applies the half of the year of event costs and the QoL values to the first two 6 month cycles of an event, and thereafter applies half the year subsequent to event costs and the QoL values to all subsequent cycles. It would be much appreciated if an outline of where and how the VBA calculates this.*

Response: Based on the subroutines 'first_steps_effects_diabetes' and 'higher_steps_effects_diabetes' the model estimates whether a patient has experienced one of the seven relevant complications in that cycle or in a previous cycle, and the information is stored in the following arrays:

- MatLTC_IHD(t)
- MatLTC_MI (t)
- MatLTC_CHF(t)
- MatLTC_stroke(t)
- MatLTC_Amp(t)
- MatLTC_Blind(t)
- MatLTC_Renal(t)

where t = cycle number, and the values of each of the elements of the arrays are = 0 if no event had happened in that cycle or in previous cycles, and = 1 if the event had happened either in that cycle or in previous cycles.
Then in the soubroutine 'results_summary' the model estimates whether long term complications had happened specifically in a cycle or not, by identifying the change of value from 0 to 1 between two cycles, and stores the corresponding values in the following arrays:

- MatSum_IHD(t)
- MatSum_MI (t)
- MatSum_CHF(t)
- MatSum_stroke(t)
- MatSum_Amp(t)
- MatSum_Blind(t)
- MatSum_Renal(t)

For each cycle (i.e. t), the array stores a value per element = 0 if the event did not happen in that cycle, or = 1 if the event happened in that specific cycle.
This information is then used for the estimation of costs and QALYs, under the subroutines 'computation_costs' and 'computations_QALY_LY'.

In the subroutine 'computation_costs':

- The model stores the information from the MatSum_xxx() arrays into another array: 'part1_prod(i, #), with i = cycle number and # = number related to the

corresponding complications for which the values are stored (=1 if the complication had occurred on that cycle, = 0 otherwise)

- part2_prod(i, 1) stores the cycle numbers
- In array 'part3_prod(i,1) the model stores the information on the unit costs incurred, per year, for each of the long term complications, related to subsequent years (i.e. to be applied from cycle 3 onwards after a complication had occurred). i = 7 relates to the seven relevant complications estimated in the model.
- In array 'part4_prod(i, 1)' the model stores the information for each of the unit costs during the first year for each of the complications (i=7 again, because of having 7 relevant complications estimated). These unit costs are to be applied to the first two cycles after a complication occurs (i.e. to the cycle in which the complication happens and the cycle following that).

Then the model stores in the array 'part5_prod(i, j)' the annual costs of complications depending on whether the complication had happened or not at that point or previously (i.e. part1_prod(i, j) = 1) and if it had happened, whether it was identified to happen in this cycle or the previous one (i.e. (part1_prod(i, j) = 1 Or (part1_prod(i, j) = 0 And part1_prod(i - 1, j) = 1)) so that the 'first year' cost is applied) or in subsequent cycles (i.e. part1_prod(i, j) = 0 And part1_prod(i - 1, j) = 0 And MatLTC(i, j) > 0, so that the cost of subsequent years would be applied instead).

It should be noted that the code is slightly different for the very first cycle of the model (i = 1), since it was necessary to identify whether if a patient had suffered an event by cycle 1, whether the event had happened on that very first cycle 1 or previously to enter in the model, as part of the disease history of the patient.

Once the array 'part5_prod(i, j)' had stored the information on the unit costs to apply according to the occurrence of events, then the next step was to adjust those costs, that had been initially stored as unit costs per year, so that they would reflect half-a-year costs instead (by multiplying the values in the array by the cycle length, e.g. MatSumDirC_IHD(i) = part5_prod(i, 1) * cycle_length).

For the costs of death, the full cost of death was applied whenever a death occurred (e.g. If MatSum_MI_fatal(i) = 1), so this was not adjusted with the cycle length since the full cost was to be applied to the cycle when the patient died.

The subsequent lines of code aggregate costs by category and estimates cumulative cost, undiscounted and discounted.

In the subroutine 'computation_QALY_LY':

A similar approach is taken for the computation of the 6-month QALYs according to whether complications happened in a cycle or the previous cycle (so that disutilities related to 'first year' complication would apply) or they had happened but in previous cycles (so that disutilities related to 'subsequent years' would apply instead). In the case of the estimation of disutilities related to complications (first year vs. subsequent years):

- The model stores the information from the MatSum_xxx() arrays into another array: 'part1_prod(i, #), with i = cycle number and # = number related to the

corresponding complications for which the values are stored (=1 if the complication had occurred on that cycle, = 0 otherwise)

- part2_prod(i, 1) stores the cycle numbers
- In array 'part3_prod(i,1) the model stores the information on the disutilities to apply per year for each of the long term complications, related to subsequent years (i.e. to be applied from cycle 3 onwards after a complication had occurred). i = 7 relates to the seven relevant complications estimated in the model. The disutilities for the first year are taken from the first 24 elements of the array 'MatUtilities_value(#)', with the elements 2 to 8 relating to the disutilities of the 7 complications considered in the analysis.
- In array 'part4_prod(i, 1)' the model identifies whether a LTC had happened in that cycle or previously (MatLTC=1) or had not happened until that cycle, including the assessed cycle (MatLTC=0).

Then the model stores in the array 'part5_prod(i, j)' the total annual disutility per complication depending on whether the complication had happened or not at that point or previously (i.e. part1_prod(i, j) = 1) and if it had happened, whether it was identified to happen in this cycle or the previous one (i.e. (part1_prod(i, j) = 1 Or (part1_prod(i, j) = 0 And part1_prod(i - 1, j) = 1)) so that the 'first year' disutility is applied) or in subsequent cycles (i.e. part1_prod(i, j) = 0 And part1_prod(i - 1, j) = 0 And MatLTC(i, j) > 0, so that the disutility of subsequent years would be applied instead).

Once the array 'part5_prod(i, j)' had stored the information on the annual disutilities to apply according to the occurrence of events, then the next step was to adjust those disutilities, that had been initially stored as disutilities to apply per year, so that they would reflect half-a-year disutilities instead (by multiplying the values in the array by the cycle length, e.g. MatSumQALYs_IHD (i) = part5_prod(i, 1) * cycle_length).

As previously mentioned for costs, it should be noted that the code is slightly different for the very first cycle of the model (i = 1), since it was necessary to identify whether if a patient had suffered an event by cycle 1, whether the event had happened on that very first cycle 1 or previously to enter in the model, as part of the disease history of the patient). If it happened in the very first cycle, then the disutility of the first year would be applied; otherwise, the disutility of subsequent years was applied.

B29. *Within the procedure GenerateRandomValuesPat please why is it necessary for RandomMatrix2 to be dynamic, due to the variable patient_run which changes with each patient simulated being a determinant of RandomMatrixRows2.*

Response: The idea was to have different random values per sample and per patient, to ensure that within each sample, although the same parameter values were applied in terms of efficacy, safety, costs, etc., each patient would have different baseline characteristics and random values determining the occurrence or not of events. Given that this was a microsimulation model, it was considered that each patient should have the potential to be different to the other simulated patients, and therefore, allowing for a dynamic array of random values that would be estimated on the basis of the number of patient run was considered appropriate. Fixing the random seeds at the sample level (i.e. PSA iteration for 2nd order uncertainty) and the patient level (i.e. iteration for patients' heterogeneity) allowed to ensure the same patient would be subject to the intervention and the comparator

considered in the analysis, while having the dynamic arrays for samples and patients allowed the full variability across samples and patients to be taken into account.

B30. *Within the procedures First_Steps_Effects_Diabetes and Higher_ Steps_Effects_Diabetes it appears that the procedures work through the risks of events sequentially rather than randomising the order of the assessment of these. The submission suggests that these are evaluated in random order. Please outline how within the visual basic the order in which the evaluation of events is randomised.*

Response: For clarification of how the code considers randomness in the occurrence of complications, it is important to consider how the events interact with each other:

- From the UKPDS68 risk equations it can be seen that the probability of experiencing a first IHD, CHF or blindness was not dependent on having experienced previous complications. Therefore, these probabilities were the first ones to be estimated in the code and randomization to identify whether they happened before or after another event within the same cycle was not necessary since this did not impact their occurrence.
- On the other hand, the probability of experiencing a first MI depends, among other factors, on whether the patient had previously experienced IHD and CHF. Therefore, it was important to know if the MI had occurred previously to the IHD and the CHF or not. According to the authors of the UKPDS68 risk equations, "We only recorded IHD and CHF events if they occurred prior to an MI event; a patient who had experienced an MI was not classified subsequently as developing IHD."[3] Therefore, if a patient had previously experienced a MI, a potential occurrence of a first IHD would not be finally allocated because of this consideration from the UKPDS68 equations. The same applied to CHF. Otherwise, when estimating the probability of MI and actual occurrence of a first MI, the update of the variables involved in the equation took into account three additional random numbers: r_ihd, r_mi and r_CHF, which allowed to randomly update the values of the corresponding variables so that the occurrence of the first MI would take into account either the update based on the current cycle or on the previous cycle. In the case of the subroutine 'first_steps_effects_diabetes' the part of the code that considers this random order for the MI occurrence is as follows:

```
'IHD

If r_ihd < r_mi Then

   term8 = MatLTC_IHD_value(1) * MI_Risk_value(10)

Else

   term8 = MatLTC_IHD(0) * MI_Risk_value(10)

End If
```

'For the update of the variable for IHD included as part of the MI risk equation, depending on the random values simulated and the rule applied, the previous code determines whether the update of the occurrence of IHD is considered from the current cycle (1) (i.e. prioritising the occurrence of an IHD in this cycle over that of an MI) or for the previous cycle/baseline (0) (allowing then IHD to have occurred in the previous cycle, but prioritising then the occurrence of MI in this cycle and therefore considering the occurrence of IHD from the previous cycle).

```
'CHF
```

```
If r_CHF < r_mi Then

   term9 = MatLTC_CHF_value(1) * MI_Risk_value(11)

Else

   term9 = MatLTC_CHF(0) * MI_Risk_value(11)

End If
```

'The same applies to the update of the variable for CHF included as part of the MI risk equation: depending on the random values simulated and the rule applied, the previous code determines whether the occurrence of CHF is prioritised over that of MI for the current cycle (1) or the opposite when updating the corresponding CHF variable that is considered as part of the MI risk equation to estimate the probability of a first MI to happen.

- Moreover, the probability of experiencing a first stroke depends on whether the patient had previously experienced CHF. For this, a similar approach as that used for MI was considered. The part of the code related to the random running of the equations is presented as follows:

```
'CHF

If r_CHF < r_Stroke Then

   term8 = MatLTC_CHF_value(1) * stroke_Risk_value(10)

Else

   term8 = MatLTC_CHF(0) * stroke_Risk_value(10)

End If
```

'Here, for the update of the variable for CHF included as part of the stroke risk equation, depending on the random values simulated and the rule applied, the previous code determines whether the occurrence of CHF is considered from the current cycle (1) (i.e. whenever r_CHF < r_Stroke, allowing therefore a CHF to have potentially occurred in the this cycle and prioritising its occurrence over that of a stroke on this cycle) or for the previous cycle/baseline (0) (allowing then CHF to have occurred in the previous cycle but not yet in this cycle, and therefore prioritising the occurrence of a stroke over a CHF in this cycle).

- Both the probability of experiencing first renal failure and that of experiencing first amputation depend on whether the patient had previously experienced blindness.
    - For amputation, the lines of code that allow randomization of the occurrence of amputation vs. blindness is as follows:

```
'blind

If R_BLIND < R_AMP Then

   term4 = MatLTC_Blind_value(1) * amput_Risk_value(6)

Else

   term4 = MatLTC_BLIND(0) * amput_Risk_value(6)

End If
```

- For renal failure, the lines of code that allow randomization of the occurrence of renal failure vs. blindness is as follows:

```
'blind

If R_BLIND < R_renal Then

   term2 = MatLTC_Blind_value(1) * renal_Risk_value(4)

Else

   term2 = MatLTC_BLIND(0) * renal_Risk_value(4)

End If
```

Therefore, randomisation in terms of the order of how complications occurred was applied when estimating the occurrence of MI, stroke, amputation and renal failure. A similar approach was also taken under the subroutine 'higher_steps_effects_diabetes' using the same random values identified above: r_ihd, r_mi, r_CHF, r_Stroke, R_BLIND, R_AMP and R_renal.

B31. PRIORITY *Within the procedures First_Steps_Effects_Diabetes and Higher_ Steps_Effects_Diabetes the visual basic code for adverse event deaths, immediately following the comment 'Adverse events death, may not be required. Please confirm if this can be safely deleted from the visual basic without affecting the running or outputs of the model, and if it cannot be safely deleted please outline why.*

Response: The model was built as a reference/global model that could be used for different health authorities. For this, additional adverse events were considered, including cardiovascular deaths due to adverse events. Given that these types of AEs were not relevant for the NICE submission, they were deactivated by setting all the relevant parameters to null values. Therefore, these parameters do not have an impact in the results of the model since the model in the first instance do not take any positive value for them into account (see columns CA:CM under the module 'Adverse events', i.e. worksheet 'Adverse events'; all values for the relevant input columns are null, and the information was hidden since it does not impact the effect of treatments presented in the NICE submission).

In 'first_steps_effects_diabetes' the following first bit of code can be removed safely:

```
'--------------------

'Adverse events death

'--------------------

'The annual prob is transformed into six month prob

'to reflect the actual prob of dying due to CV AEs in one cycle/6 months

If RandMatCardioAE(1, 5) < (1 - Exp(Log(1 - MatCVdeaths(identifier_treatment)) *
cycle_length)) * MatAE_CVnon_fatal_Spec(2) Then

   AE_d = 1

Else
```

```
    AE_d = 0

  End If
```

From the next line of code the bit of code double-struck through can be removed safely:

```
  If evp_d + dip_d + odp_d + AE_d > 0 Then

    evp_d2 = (evp_d + AE_d) / (evp_d + dip_d + odp_d + AE_d) 'RAI: Although initially not included in the original model, AE proportion now included to consider the prop of deaths due to AEs

    dip_d2 = dip_d / (evp_d + dip_d + odp_d + AE_d)

    odp_d2 = odp_d / (evp_d + dip_d + odp_d + AE_d)
```

In 'first_steps_effects_diabetes' the following second bit of code can be removed safely:

```
  'To estimate whether MatSum_Diab_death was due to CV AEs

  If AE_d = 1 Then

    MatSum_CV_AE_death(1) = 1

  Else

    MatSum_CV_AE_death(1) = 0

  End If
```

In 'higher_steps_effects_diabetes' the following first bit of code can be removed safely:

```
    '--------------------

    'Adverse events death

    '--------------------

    If MatTx_Current(index_cycle + 1) <> MatTx_Current(1 + index_cycle - 1) Then        'Tx change occurred

      'RAI: Adjustment of death per cycle has been applied here to reflect 6-month probs , instead of annual prob (as inputted in the model)

      'since mortality is adjusted per year, as stated somewhere above

      If RandMatCardioAE(index_cycle, 5) < (1 - Exp(Log(1 - MatCVdeaths(identifier_treatment)) * cycle_length)) * MatAE_CVnon_fatal_Spec(2) Then

        AE_d = 1

      Else
```

```
            AE_d = 0

        End If

    Else

            'RAI: the line of code below was modified since the original model considered that
CV mortality was to be applied only for the first 2 years on same tx

            'However, this period should reflect the choice of the user regarding
MatAE_CV_Spec(5):

            '= 0 if only to be applied in 1st cycle,

            '= 2 if to be applied in 2 years,

            '= 999 if to be applied for full time horizon

            'Also, adjustment of death per cycle has been applied to reflect 6-month probs
instead of 1-year prob (as inputs in the model are annual probs)

        If MatTimeonXTx_Current(index_cycle + 1) <= MatAE_CV_Spec(5) Then          'If
CV death is to be taken into account based on user's selection

            If RandMatCardioAE(index_cycle, 5) < (1 - Exp(Log(1 -
MatCVdeaths(identifier_treatment)) * cycle_length)) * MatAE_CVnon_fatal_Spec(2) Then

                AE_d = 1

            Else

                AE_d = 0

            End If

        Else

            AE_d = 0

        End If

    End If
```

From the next lines of code the bit of code double-struck through can be removed safely:

```
    'Sampling which type of death

    If ev + di + od + AE_d > 0 Then

        evp_d = (ev + AE_d) / (ev + di + od + AE_d) 'Although initially not included in the
original model, this proportion is including death due to AEs

        dip_d = di / (ev + di + od + AE_d)
```

```
odp_d = od / (ev + di + od + AE_d)
```

In 'higher_steps_effects_diabetes' the following second bit of code can be removed safely:

```
'To estimate whether MatSum_Diab_death was due to CV AEs

If MatTimeonXTx_Current(index_cycle + 1) <= MatAE_CV_Spec(5) And AE_d = 1 Then

    MatSum_CV_AE_death(1 + index_cycle) = 1

Else

    MatSum_CV_AE_death(1 + index_cycle) = 0

End If
```

Response: Removing these bits of code will keep the value of the variable: AE_d = 0, in the same way as if the code would not have been removed. The reason for this is that the relevant values of the variable identifying CV deaths due to adverse events were already null. Deaths related to CV AEs have been deactivated in the model submitted to NICE (i.e. they have all been set up to zero) and therefore, removing or not these bits of code will not affect the simulations and corresponding results.

B32. *The visual basic notes that we want to have sum_weight_end - sum_weight start for the two next cycles. Call this difference b. Then weight half is equal to 1/3 a + 1/3 b in order to obtain linear change in H(t+1) - H(t) and to obtain correct estimates. The ERG is having difficulty understanding the logic behind this calculation and would much appreciate some further explanation of it.*

Response: The model was developed considering 6-month cycles (so that patients could experience treatment changes as soon as 6 months after treatment initiation, following the feedback from the experts consulted at the initial development stages). However, the model was based on the UKPDS68 risk equations, which reflected one-year probabilities (see answer to question B33 below). The aim was therefore to obtain probabilities that could be applied in each 6-month cycle based on the one-year probability estimation of the UKPDS68 equations, without altering the cumulative, annual probability by using 6-month probabilities, and aiming to be as regular and smooth as possible in the changes.

For this, when looking at the difference H(t+1)-H(t), which refers to the difference after one cycle/6-month have passed (i.e. the difference between one cycle and the next one), we also considered the changes H(t)-H(t-1) and H(t+2)-H(t+1), e.g. we considered the changes during the prior cycle and the next cycle.

The following steps justify the calculation that has been made:

H(t+1) = H(t) + 1/3 [H(t+2)-H(t-1)] # There are 3 periods between (t-1) and (t+2): (t-1)—t ; t—(t+1) ; (t+1) – (t+2)

H(t+1)= H(t) + 1/3 [H(t+2)-H(t)+H(t) -H(t-1)] # H(t)-H(t)=0

H(t+1)=H(t) + 1/3 [H(t+2)-H(t)] +1/3[H(t)-H(t-1)] # rewriting of the line

H(t+1)=H(t) + 1/3 * b + 1/3 * a # With b=H(t+2)-H(t) and a=H(t)-H(t-1)

Therefore the change between H(t+1) and H(t) corresponded to 1/3 a + 1/3 b.

B33. PRIORITY *Within the procedure Higher_ Steps_Effects_Diabetes the calculation of whether an event happens appears to be dependent upon the condition If Mat_Update_RiskEqs(index_cycle + 1) = 1 Then; i.e. if the cycle is the first half of a year or not. The calculation of whether an event happens appears to be then based upon a six monthly probability. But it is unclear how or where the calculation of whether an event happens in the second half of a year occurs; i.e. when Mat_Update_RiskEqs(index_cycle + 1) = 0. If the probability of an event happening in the second half of the year is by default zero, it would seem that the calculation of the probability of an event happening in the first half of the year should be based upon the annual risk rather than the six monthly risk. Please provide an explanation for this, including if relevant where in the visual basic the calculation of whether an event happens in the second half of a year occurs.*

Response: The UKPDS68 risk equations (Clarke 2004) that we used in the model to estimate the occurrence of long term complications had been estimated per year based on annual data. However, as mentioned in question B32, the cycle length in the model was 6 months. Therefore, the adjustment mentioned above (see question B32) was conducted to take into account that events could happen in each cycle rather than only once per year. For this, the variables impacting the risk equations were updated only once per year so that the annual number of events estimated by the risk equations would be as closely reflected in the model as possible. For this, the variable 'Mat_Update_RiskEqs(index_cycle + 1)' was used as an indicator of the extremes of the year:

- Whenever the variables needed to be updated because they reflected being at the very beginning or at the very end of a period of one year, then Mat_Update_RiskEqs(index_cycle + 1) =1
- For cycles in which the variables were not to be updated, then Mat_Update_RiskEqs(index_cycle + 1) = 0 (or 'Else' as part of the VBA code).

In this way, the same value for the variables considered in the risk equations would be used in a cycle corresponding, for example, with year 1, and in the next cycle, corresponding to year 1.5, so that the cumulative probability of the event would reflect a similar probability to the one that would have been obtained if annual cycles had been used, with annual updates of variables and of the occurrence of events.

Once variables were updated only once per year, the probabilities per cycle were estimated, which corresponded to 6-month probabilities, rather than to annual probabilities, to reflect the cycle duration considered in the model. The aim was to obtain a similar number of events happening when considering 6-month cycles rather than annual cycles.

B34. *Similarly to the above question, the MatEventDeath_Prob(1) = 1 - sqrt_one_minus_prob_year appears to be the six monthly probability of an event related death. The model should presumably apply this probability for two consecutive cycles given that the UKPDS 68 calculates annual probabilities. Please identify where and how in the VBA this occurs.*

Response: The same justification presented for question B33 applies here. To reflect as closely as possible the annual probabilities as estimated by the UKPDS 68 risk equations, the values of the variables affecting the risk equations were updated once per year, while the

occurrence of events was estimated per cycle considering that the cumulative probabilities should be similar to those estimated annually by the risk equations.

B35. PRIORITY *There are a number of variables within the excel front end that are hidden that feed global variables into the VBA, for example MatAE_CV_Spec(5). These hidden variables run throughout the VBA code. Please provide a list of these hidden variables identified by their excel location, also identified by their variable name within the VBA, what their default value should be for the correct running of the model and what is the logic of the default values.*

Response: The model was developed as a global/reference model that could be used to assess a wider range of treatments and AEs from those finally included in the NICE submission. The analyses considered for the submission focused on comparisons of empagliflozin against another SGLT2 and against sitagliptin 100mg (as the most common DPP4 used in the UK clinical practice). Therefore, there were AEs that were not relevant for the analyses given that they are not relevant AEs for SGLT2s or DPP4s (e.g. peripheral oedema, gastrointestinal events, need for renal monitoring and cardiovascular AEs including transient ischemic attacks, strokes, myocardial infarctions and other myocardial ischemias). These AEs were therefore deactivated by using null values for their probability of patients experiencing each of them, which can be seen under the worksheet 'Adverse events', in columns:

- V:AE for peripheral oedema,
- AF:AO for gastrointestinal events
- AP:AT for the need for renal monitoring
- BO:CW for CV AEs, CV death and for an additional AE included to allow the user to define one additional AE in the model if needed.

Under 'Model scope' the definition of each of these variables in terms of when they would happen is identified under the range CE15:CE29, and this range was used as part of the VBA code as an array named 'MatAE_All_Spec'. This array was created to identify whether each of the AEs would happen during the first cycle after treatment initiation (in which case, the corresponding value for the variable was '0') or they would happen in all cycles (in which case the value of the variable would be '1'). For CV AEs, there was also the possibility of applying the CV AEs to a period of observation for which it was considered that data would be available and it was assumed to be 2 years. According to whether the CV AEs were to be applied to the first cycle, during the first 2 years or during the full time the patient was on the treatment, the variable took values 1, 2 or 3. Then the array 'MatAE_CV_Spec' was created in VBA, using the values in the range CF24:CF28 under the worksheet 'Model scope, so that in the code we could identify whether a patient had been on the treatment for a specific period and see if the CV AE would apply to that period or not.

It should be noted that given that the probabilities of these other AEs to happen were set up as null in the model, it does not matter what setting is used in the base case analysis, since none of these AEs will happen because of their null values.

Under the worksheet 'Model scope' there was an additional set of variables (located in the range BW38:BW41), with the corresponding values inputted to the array 'MatAE_CVnon_fatal_Spec' in the VBA code located in the range CE38:CE41, which was

hidden since it was not relevant for the NICE submission. This set of variables was created with the objective of assessing different structural assumptions, including:

- The consideration or not, as part of the modelled effects, of the UKPDS68 risk equations related to CV events (i.e. CHF, stroke, MI and IHDs), which corresponds to cell BW38 under the worksheet 'Model scope', and to the array and location 'MatAE_CVnon_fatal_Spec(1)' in the VBA code. For all the analyses in the NICE submission it was considered that all the risk equations should be included, and therefore this variable was set to 'Yes' in all the analyses, which meant that 'MatAE_CVnon_fatal_Spec(1)' as part of the VBA code was set to 1 (as identified in cell CE38).
- The other variables, selected in cells BW39:BW41, related to different sets of assumptions with regards to the CV AEs considered in the model (including whether they should be included or not as part of the analyses, and if included, whether their impact on QALYs and costs, and on the occurrence of long term complications, should be incorporated or not in the analysis. As mentioned above, given that the probabilities of CV AEs were set up to null values, therefore, deactivated, these additional structural settings were not relevant for the model. In any case, for all the analyses presented in the NICE submission the values considered were 'No' for the three variables, meaning that they were to be ignored/deactivated in the analyses, so that the impact of these CV AEs were not to be considered on QALYs, costs or as an additional factor to influence the occurrence of long-term complications.

Section C: Textual clarifications and additional points

C1. *The committee are provided with black and white printed versions of graphs. Printed in black and white the lines in the CEAC figures are poorly reproduced. In particular please supply versions of Figures 36 and 37 that print in black and white with all lines distinguishable and clearly labelled with regard to their intervention, and similarly for Figures 34 and 35.*

Response: The diagrams are included below for all comparisons in black and white.

Figure 7 Black and white version of Figure 34: Average discounted QALYs per surviving patient per cycle for empagliflozin 25mg compared to sitagliptin 100mg

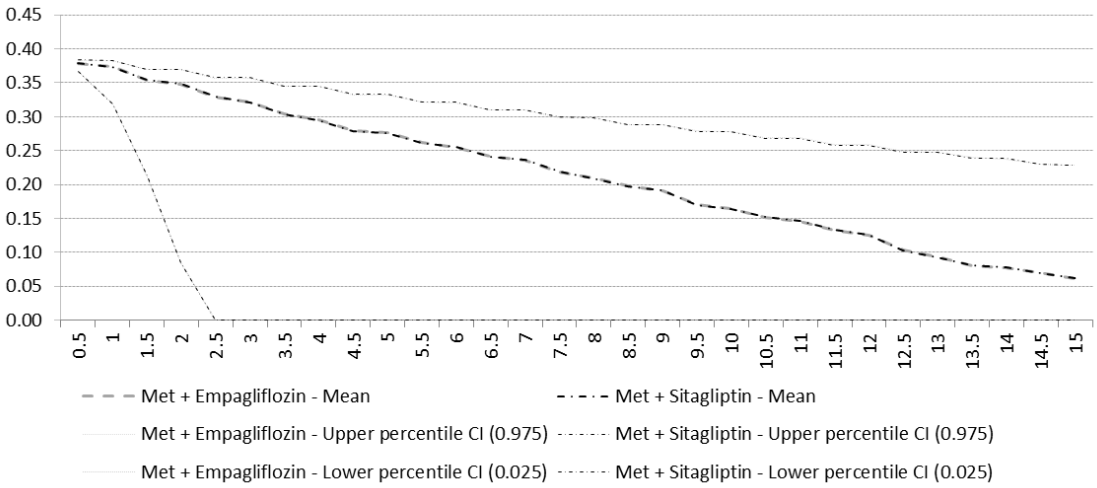


Figure 8 Black and white version of Figure 35: Average discounted NHS costs per surviving patient per cycle for empagliflozin 25mg compared to sitagliptin 100mg

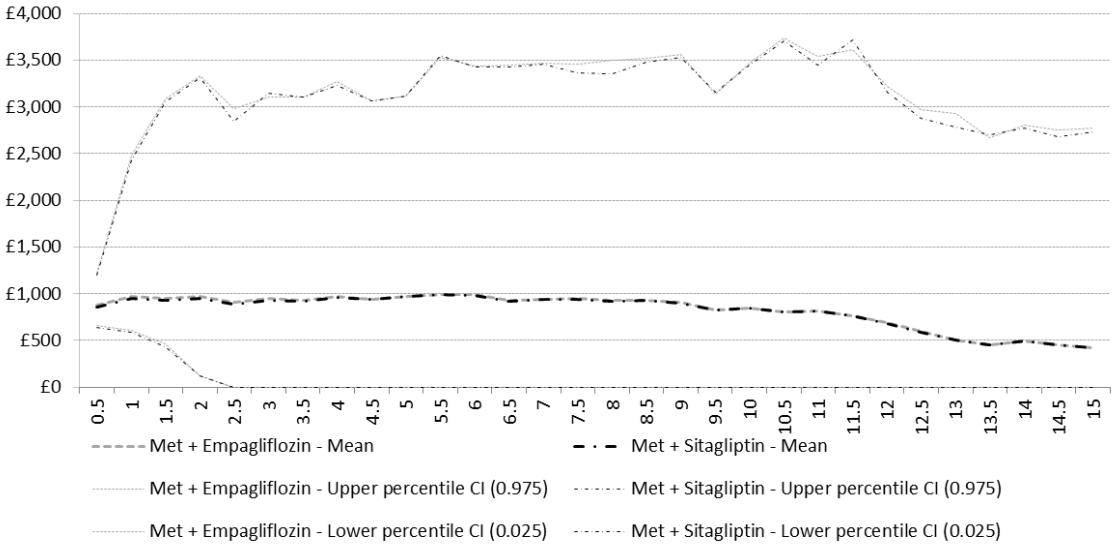


Figure 9 black and white version of Figure 36: Cost effectiveness acceptability curve – dual therapy

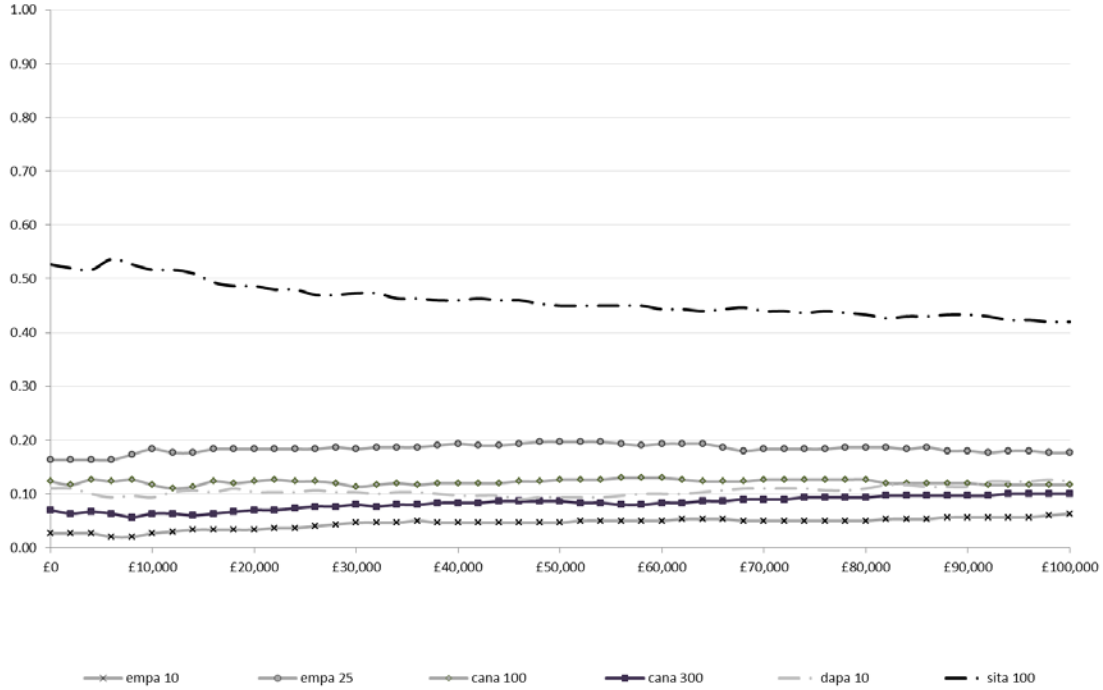


Figure 10 black and white version of Figure 37: Cost Effectiveness Acceptability Curve - triple therapy (met + SU)

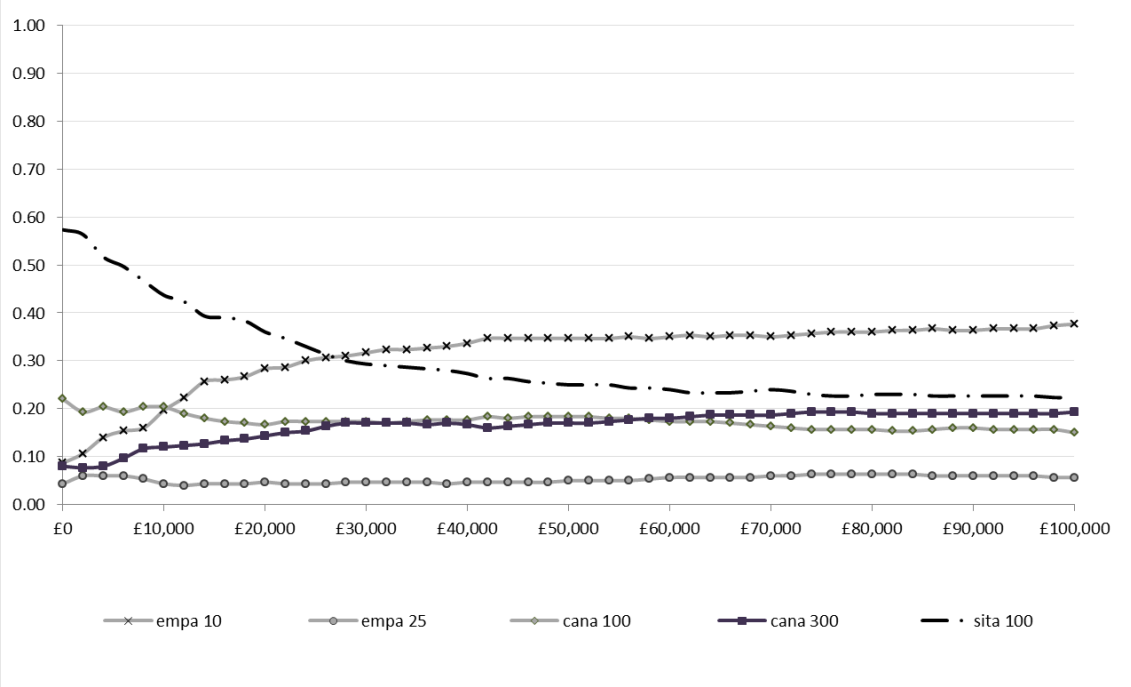


Figure 11 Black and white version of Figure 38: Cost effectiveness acceptability curve – triple therapy (met + TZD)

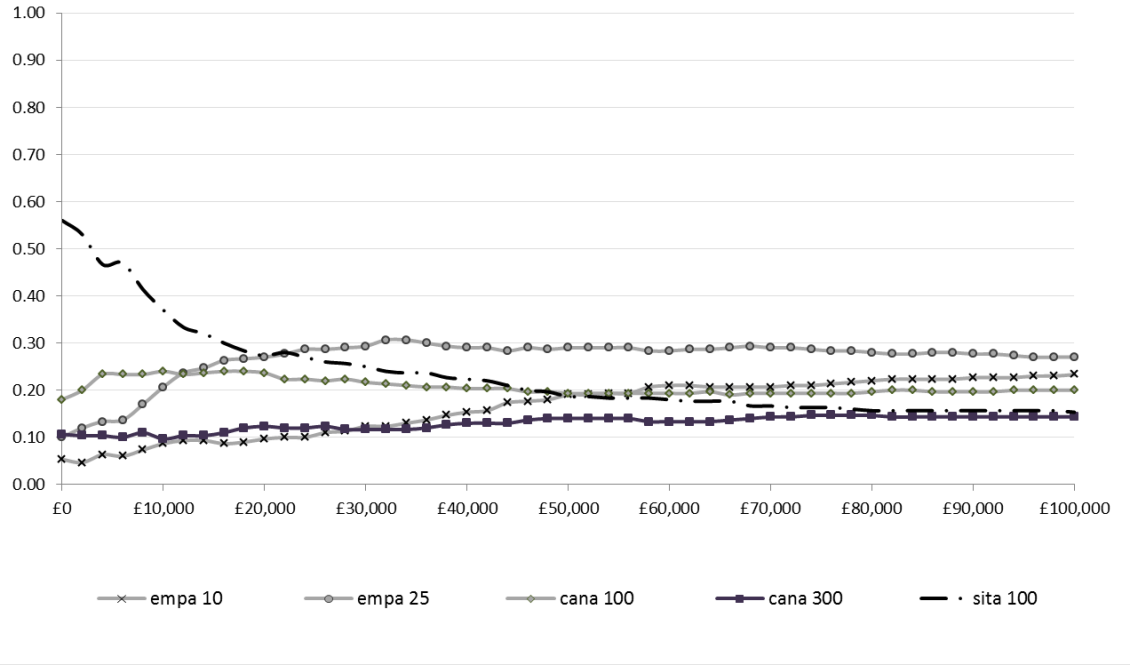
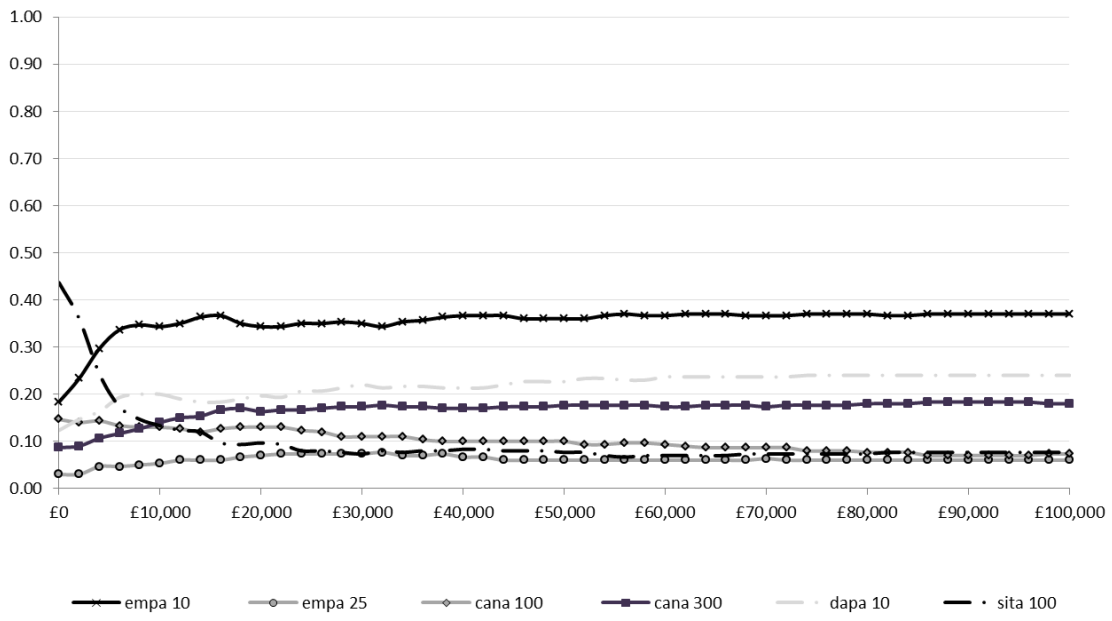


Figure 12 black and white version of Figure 39: Cost effectiveness acceptability curve – insulin combinations



C2. *Please check the title of figure 16, which includes OLS.*

Response: Apologies the correct titles for figures 15 and 16 are:

Figure 15: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.23 - metformin only) – FAS (LOCF)

Figure 16: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time in study 1245.23 (metformin plus SU) – FAS (LOCF)

C3. *Titles to Figures 18 to 21 contain the abbreviation OC. Please define.*

Response: In all the figures 'OC' stands for observed cases.

C4. *Please confirm that the terms second line and third line (as used in Tables 29, 31 etc.) refer to "dual therapy" and "triple therapy". We prefer to use dual and triple, because "second-line" could encompass substitution as well as addition.*

Response: We can confirm that the terms second line and third line refer to dual and triple therapy.

Additional issues identified

Some typographical errors have been identified in the following tables:

- Characteristics of participants in the RCTs across randomised groups (FAS) (Page 68)
- Summary of primary and secondary endpoints in study 1245.19 (Page 109)
- Summary of primary and secondary endpoints in study 1245.23 (metformin plus SU) (Page 115)
- Summary of efficacy endpoints in 1245.31 extension study (Page 122)

- Summary of AEs in study 1245.28 (Page 203)

The correct tables are presented in appendix 3

References

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2. Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004; 47:1747-1759
3. Kim G, Gerich J, Salsali A et al Empagliflozin Increases Genital Infections but Not Urinary Tract Infections (UTIs) in Pooled Data from Four Pivotal Phase III Trials, 2014 poster (not published)
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Appendix 1

Question A1.

Table 16: Frequency of analysis of treat to target efficacy response at week 24 - FAS (NCF), OLS (NCF) - 1245.23 (metformin only)

	Proportion of patients achieving HbA_{1C} levels by 24 weeks											
	6.5% or less				7.0% or less				7.5% or less			
1245.23 (EMPA-REG MET, EMPA-REG METSU) – metformin only	Placebo (n=207)	Empa 10mg (n=217)	Empa 25mg (n=213)	Empa 25mg OL (n=69)	Placebo (n=207)	Empa 10mg (n=217)	Empa 25mg (n=213)	Empa 25mg OL (n=69)	Placebo (n=207)	Empa 10mg (n=217)	Empa 25mg (n=213)	Empa 25mg OL (n=69)
Baseline HbA_{1C}												
<8.0%	14 (11.6)	26 (21.3)	39 (31.5)	0 (0)	37 (30.6)	73 (59.8)	72 (58.1)	0 (0)	78 (64.5)	104 (85.2)	106 (85.5)	0 (0)
8.0-8.9%	0 (0)	6 (9.0)	10 (15.2)	0 (0)	2 (3.3)	18 (26.9)	28 (42.4)	0 (0)	10 (16.7)	39 (58.2)	39 (59.1)	0 (0)
9.0 % and over	0 (0)	2 (7.1)	0 (0)	1 (1.5)	2 (7.7)	7 (25.0)	4 (17.4)	8 (11.9)	3 (11.5)	11 (39.3)	7 (30.4)	18 (26.9)
All baseline HbA_{1C}	14 (6.8)	34 (15.7)	49 (23.0)	1 (1.4)	41(19.8)	98 (45.2)	104 (48.8)	8 (11.6)	91 (44.0)	154 (71.0)	152 (71.4)	18 (26.1)

FAS = full analysis set; NCF = non-completers considered failure; OLS = open-label set

Table 17: Frequency of analysis of treat to target efficacy response at week 24 - FAS (NCF), OLS (NCF) - 1245.23 (metformin plus SU)

	Proportion of patients achieving HbA_{1C} levels by 24 weeks											
	6.5% or less				7.0% or less				7.5% or less			
1245.23 (EMPA-REG MET, EMPA-REG METSU) – metformin plus SU	Placebo (n=225)	Empa 10mg (n=225)	Empa 25mg (n=216)	Empa 25mg OL (n=101)	Placebo (n=225)	Empa 10mg (n=225)	Empa 25mg (n=216)	Empa 25mg OL (n=101)	Placebo (n=225)	Empa 10mg (n=225)	Empa 25mg (n=216)	Empa 25mg OL (n=101)
Baseline HbA_{1C}												
<8.0%	10 (8.9)	24 (21.8)	25 (23.8)	0 (0)	26 (23.2)	56 (50.9)	52 (49.5)	0 (0)	55 (49.1)	77 (70.0)	73 (69.5)	0 (0)
8.0-8.9%	1 (1.4)	5 (6.2)	8 (10.3)	2 (100)	4 (5.6)	20 (24.7)	24 (30.8)	2 (100)	17 (23.9)	39 (48.1)	45 (57.7)	2 (100)
9.0 % and over	0 (0)	3 (8.8)	1 (3.0)	4 (4.0)	1 (2.4)	4 (11.8)	3 (9.1)	8 (8.1)	1 (2.4)	13 (38.2)	8 (24.2)	18 (18.2)

	Proportion of patients achieving HbA_{1C} levels by 24 weeks											
All baseline HbA_{1C}	11 (4.9)	32 (14.2)	34 (15.7)	6 (5.9)	31 (13.8)	80 (35.6)	79 (36.6)	10 (9.9)	73 (32.4)	129 (57.3)	126 (58.3)	20 (19.8)

FAS = full analysis set; NCF = non-completers considered failure; OLS = open-label set

Table 18: Frequency of analysis of treat to target efficacy response at week 18 - FAS (NCF) - 1245.33

	Proportion of patients achieving HbA_{1C} levels by 18 weeks								
	6.5% or less			**7.0% or less**			**7.5% or less**		
1245.33 (EMPA-REG BASAL)	Placebo (n=170)	Empa 10mg (n=169)	Empa 25mg (n=155)	Placebo (n=170)	Empa 10mg (n=169)	Empa 25mg (n=155)	Placebo (n=170)	Empa 10mg (n=169)	Empa 25mg (n=155)
Baseline HbA_{1C}									
<8.0%	3 (4.2)	8 (11.1)	9 (13.0)	10 (4.1)	25 (34.7)	22 (31.9)	31 (43.7)	43 (59.7)	36 (52.2)
8.0-8.9%	1 (1.5)	3 (5.2)	1 (2.1)	4 (6.0)	8 (13.8)	9 (19.1)	8 (11.9)	25 (43.1)	16 (34.0)
9.0 % and over	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.1)	5 (12.8)	3 (9.4)	8 (20.5)	10 (25.6)
All baseline HbA_{1C}	4 (2.4)	11 (6.5)	10 (6.5)	14 (8.2)	35 (20.7)	36 (23.2)	42 (24.7)	76 (45.0)	62 (40.0)

FAS = full analysis set; NCF = non-completers considered failure

Table 19: Frequency of analysis of treat to target efficacy response at week 18 - FAS (NCF) - 1245.49

	Proportion of patients achieving HbA_{1C} levels by 18 weeks								
	6.5% or less			**7.0% or less**			**7.5% or less**		
1245.49 (EMPA-REG MDI)	Placebo (n=188)	Empa 10mg (n=186)	Empa 25mg (n=189)	Placebo (n=188)	Empa 10mg (n=186)	Empa 25mg (n=189)	Placebo (n=188)	Empa 10mg (n=186)	Empa 25mg (n=189)
Baseline HbA_{1C}									
<8.0%	7 (10.8)	6 (11.1)	15 (22.4)	19 (29.2)	20 (37.0)	32 (47.8)	34 (52.3)	35 (64.8)	42 (62.7)
8.0-8.9%	3 (3.7)	5 (5.9)	12 (14.3)	10 (12.3)	17 (20.0)	30 (35.7)	30 (37.0)	38 (44.7)	51 (60.7)
9.0 % and over	3 (7.1)	4 (8.5)	2 (5.3)	3 (7.1)	11 (23.4)	6 (15.8)	3 (7.1)	22 (46.8)	12 (31.6)
All baseline HbA_{1C}	13 (6.9)	15 (8.1)	29 (15.3)	32 (17.0)	48 (25.8)	68 (36.0)	67 (35.6)	95 (51.1)	105 (55.6)

FAS = full analysis set; NCF = non-completers considered failure

Appendix 2 – NMA patient characteristics, diagrams and results

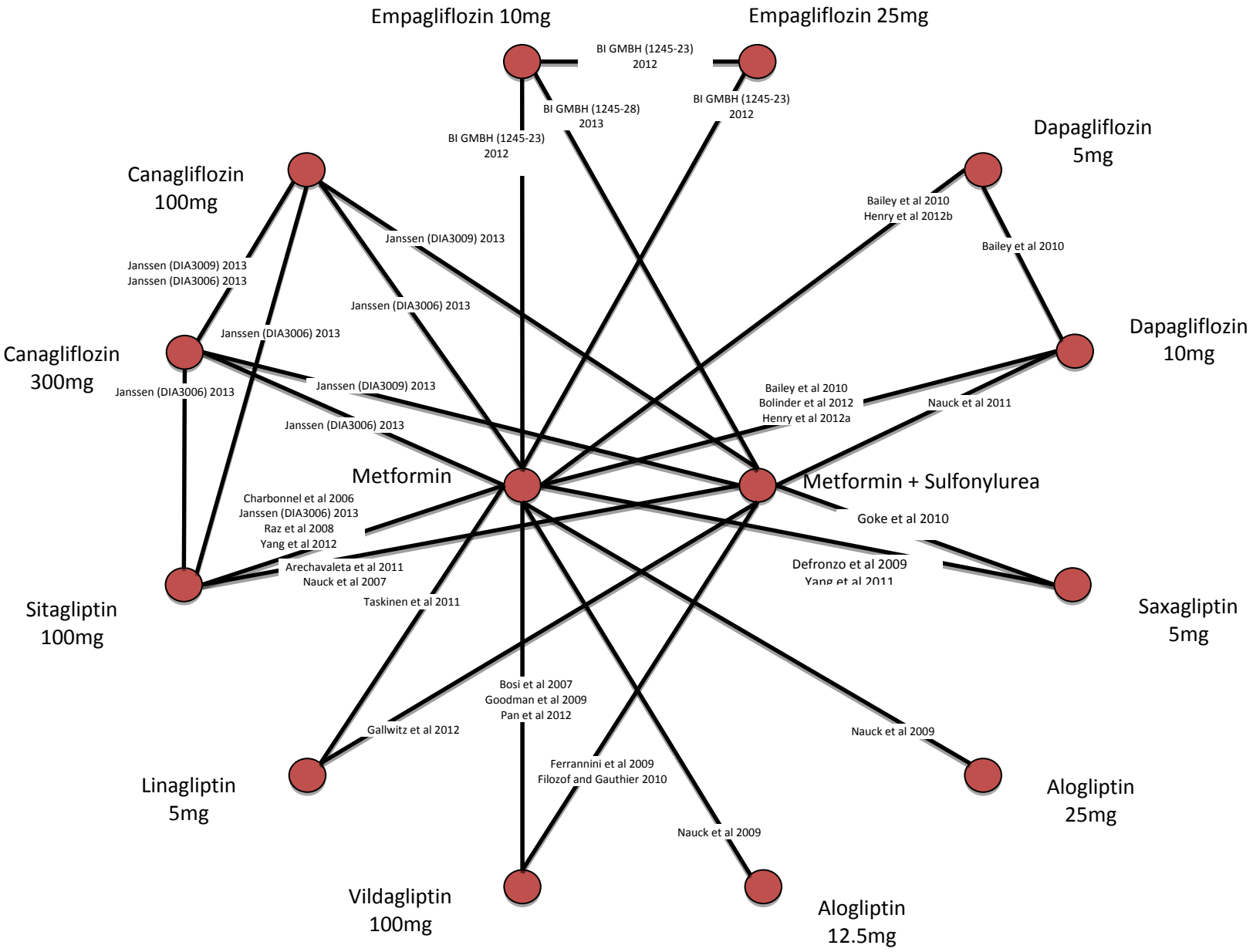
Dual therapy (Met)

Study and patient characteristics of included trials (24 weeks)

Study	Interventions/Comparators	Age (years)	Male (%)	Mean Baseline HbA_{1C} (%)	Mean Body Weight (kg)	Total Sample Size
Second line						
BI GMBH (1245-23) 2012 (9)	Empagliflozin 10 mg + Met	55.5	57.6	7.9	81.6	637
	Empagliflozin 25 mg + Met	55.6	56.3	7.9	82.2	
	Placebo + Met	56	56	7.9	79.7	
BI GMBH (1245-28) 2013 (11)	Empagliflozin 25 mg + Met	56.2	56.6	7.9	82.5	1545
	Placebo + Met +SU	55.7	54	7.9	83	
Gallwitz et al. 2012 (45)	Linagliptin + Met	59.8	60	7.7	86.1	1551
	Met + SU	59.8	61	7.7	86.8	
Taskinen et al. 2011 (46)	Linagliptin + Met	56.5	53	8.1	82.2	700
	Placebo + Met	56.6	57	8	83.3	
Defronzo et al. 2009 (47)	Saxagliptin (2.5 mg) + Met	54.7	43.2	8.1	86	743
	Saxagliptin (5 mg) + Met	54.7	53.9	8.1	87.3	
	Saxagliptin (10 mg) + Met	54.2	52.5	8	87.8	
	Placebo + Met	54.8	53.6	8.1	87.1	
Goke et al. 2010(48)	Saxagliptin + Met	57.5	49.5	7.7	88.7	858
	Met + SU	57.6	54	7.7	88.6	
Yang et al. 2011 (49)	Saxagliptin + Met	53.8	48.1	7.9	68.9	570
	Placebo + Met	54.4	48.4	7.9	69	
Arechavaleta et al. 2011 (50)	Sitagliptin + Met	56.3	55	7.5	80.6	1,035
	Met + SU	56.2	53.8	7.5	82	
Charbonnel et al. 2006 (51)	Sitagliptin + Met	54.4	55.8	8	86.7	701
	Placebo + Met	54.7	59.5	8	89.6	
Nauck et al. 2007 (52)	Sitagliptin + Met	56.8	57.1	7.7	89.5	1,172
	Met + SU	56.6	61.3	7.6	89.7	
Raz et al. 2008 (53)	Sitagliptin + Met	53.6	51	9.3	81.5	190

	Placebo + Met	56.1	41.5	9.1	81.2	
Scott et al. 2008 (54)	Sitagliptin + Met	55.2	55	7.8	83.1	186
	Placebo + Met	55.3	59	7.7	84.6	
Yang et al. 2012 (55)	Sitagliptin + Met	54.1	47	8.5	67.9	395
	Placebo + Met	55.1	55	8.5	68.9	
Charpentier et al. 2001 (56) Details included for completeness not included in NMAs below	Met + SU	58.8	59	6.4	81.2	372
	Placebo + Met	60.7	60	6.8	82.2	
Bosi et al. 2007 (57)	Vildagliptin + Met	53.9	61.5	8.4	95.3	367
	Placebo + Met	54.5	53.1	8.3	94.8	
Ferrannini et al 2009 (58)	Vildagliptin + Met	57.5	52.8	7.3	89	2789
	Met + SU	57.5	54.1	7.3	88.6	
Filozof et al 2010 (59)	Vildagliptin + Met	59.2	52.2	8.5	85.7	1007
	Met + SU	59.7	51.8	8.5	84.2	
Goodman et al 2009 (60)	Vildagliptin + Met	55	52.8	8.5	NR	372
	Placebo + Met	54.5	67.2	8.7	NR	
Pan et al 2012 (61)	Vildagliptin + Met	54.2	50	8.1	71.6	290
	Placebo + Met	54.5	45.8	8	69.8	
Janssen (DIA3009) 2013 (62)	Met + SU	56.2	52.1	7.8	86.6	1452
	Canagliflozin 100 mg + Met	56.2	52.1	7.8	86.9	
	Canagliflozin 300 mg + Met	56.2	52.1	7.8	86.6	
Janssen (DIA3006) 2013 (63)	Placebo + Met	55.4	47.1	8	86.6	1284
	Sitagliptin + Met	55.4	47.1	8	87.7	
	Canagliflozin 100 mg + Met	55.4	47.1	8	88.8	
	Canagliflozin 300 mg + Met	55.4	47.1	8	85.4	
Bolinder et al 2012 (64)	Placebo + Met	60.8	56	7.2	90.9	182
	Dapagliflozin 10 mg + Met	60.6	55.1	7.2	92.1	
Henry et al 2012a (65)	Placebo + Met	52.7	46.6	9.1	87.2	419
	Dapagliflozin 10 mg + Met	51	50.2	9.1	88.4	
Henry et al 2012b (65)	Placebo + Met	51.8	47.3	9.2	85.6	395
	Dapagliflozin 5 mg + Met	51.7	40.2	9.2	84.1	
Bailey et al 2010 (66)	Placebo + Met	53.7	55	8.1	87.7	409
	Dapagliflozin 5 mg + Met	54.3	50	8.2	84.7	

	Dapagliflozin 10 mg + Met	52.7	57	7.9	86.3	
Nauck et al 2011 (67)	Met + SU	59	54.9	7.7	87.6	814
	Dapagliflozin 10 mg + Met	58	55.3	7.7	88.4	


Empagliflozin 10mg
Empagliflozin 25mg
BI GMBH (1245-23) 2012
BI GMBH (1245-28) 2013
BI GMBH (1245-23) 2012
BI GMBH (1245-23) 2012
Dapagliflozin 5mg
Canagliflozin 100mg
Bailey et al 2010
Henry et al 2012b
Bailey et al 2010
Janssen (DIA3009) 2013
Janssen (DIA3009) 2013
Janssen (DIA3006) 2013
Janssen (DIA3006) 2013
Janssen (DIA3006) 2013
Dapagliflozin 10mg
Canagliflozin 300mg
Janssen (DIA3006) 2013
Janssen (DIA3009) 2013
Bailey et al 2010
Bolinder et al 2012
Henry et al 2012a
Nauck et al 2011
Janssen (DIA3006) 2013
Metformin
Metformin + Sulfonylurea
Charbonnel et al 2006
Janssen (DIA3006) 2013
Raz et al 2008
Yang et al 2012
Goke et al 2010
Arechavaleta et al 2011
Nauck et al 2007
Defronzo et al 2009
Yang et al 2011
Taskinen et al 2011
Sitagliptin 100mg
Saxagliptin 5mg
Bosi et al 2007
Goodman et al 2009
Pan et al 2012
Gallwitz et al 2012
Nauck et al 2009
Ferrannini et al 2009
Filozof and Gauthier 2010
Linagliptin 5mg
Alogliptin 25mg
Nauck et al 2009
Vildagliptin 100mg
Alogliptin 12.5mg

[diagram]

Table 20: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for the second line treatment of T2DM (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	-0.83 (-0.99 to -0.68)	--	--	--	--	--	--	--
Empagliflozin 10mg	-0.6 (-0.93 to -0.27)	0.24 (-0.11 to 0.58)	--	--	--	--	--	--
Empagliflozin 25mg	-0.7 (-0.96 to -0.44)	0.13 (-0.12 to 0.39)	-0.1 (-0.44 to 0.23)	--	--	--	--	--
Canagliflozin 100mg	-0.67 (-0.94 to -0.4)	0.17 (-0.1 to 0.43)	-0.07 (-0.49 to 0.35)	0.03 (-0.32 to 0.39)	--	--	--	--
Canagliflozin 300mg	-0.79 (-1.06 to -0.53)	0.04 (-0.22 to 0.3)	-0.19 (-0.61 to 0.22)	-0.09 (-0.44 to 0.26)	-0.12 (-0.37 to 0.13)	--	--	--
Dapagliflozin 5mg	-0.47 (-0.74 to -0.2)	0.36 (0.06 to 0.67)	0.13 (-0.31 to 0.56)	0.23 (-0.15 to 0.6)	0.19 (-0.18 to 0.57)	0.32 (-0.05 to 0.69)	--	--
Dapagliflozin 10mg	-0.56 (-0.75 to -0.36)	0.27 (0.06 to 0.5)	0.04 (-0.34 to 0.42)	0.14 (-0.17 to 0.46)	0.11 (-0.21 to 0.43)	0.23 (-0.08 to 0.55)	-0.09 (-0.38 to 0.22)	--
Alogliptin 12.5mg	-0.5 (-0.93 to -0.07)	0.34 (-0.13 to 0.79)	0.1 (-0.45 to 0.64)	0.2 (-0.31 to 0.71)	0.17 (-0.34 to 0.67)	0.29 (-0.22 to 0.8)	-0.03 (-0.54 to 0.48)	0.06 (-0.42 to 0.53)
Alogliptin 25mg	-0.5 (-0.93 to -0.06)	0.34 (-0.13 to 0.8)	0.1 (-0.45 to 0.64)	0.2 (-0.3 to 0.71)	0.17 (-0.34 to 0.68)	0.29 (-0.22 to 0.81)	-0.03 (-0.53 to 0.49)	0.06 (-0.41 to 0.53)
Linagliptin 5mg	-0.59 (-0.86 to -0.33)	0.25 (-0.02 to 0.5)	0.01 (-0.41 to 0.42)	0.11 (-0.24 to 0.46)	0.08 (-0.28 to 0.43)	0.2 (-0.15 to 0.55)	-0.12 (-0.49 to 0.25)	-0.03 (-0.34 to 0.27)
Saxagliptin 5mg	-0.62 (-0.84 to -0.41)	0.21 (-0.02 to 0.44)	-0.03 (-0.42 to 0.36)	0.08 (-0.25 to 0.4)	0.04 (-0.29 to 0.37)	0.17 (-0.15 to 0.5)	-0.15 (-0.5 to 0.2)	-0.06 (-0.35 to 0.21)
Sitagliptin 100mg	-0.79 (-0.97 to -0.62)	0.05 (-0.15 to 0.22)	-0.19 (-0.57 to 0.17)	-0.09 (-0.39 to 0.2)	-0.12 (-0.43 to 0.17)	0 (-0.3 to 0.29)	-0.32 (-0.65 to 0)	-0.23 (-0.49 to 0.01)
Vildagliptin 100mg	-0.78 (-0.97 to -0.59)	0.06 (-0.13 to 0.25)	-0.18 (-0.55 to 0.19)	-0.07 (-0.38 to 0.23)	-0.11 (-0.41 to 0.19)	0.02 (-0.28 to 0.32)	-0.3 (-0.64 to 0.02)	-0.21 (-0.48 to 0.04)

Mean reduction in body weight, kg (95% credible interval)

intervention/ comparator	Metformin	Metformin +SU	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Metformin +SU	2.59 (2.22 to 2.96)	--	--	--	--	--	--	--
Empagliflozin 10mg	-1.7 (-2.26 to -1.1)	-4.29 (-4.89 to -3.6)	--	--	--	--	--	--
Empagliflozin 25mg	-2.14 (-2.56 to -1.69)	-4.73 (-5.1 to -4.31)	-0.44 (-1.02 to 0.13)	--	--	--	--	--
Canagliflozin 100mg	-1.91 (-2.38 to -1.4)	-4.49 (-4.95 to -4)	-0.18 (-0.93 to 0.49)	0.24 (-0.35 to 0.79)	--	--	--	--
Canagliflozin 300mg	-2.59 (-3.08 to -2.1)	-5.17 (-5.66 to -4.7)	-0.9 (-1.64 to -0.2)	-0.45 (-1.05 to 0.1)	-0.69 (-1.14 to -0.26)	--	--	--
Dapagliflozin 5mg	-1.77 (-2.28 to -1.3)	-4.37 (-4.95 to -3.8)	-0.07 (-0.83 to 0.65)	0.37 (-0.29 to 0.97)	0.12 (-0.55 to 0.78)	0.8 (0.14 to 1.48)	--	--
Dapagliflozin 10mg	-1.95 (-2.32 to -1.56)	-4.54 (-4.93 to -4.1)	-0.24 (-0.91 to 0.4)	0.2 (-0.33 to 0.68)	-0.04 (-0.61 to 0.52)	0.65 (0.08 to 1.24)	-0.17 (-0.69 to 0.4)	--
Linagliptin 5mg	0.13 (-1.17 to 1.39)	-2.46 (-3.8 to -1.11)	1.85 (0.4 to 3.21)	2.28 (0.9 to 3.63)	2.03 (0.67 to 3.39)	2.72 (1.33 to 4.05)	1.91 (0.52 to 3.27)	2.08 (0.73 to 3.41)
Saxagliptin 5mg	-0.07 (-0.47 to 0.37)	-2.66 (-3.2 to -2.09)	1.64 (0.91 to 2.34)	2.08 (1.47 to 2.67)	1.84 (1.19 to 2.48)	2.53 (1.89 to 3.17)	1.71 (1.07 to 2.38)	1.88 (1.33 to 2.44)
Sitagliptin 100mg	0.51 (0.05 to 0.93)	-2.08 (-2.49 to -1.72)	2.22 (1.49 to 2.85)	2.65 (2.09 to 3.12)	2.41 (1.8 to 2.96)	3.11 (2.51 to 3.66)	2.29 (1.64 to 2.92)	2.45 (1.92 to 2.94)
Vildagliptin 100mg	0.74 (0.41 to 1.06)	-1.86 (-2.34 to -1.37)	2.44 (1.77 to 3.06)	2.89 (2.33 to 3.39)	2.65 (2.06 to 3.2)	3.33 (2.75 to 3.9)	2.52 (1.94 to 3.11)	2.69 (2.19 to 3.17)

Mean reduction in SBP, mmHg (95% credible interval)

intervention/ comparator	Metformin	Metformin +SU	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Metformin +SU	0.17 (-1.8 to 2.14)	--	--	--	--	--	--	--
Empagliflozin 10mg	-4.28 (-7.23 to -1.19)	-4.44 (-7.6 to -1.06)	--	--	--	--	--	--
Empagliflozin 25mg	-5.1 (-7.46 to -2.68)	-5.26 (-7.5 to -2.87)	-0.82 (-3.86 to 2.11)	--	--	--	--	--
Canagliflozin 100mg	-4.15 (-6.6 to -1.79)	-4.3 (-6.7 to -1.98)	0.12 (-3.73 to 3.74)	0.96 (-2.24 to 3.88)	--	--	--	--
Canagliflozin 300mg	-5.46 (-7.97 to -3.08)	-5.62 (-7.9 to -3.32)	-1.16 (-5 to 2.37)	-0.34 (-3.51 to 2.54)	-1.32 (-3.42 to 0.79)	--	--	--
Dapagliflozin 5mg	-2.22 (-4.86 to 0.23)	-2.4 (-5.6 to 0.7)	2.06 (-2.09 to 5.8)	2.87 (-0.71 to 6.21)	1.92 (-1.65 to 5.43)	3.23 (-0.34 to 6.68)	--	--
Dapagliflozin 10mg	-3.82 (-5.62 to -1.79)	-4.01 (-6.07 to -1.6)	0.44 (-2.98 to 3.96)	1.27 (-1.49 to 4.16)	0.3 (-2.4 to 3.37)	1.62 (-1.04 to 4.69)	-1.57 (-4.43 to 1.54)	--
Saxagliptin 5mg	0.94 (-3.36 to 5.12)	0.76 (-3.94 to 5.51)	5.22 (-0.05 to 10.37)	6.02 (1.04 to 10.88)	5.1 (0.21 to 9.99)	6.41 (1.55 to 11.32)	3.16 (-1.74 to 8.06)	4.76 (-0.09 to 9.36)
Sitagliptin 100mg	-2.11 (-5.39 to 1.17)	-2.28 (-6.06 to 1.5)	2.19 (-2.33 to 6.56)	2.97 (-1.1 to 7)	2.03 (-1.92 to 6.09)	3.34 (-0.61 to 7.43)	0.14 (-3.97 to 4.39)	1.73 (-2.14 to 5.41)
Vildagliptin 100mg	-1.68 (-4.79 to 1.42)	-1.84 (-5.54 to 1.78)	2.58 (-1.82 to 6.83)	3.44 (-0.56 to 7.25)	2.46 (-1.38 to 6.42)	3.8 (-0.02 to 7.69)	0.55 (-3.36 to 4.58)	2.17 (-1.64 to 5.62)

Hypoglycaemia, RR (95% credible interval)

intervention/ comparator	Metformin	Metformin +SU	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Metformin +SU	4.05 (0.15 to 55.77)	--	--	--	--	--	--	--
Empagliflozin 10mg	5.19 (0.51 to 36.66)	1.12 (0.04 to 55.51)	--	--	--	--	--	--
Empagliflozin 25mg	3.44 (0.3 to 34.12)	NA	0.75 (0.09 to 4.63)	--	--	--	--	--

Canagliflozin 100mg	N/A	N/A	N/A	N/A	--	--	--	--
Canagliflozin 300mg	N/A	N/A	N/A	N/A	N/A	--	--	--
Dapagliflozin 5mg	2.23 (0.65 to 9.05)	NA	NA	0.65 (0.05 to 10.53)	N/A	N/A	--	--
Dapagliflozin 10mg	1.24 (0.43 to 3.57)	0.29 (0.02 to 10.49)	0.23 (0.03 to 3.28)	0.35 (0.03 to 5.42)	N/A	N/A	0.57 (0.12 to 2.18)	--
Alogliptin 12.5mg	0.18 (0.01 to 1.66)	0.04 (0 to 2.23)	0.03 (0 to 0.97)	0.05 (0 to 1.47)	N/A	N/A	NA	NA
Linagliptin 5mg	0.18 (0.03 to 1.17)	0.04 (0 to 2.09)	0.03 (0 to 0.86)	0.05 (0 to 1.17)	NA	N/A	NA	0.14 (0.02 to 1.33)
Saxagliptin 5mg	1.02 (0.29 to 3.36)	0.25 (0.01 to 7.72)	0.2 (0.02 to 2.65)	0.3 (0.02 to 4.27)	N/A	N/A	0.46 (0.07 to 2.52)	0.81 (0.16 to 4.18)
Sitagliptin 100mg	0.53 (0.11 to 2.05)	0.13 (0.01 to 5.15)	0.1 (0.01 to 1.44)	0.15 (0.01 to 2.38)	N/A	N/A	0.24 (0.03 to 1.38)	0.42 (0.07 to 2.34)
Vildagliptin 100mg	2.67 (0.37 to 18.46)	0.61 (0.02 to 32.37)	0.55 (0.03 to 11.2)	0.74 (0.03 to 16.38)	N/A	N/A	1.2 (0.12 to 10.97)	2.17 (0.22 to 18.63)

Hypoglycaemia (non-severe), RR (95% credible interval)

intervention/ comparator	Metformin	Metformin +SU	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Metformin +SU	3.54 (0.11 to 59.96)	--	--	--	--	--	--	--
Empagliflozin 10mg	4.81 (0.45 to 38.85)	NA	--	--	--	--	--	--
Empagliflozin 25mg	3.5 (0.29 to 31.91)	NA	0.79 (0.09 to 4.96)	--	--	--	--	--
Canagliflozin 100mg	NA	NA	NA	NA	--	--	--	--
Canagliflozin 300mg	NA	NA	NA	NA	NA	--	--	--
Dapagliflozin 5mg	2.31 (0.66 to 9.75)	NA	0.46 (0.04 to 8.51)	0.64 (0.05 to 12.9)	NA	NA	--	--

Dapagliflozin 10mg	1.38 (0.46 to 4.2)	0.39 (0.02 to 13.81)	0.28 (0.03 to 3.99)	0.38 (0.03 to 5.81)	NA	NA	0.6 (0.12 to 2.41)	--
Linagliptin 5mg	0.19 (0.02 to 1.35)	0.05 (0 to 3.06)	0.04 (0 to 0.81)	0.05 (0 to 1.27)	NA	NA	NA	NA
Saxagliptin 5mg	1.01 (0.3 to 3.49)	NA	0.21 (0.02 to 3.16)	0.29 (0.02 to 4.65)	NA	NA	NA	0.75 (0.14 to 3.82)
Sitagliptin 100mg	0.5 (0.11 to 2.06)	0.14 (0.01 to 5.62)	0.1 (0.01 to 1.77)	0.14 (0.01 to 2.67)	NA	NA	NA	0.36 (0.05 to 2.23)
Vildagliptin 100mg	2.58 (0.32 to 18.91)	0.74 (0.02 to 42.63)	0.52 (0.03 to 12.89)	0.7 (0.03 to 19.39)	NA	NA	1.15 (0.09 to 11.61)	1.85 (0.16 to 18.04)
UTIs, RR (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.15 (0.06 to 16.5)	--	--	--	--	--	--	--
Empagliflozin 25mg	1.09 (0.06 to 15.5)	N/A	0.96 (0.06 to 15.2)	--	--	--	--	--
Canagliflozin 100mg	N/A	N/A	N/A	N/A	--	--	--	--
Canagliflozin 300mg	N/A	N/A	N/A	N/A	N/A	--	--	--
Dapagliflozin 5mg	0.99 (0.05 to 14.9)	N/A	0.87 (0.02 to 43.3)	0.91 (0.02 to 43.1)	N/A	N/A	--	--
Dapagliflozin 10mg	2.21 (0.26 to 19.9)	N/A	N/A	N/A	N/A	N/A	N/A	--
Linagliptin 5mg	0.80 (0.04 to 12.4)	N/A	0.70 (0.01 to 34.4)	0.72 (0.01 to 36.0)	N/A	N/A	0.78 (0.02 to 40.5)	0.36 (0.01 to 9.79)
Saxagliptin 5mg	1.43 (0.17 to 10.4)	N/A	1.24 (0.05 to 40.6)	1.30 (0.05 to 40.7)	N/A	N/A	1.45 (0.05 to 47.4)	0.64 (0.03 to 10.7)
Sitagliptin 100mg	0.87 (0.05 to 13.1)	N/A	0.76 (0.02 to 37.8)	0.79 (0.02 to 37.6)	N/A	N/A	0.87 (0.02 to 46.9)	0.40 (0.01 to 10.4)
Vildagliptin 100mg	0.91 (0.04 to 12.5)	N/A	0.81 (0.02 to 34.9)	0.83 (0.02 to 36.9)	N/A	N/A	0.92 (0.02 to 40.8)	0.42 (0.01 to 11.2)

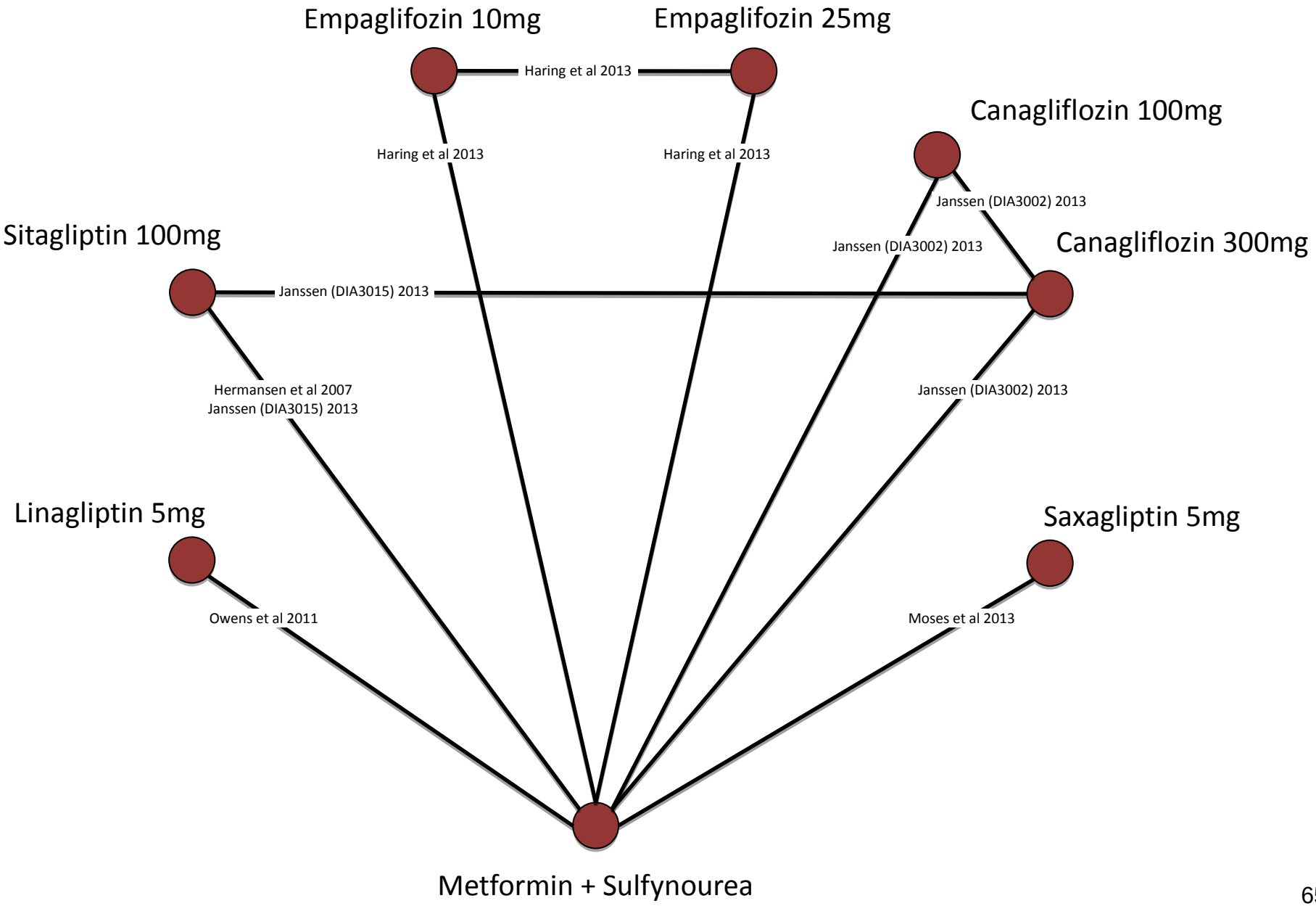
Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row).

Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Triple therapy (Met+SU)

Study and patient characteristics of included trials (24 weeks)

Triple therapy (met+su)						
	Interventions/Comparators	**Age (years)**	**Male (%)**	**Mean Baseline HbA_{1C} (%)**	**Mean Body Weight (kg)**	**Total Sample Size**
Haring et al. 2013 (9)	Empagliflozin 10 mg + Met + SU	57	50.2	8.07	77.1	669
	Empagliflozin 25 mg + Met + SU	57.4	52.8	8.1	77.5	
	Placebo + Met + SU	56.9	49.8	8.15	76.2	
Owens et al. 2011 (68)	Linagliptin + Met + SU	58.3	46.8	8.15	76.5	1058
	Placebo + Met + SU	57.6	48.3	8.14	76.8	
Hermansen et al. 2007 (69)	Sitagliptin + Met + SU	56.6	52.6	8.27	87.2	229
	Placebo + Met + SU	57.7	52.2	8.34	86.7	
Moses et al. 2013 (70)	Saxagliptin + Met + SU	57.2	56.9	8.38	89.1	257
	Placebo + Met + SU	56.8	54.9	8.19	87.4	
Janssen (DIA3015) 2013 (63)	Sitagliptin + Met + SU	56.7	56.9	8.1	89.1	756
	Canagliflozin 300 mg + Met + SU	56.7	54.9	8.1	87.4	
Janssen (DIA3002) 2013 (63)	Canagliflozin 100 mg + Met + SU	56.7	51	8.13	92.6	469
	Canagliflozin 300 mg + Met + SU	56.7	51	8.13	92.6	
	Placebo + Met + SU	56.7	51	8.13	92.6	


Empaglifozin 10mg
Empaglifozin 25mg
Haring et al 2013
Haring et al 2013
Haring et al 2013
Canagliflozin 100mg
Janssen (DIA3002) 2013
Janssen (DIA3002) 2013
Canagliflozin 300mg
Sitagliptin 100mg
Janssen (DIA3015) 2013
Hermansen et al 2007
Janssen (DIA3015) 2013
Janssen (DIA3002) 2013
Linagliptin 5mg
Saxagliptin 5mg
Owens et al 2011
Moses et al 2013
Metformin + Sulfynourea

Dual therapy (TZD)

Study and patient characteristics of included trials (24 weeks)

TZD failure						
	Interventions/Comparators	**Age (years)**	**Male (%)**	**Mean Baseline HbA_{1C} (%)**	**Mean Body Weight (kg)**	**Total Sample Size**
Kovacs et al. 2012 (7)	Placebo + TZD	54.6	44.2	8.2	78.1	499
	Empagliflozin 10 mg + TZD	54.7	50.3	8.1	78	
	Empagliflozin 25 mg + TZD	54.2	50.6	8.1	78.9	
Rosenstock et al. 2012 (71)	Placebo + TZD	53.5	51.1	8.3	86.4	420
	Dapagliflozin 5 mg + TZD	53.2	55.3	8.4	87.8	
	Dapagliflozin 10 mg + TZD	53.8	42.1	8.4	84.8	
Pratley et al 2009 (72)	Placebo + TZD	55.2	54.6	8	NR	493
	Alogliptin 12.5 mg + TZD	55.5	55.3	8.1	NR	
	Alogliptin 25 mg + TZD	55.4	62.8	8	NR	
Hollander et al 2009 (73)	Placebo + TZD	54	46.2	8.2	80.9	565
	Saxagliptin 2.5 mg + TZD	54.9	54.4	8.3	82.1	
	Saxagliptin 5 mg + TZD	53.2	47.8	8.4	80.4	
Garber et al 2007 (75)	Placebo + TZD	54.8	50.7	8.7	NR	463
	Vildagliptin 50 mg + TZD	54	54.8	8.6	NR	
	Vildagliptin 100 mg + TZD	54	44.9	8.7	NR	
Derosa et al 2010 (74)	Placebo + MET + TZD	58	51.3	8.4	77.3	151
	Sitagliptin 100 mg + TZD	57	49.3	8.5	78.7	

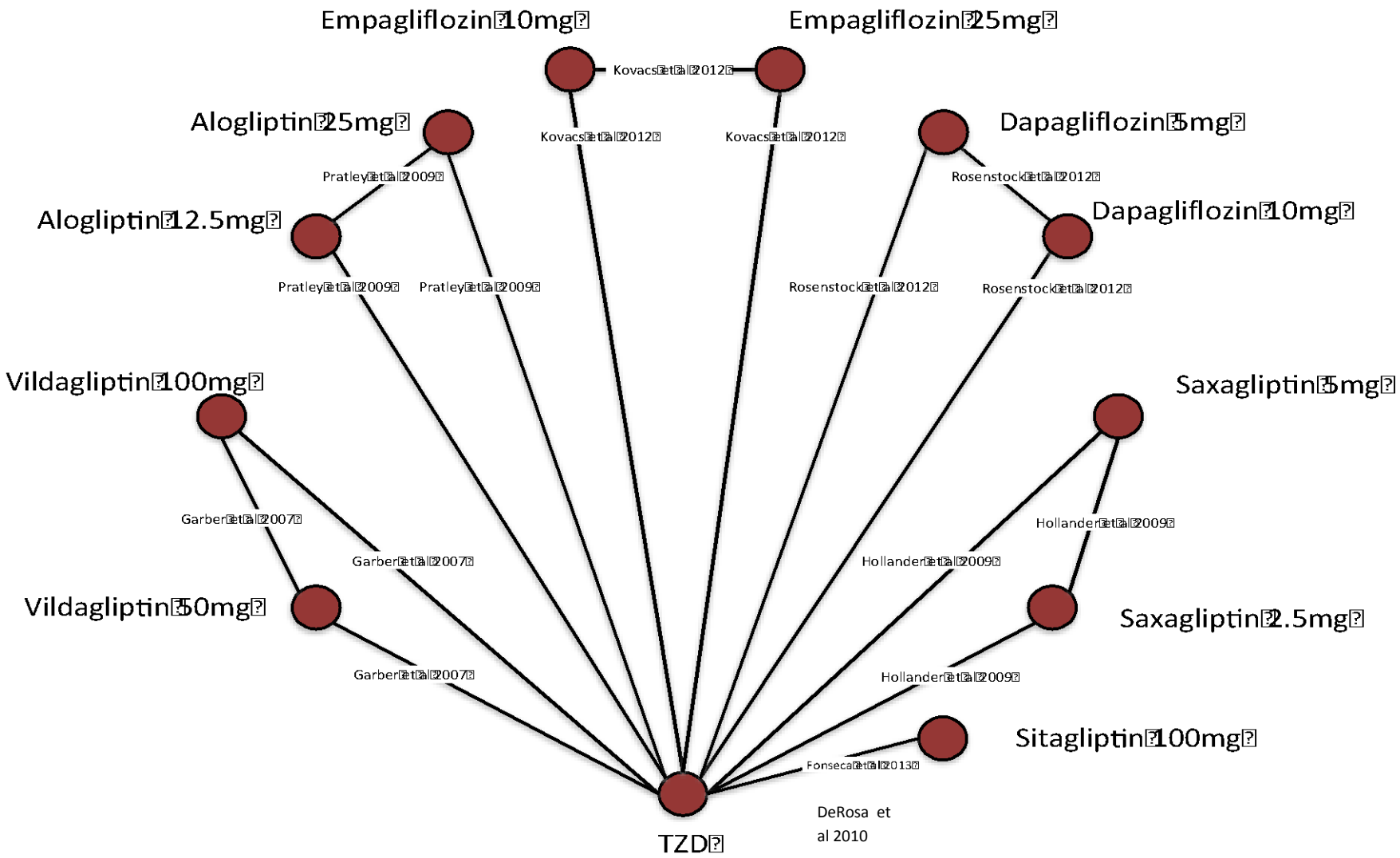

Empagliflozin 10mg
Empagliflozin 25mg
Kovacs et al 2012
Kovacs et al 2012
Kovacs et al 2012
Alogliptin 25mg
Dapagliflozin 5mg
Pratley et al 2009
Rosenstock et al 2012
Alogliptin 12.5mg
Dapagliflozin 10mg
Pratley et al 2009
Pratley et al 2009
Rosenstock et al 2012
Rosenstock et al 2012
Vildagliptin 100mg
Saxagliptin 5mg
Garber et al 2007
Hollander et al 2009
Garber et al 2007
Hollander et al 2009
Vildagliptin 50mg
Saxagliptin 2.5mg
Garber et al 2007
Hollander et al 2009
Sitagliptin 100mg
Fonseca et al 2013
TZD
DeRosa et al 2010

Table 21: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing TZD monotherapy (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-0.55 (-0.93 to -0.16)**	--	--	--	--
Empagliflozin 25mg	**-0.67 (-1.05 to -0.28)**	-0.12 (-0.51 to 0.27)	--	--	--
Dapagliflozin 5mg	**-0.40 (-0.62 to -0.18)**	0.15 (-0.30 to 0.60)	0.27 (-0.18 to 0.72)	--	--
Dapagliflozin 10mg	**-0.55 (-0.77 to -0.33)**	0.00 (-0.45 to 0.44)	0.12 (-0.33 to 0.57)	-0.15 (-0.37 to 0.07)	--
Alogliptin 12.5mg	**-0.47 (-0.77 to -0.17)**	0.08 (-0.41 to 0.57)	0.20 (-0.29 to 0.69)	-0.07 (-0.44 to 0.30)	0.08 (-0.28 to 0.45)
Alogliptin 25mg	**-0.61 (-0.90 to -0.32)**	-0.06 (-0.55 to 0.43)	0.06 (-0.43 to 0.55)	-0.21 (-0.58 to 0.16)	-0.06 (-0.43 to 0.31)
Saxagliptin 5mg	**-0.64 (-0.84 to -0.45)**	-0.09 (-0.53 to 0.34)	0.03 (-0.40 to 0.46)	-0.24 (-0.54 to 0.06)	-0.09 (-0.39 to 0.21)
Sitagliptin 100mg	-0.21 (-0.57 to 0.16)	0.35 (-0.01 to 0.71)	**0.47 (0.10 to 0.83)**	0.20 (-0.21 to 0.63)	0.35 (-0.06 to 0.78)
Vildagliptin 50mg	**-0.50 (-0.78 to -0.22)**	0.05 (-0.43 to 0.52)	0.17 (-0.31 to 0.64)	-0.10 (-0.45 to 0.25)	0.05 (-0.30 to 0.41)
Vildagliptin 100mg	**-0.70 (-0.98 to -0.42)**	-0.15 (-0.63 to 0.32)	-0.03 (-0.50 to 0.44)	-0.30 (-0.65 to 0.05)	-0.15 (-0.50 to 0.20)
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-1.35 (-2.56 to -0.14)**	--	--	--	--
Empagliflozin 25mg	**-1.35 (-2.56 to -0.14)**	0.01 (-1.20 to 1.22)	--	--	--
Dapagliflozin 5mg	**-1.54**	-0.19	-0.20	--	--

	(-2.32 to -0.78)	(-1.63 to 1.24)	(-1.62 to 1.22)		
Dapagliflozin 10mg	**-1.78 (-2.56 to -1.00)**	-0.43 (-1.86 to 1.01)	-0.44 (-1.85 to 0.98)	-0.23 (-1.02 to 0.54)	--
Saxagliptin 5mg	0.50 (-0.20 to 1.19)	**1.85 (0.46 to 3.24)**	**1.84 (0.46 to 3.20)**	**2.04 (1.01 to 3.08)**	**2.27 (1.24 to 3.32)**
Sitagliptin 100mg	0.52 (-0.97 to 2.02)	**1.87 (0.38 to 3.39)**	**1.86 (0.37 to 3.35)**	**2.06 (0.39 to 3.75)**	**2.30 (0.62 to 3.98)**
Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	-2.64 (-7.43 to 2.29)	--	--	--	--
Empagliflozin 25mg	**-6.91 (-11.66 to -2.08)**	-4.32 (-9.08 to 0.55)	--	--	--
Dapagliflozin 5mg	-2.09 (-5.33 to 1.30)	0.56 (-5.49 to 6.38)	4.85 (-1.08 to 10.65)	--	--
Dapagliflozin 10mg	**-4.70 (-8.01 to -1.39)**	-2.06 (-8.10 to 3.80)	2.24 (-3.71 to 8.05)	-2.60 (-5.96 to 0.68)	--
Hypoglycaemia, RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.90 (0.00 to 44.93)	--	--	--	--
Empagliflozin 25mg	1.87 (0.01 to 43.89)	N/A	--	--	--
Dapagliflozin 5mg	2.62 (0.40 to 22.69)	N/A	N/A	--	--
Dapagliflozin 10mg	0.20 (0.00 to 4.87)	N/A	N/A	0.08 (0.00 to 1.14)	--
Alogliptin 12.5mg	1.01 (0.35 to 3.37)	N/A	N/A	0.39 (0.04 to 3.63)	N/A
Alogliptin 25mg	1.45 (0.54 to 4.58)	N/A	N/A	0.56 (0.05 to 5.02)	N/A
Saxagliptin 5mg	1.00 (0.00 to 110.70	N/A	N/A	0.37 (0.00 to 81.79)	N/A

Sitagliptin 100mg	0.91 (0.00 to 109.70)	N/A	N/A	0.34 (0.00 to 80.10)	N/A
Vildagliptin 50mg	0.08 (0.00 to 1.25)	0.04 (0.00 to 27.54)	0.04 (0.00 to 29.15)	**0.03 (0.00 to 0.92)**	N/A
Vildagliptin 100mg	0.37 (0.03 to 2.56)	N/A	N/A	0.13 (0.01 to 2.04)	N/A
Hypoglycaemia (non-severe), RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	0.04 (0.00 to 19.36)	--	--	--	--
Empagliflozin 25mg	0.05 (0.00 to 18.17)	N/A	--	--	--
Dapagliflozin 5mg	4.16 (0.46 to 44.69)	N/A	N/A	--	--
Dapagliflozin 10mg	0.02 (0.00 to 2.73)	N/A	N/A	**0.00 (0.00 to 0.51)**	--
Alogliptin 12.5mg	0.02 (0.00 to 4.93)	N/A	N/A	**0.01 (0.00 to 1.96)**	N/A
Alogliptin 25mg	2.20 (0.05 to 25.62)	N/A	N/A	0.47 (0.01 to 15.46)	N/A
Saxagliptin 5mg	0.03 (0.00 to 5.57)	N/A	N/A	0.01 (0.00 to 2.23)	N/A
Sitagliptin 100mg	1.07 (0.00 to 330.90)	N/A	N/A	0.24 (0.00 to 176.60)	N/A
Vildagliptin 50mg	**0.01 (0.00 to 0.64)**	N/A	N/A	**0.00 (0.00 to 0.28)**	N/A
Vildagliptin 100mg	0.27 (0.01 to 2.55)	N/A	N/A	0.06 (0.00 to 1.54)	N/A
UTIs, RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	6.57 (0.88 to 66.34)	--	--	--	--
Empagliflozin	**9.00**	1.34	--	--	--

25mg	**(1.37 to 75.85)**	(0.50 to 4.24)			
Dapagliflozin 5mg	1.08 (0.00 to 74.80)	0.16 (0.00 to 17.95)	0.11 (0.00 to 12.05)	--	--
Dapagliflozin 10mg	1.00 (0.00 to 75.03)	0.15 (0.00 to 18.06)	0.10 (0.00 to 11.73)	N/A	--
Alogliptin 12.5mg	0.99 (0.00 to 75.98)	0.14 (0.00 to 18.12)	0.10 (0.00 to 12.26)	N/A	N/A
Alogliptin 25mg	1.01 (0.00 to 74.07)	0.14 (0.00 to 17.84)	0.10 (0.00 to 11.59)	N/A	N/A
Saxagliptin 5mg	0.99 (0.42 to 2.23)	0.15 (0.01 to 1.31)	**0.11** **(0.01 to 0.84)**	N/A	N/A
Sitagliptin 100mg	1.05 (0.00 to 73.86)	0.15 (0.00 to 17.96)	0.11 (0.00 to 11.85)	N/A	N/A
Vildagliptin 50mg	1.75 (0.27 to 12.79)	0.26 (0.02 to 4.02)	0.19 (0.01 to 2.65)	N/A	N/A
Vildagliptin 100mg	**4.49** **(1.11 to 24.97)**	0.69 (0.05 to 8.30)	0.50 (0.04 to 5.29)	N/A	N/A

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).

Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row

Triple therapy (Met+TZD)

Study and patient characteristics of included trials (24 weeks)

TZD failure						
	Interventions/Comparators	**Age (years)**	**Male (%)**	**Mean Baseline HbA_{1C} (%)**	**Mean Body Weight (kg)**	**Total Sample Size**
Kovacs et al. 2012 (7)	Placebo + Met + TZD	54.6	44.2	8.2	79.5	499
	Empagliflozin 10 mg + Met + TZD	54.7	50.3	8.1	79.4	
	Empagliflozin 25 mg + Met + TZD	54.2	50.6	8.1	81	
Janssen (DIA3012) 2013 (63)	Placebo + Met + TZD	57.4	63.2	7.9	94.1	344
	Canagliflozin 300 mg + Met	56.7	51	8.1	92.6	
	Placebo + Met + SU	56.7	51	8.1	92.6	
Fonseca et al 2013 **	Placebo + Met + TZD	56.4	62.8	8.7	83.8	296
	Sitagliptin 100 mg + Met+ TZD	55.7	61.8	8.8	82.1	
Bosi et al 2011 (76)	Placebo + MET + TZD	55.9	51.1	8.1	88	803
	Alogliptin 25 mg + MET + TZD	54.3	52	8.2	88.2	

** Fonseca V, Staels B, Morgan JD 2nd, Shentu Y, Golm GT, Johnson-Levonas AO, Kaufman KD, Goldstein BJ, Steinberg H. Efficacy and safety of sitagliptin added to ongoing metformin and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes. *Journal of Diabetes Complications* 2013;27(2):177-83.

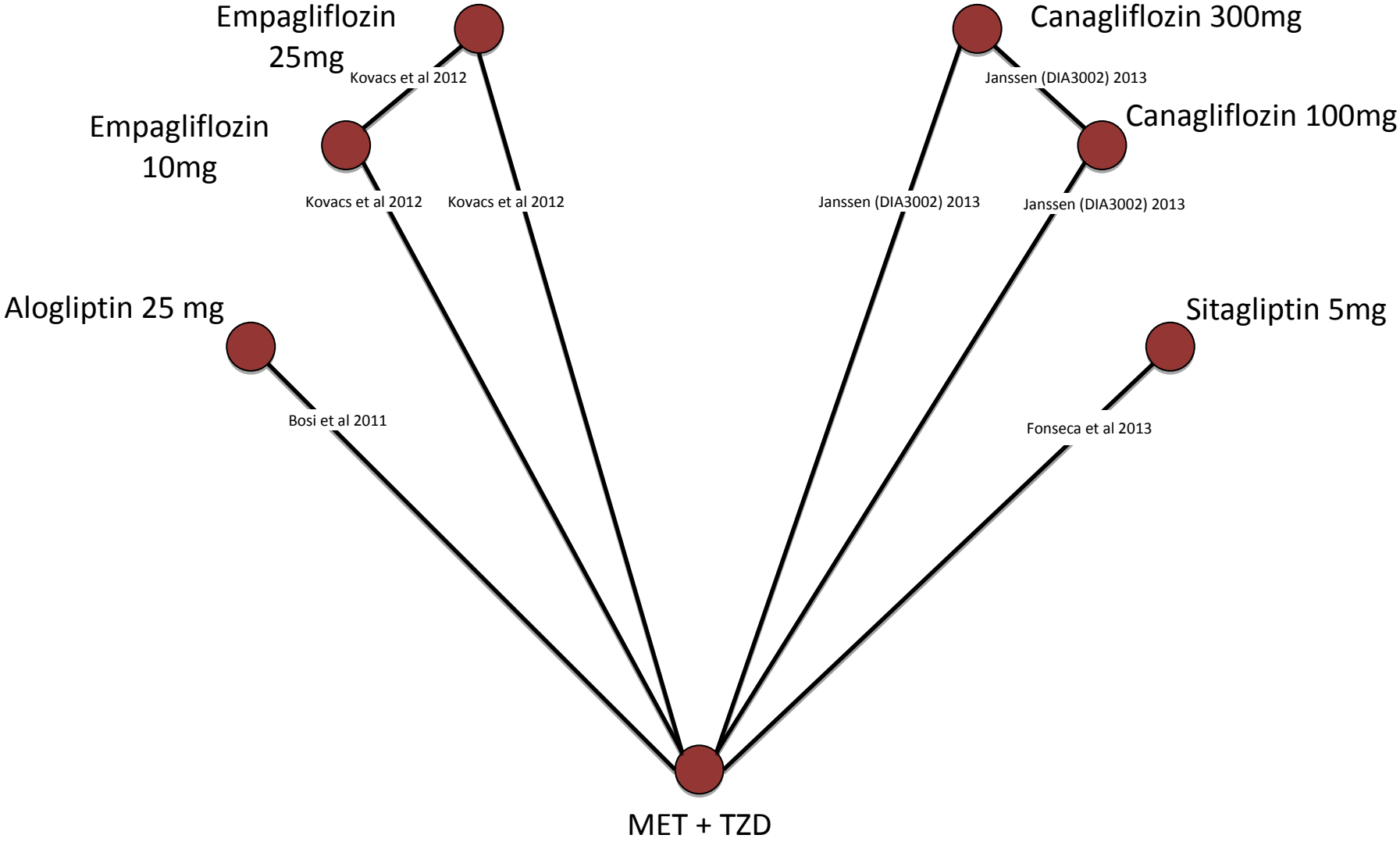

Empagliflozin 25mg
Kovacs et al 2012
Empagliflozin 10mg
Kovacs et al 2012
Kovacs et al 2012
Canagliflozin 300mg
Janssen (DIA3002) 2013
Canagliflozin 100mg
Janssen (DIA3002) 2013
Janssen (DIA3002) 2013
Alogliptin 25 mg
Bosi et al 2011
Sitagliptin 5mg
Fonseca et al 2013
MET + TZD

Table 22: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing TZD plus metformin therapy (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-0.44 (-0.66 to -0.22)**	--	--	--	--
Empagliflozin 25mg	**-0.59 (-0.80 to -0.38)**	-0.15 (-0.36 to 0.06)	--	--	--
Canagliflozin 100mg	**-0.63 (-0.82 to -0.44)**	-0.19 (-0.49 to 0.10)	-0.04 (-0.32 to 0.24)	--	--
Canagliflozin 300mg	**-0.77 (-0.93 to -0.61)**	**-0.33 (-0.61 to -0.06)**	-0.18 (-0.44 to 0.08)	-0.14 (-0.30 to 0.02)	--
Alogliptin 25mg	**-0.47 (-0.58 to -0.36)**	-0.03 (-0.28 to 0.21)	0.12 (-0.12 to 0.35)	0.16 (-0.06 to 0.39)	**0.30 (0.11 to 0.49)**
Sitagliptin 100mg	**-0.7 (-0.84 to -0.56)**	-0.26 (-0.52 to 0.00)	-0.11 (-0.36 to 0.14)	-0.07 (-0.31 to 0.17)	0.07 (-0.14 to 0.28)
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-2.14 (-2.82 to -1.45)**	--	--	--	--
Empagliflozin 25mg	**-1.98 (-2.68 to -1.28)**	0.15 (-0.54 to 0.86)	--	--	--
Canagliflozin 100mg	**-2.55 (-3.36 to -1.74)**	-0.41 (-1.48 to 0.64)	-0.57 (-1.64 to 0.49)	--	--
Canagliflozin 300mg	**-3.49 (-4.29 to -2.69)**	**-1.35 (-2.41 to -0.30)**	**-1.51 (-2.56 to -0.45)**	**-0.94 (-1.74 to -0.13)**	--
Alogliptin 25mg	**-0.79 (-1.25 to -0.33)**	**1.34 (0.52 to 2.17)**	**1.19 (0.34 to 2.02)**	**1.76 (0.82 to 2.69)**	**2.70 (1.76 to 3.61)**
Sitagliptin 100mg	0.20 (-0.40 to 0.80)	**2.33 (1.42 to 3.24)**	**2.18 (1.26 to 3.09)**	**2.75 (1.76 to 3.75)**	**3.69 (2.69 to 4.69)**

Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-4.24 (-6.91 to -1.54)**	--	--	--	--
Empagliflozin 25mg	**-4.06 (-6.72 to -1.36)**	0.18 (-2.54 to 2.82)	--	--	--
Canagliflozin 100mg	**-4.11 (-6.98 to -1.22)**	0.10 (-3.87 to 4.13)	-0.05 (-4.02 to 3.93)	--	--
Canagliflozin 300mg	**-3.54 (-6.46 to -0.54)**	0.69 (-3.29 to 4.68)	0.50 (-3.48 to 4.53)	0.59 (-2.39 to 3.55)	--
Hypoglycaemia, RR (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	0.63 (0.11 to 2.63)	--	--	--	--
Empagliflozin 25mg	1.51 (0.54 to 5.29)	2.4 (0.74 to 13.10)	--	--	--
Canagliflozin 100mg	0.1 (0.00 to 36.55)	0.17 (0.00 to 67.43)	0.07 (0.00 to 20.36)	--	--
Canagliflozin 300mg	0.11 (0.00 to 35.60)	0.19 (0.00 to 69.34)	0.07 (0.00 to 19.62)	N/A	--
Alogliptin 25mg	**2.29 (1.21 to 5.53)**	3.67 (0.87 to 24.54)	1.51 (0.44 to 5.26)	N/A	N/A
Sitagliptin 100mg	1.34 (0.58 to 3.11)	2.13 (0.42 to 14.08)	0.90 (0.20 to 3.11)	N/A	N/A
Hypoglycaemia (non-severe), RR (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	0.47 (0.06 to 2.43)	--	--	--	--
Empagliflozin 25mg	1.5 (0.44 to 5.85)	3.18 (0.75 to 23.82)	--	--	--
Canagliflozin	0.08	N/A	0.05	--	--

100mg	(0.00 to 73.06)		(0.00 to 44.10)		
Canagliflozin 300mg	0.08 (0.00 to 69.75)	N/A	0.05 (0.00 to 44.64)	N/A	--
Alogliptin 25mg	**2.46** **(1.10 to 6.26)**	5.32 (0.88 to 48.38)	1.65 (0.36 to 7.12)	N/A	N/A

Hypoglycaemia (severe), RR (95% credible interval)

intervention/ comparator	**Control (TZD+MET)**
Empagliflozin 10mg	0.96 (0.00 to 197.10)
Empagliflozin 25mg	1.08 (0.00 to 197.1)
Canagliflozin 100mg	1.00 (0.00 to 193.90)
Canagliflozin 300mg	1.03 (0.00 to 194.00)
Sitagliptin 100mg	1.18 (0.38 to 3.85)
Alogliptin 25mg	4.11 (0.35 to 22.26)

UTIs, RR (95% credible interval)

intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	1.10 (0.62 to 2.00)	--	--	--	--
Empagliflozin 25mg	0.65 (0.31 to 1.25)	0.60 (0.28 to 1.11)	--	--	--
Canagliflozin 100mg	0.11 (0.00 to 13.06)	0.10 (0.00 to 11.31)	0.18 (0.00 to 21.79)	--	--
Canagliflozin 300mg	0.12 (0.00 to 13.36)	0.11 (0.00 to 11.66)	0.19 (0.00 to 23.29)	N/A	--
Alogliptin 25mg	1.46 (0.89 to 2.63)	1.33 (0.64 to 2.93)	**2.27** **(1.02 to 5.85)**	N/A	N/A

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).

Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Insulin combinations

Study and patient characteristics of included trials (24 weeks)

Insulin failure

	Interventions/Comparators	Age (years)	Male (%)	Mean Baseline HbA_{1C} (%)	Mean Body Weight (kg)	Total Sample Size
BI GMBH (1245-49) 2013 (40)	Placebo + INS	55.3	39.9	8.33	95.5	563
	Empagliflozin 10 mg + INS	56.7	52.2	8.39	96.7	
	Empagliflozin 25 mg + INS	58	44.2	8.29	95.9	
BI GMBH (1245-33) 2013 (12)	Placebo + INS	58.1	52.9	8.18	90.46	494
	Empagliflozin 10 mg + INS	58.6	55	8.27	91.59	
	Empagliflozin 25 mg + INS	59.9	60	8.27	94.71	
Janssen (DIA3008) 2013 (63)	Placebo + INS	62.4	66.5	8.3	NR	1718
	Canagliflozin 100 mg + INS	62.4	66.5	8.3	NR	
	Canagliflozin 300 mg + INS	62.4	66.5	8.3	NR	
Wilding et al 2012 (77)	Placebo + INS	58.8	49.2	8.47	94.5	807
	Dapagliflozin 2.5 mg + INS	59.8	49.5	8.46	93	
	Dapagliflozin 5 mg + INS	59.3	47.4	8.62	93.3	
	Dapagliflozin 10 mg + INS	59.3	44.8	8.57	94.5	
Rosenstock et al 2009 (78)	Placebo + INS	55.0	48	9.3	91	390
	Alogliptin 12.5 mg + INS	55.4	42	9.3	87.9	
	Alogliptin 25 mg + INS	55.9	34	9.3	86.7	
Barnett et al 2012 (79)	Placebo + INS	57.3	45	8.6	86.2	455
	Saxagliptin + INS	57.2	40	8.7	87.7	
Vilsboll et al 2010 (80)	INS + Met	57.2	53	8.6	87.3	641
	Sitagliptin + INS	58.3	49	8.7	86.5	
Fonseca et al 2007 (81)	Placebo + INS	58.9	54.6	8.4	95.1	296
	Vildagliptin + INS	59.6	47.9	8.4	94.5	

INS = insulin therapy; Met = metformin; SU = sulphonylurea; TZD = thiazolidinediones

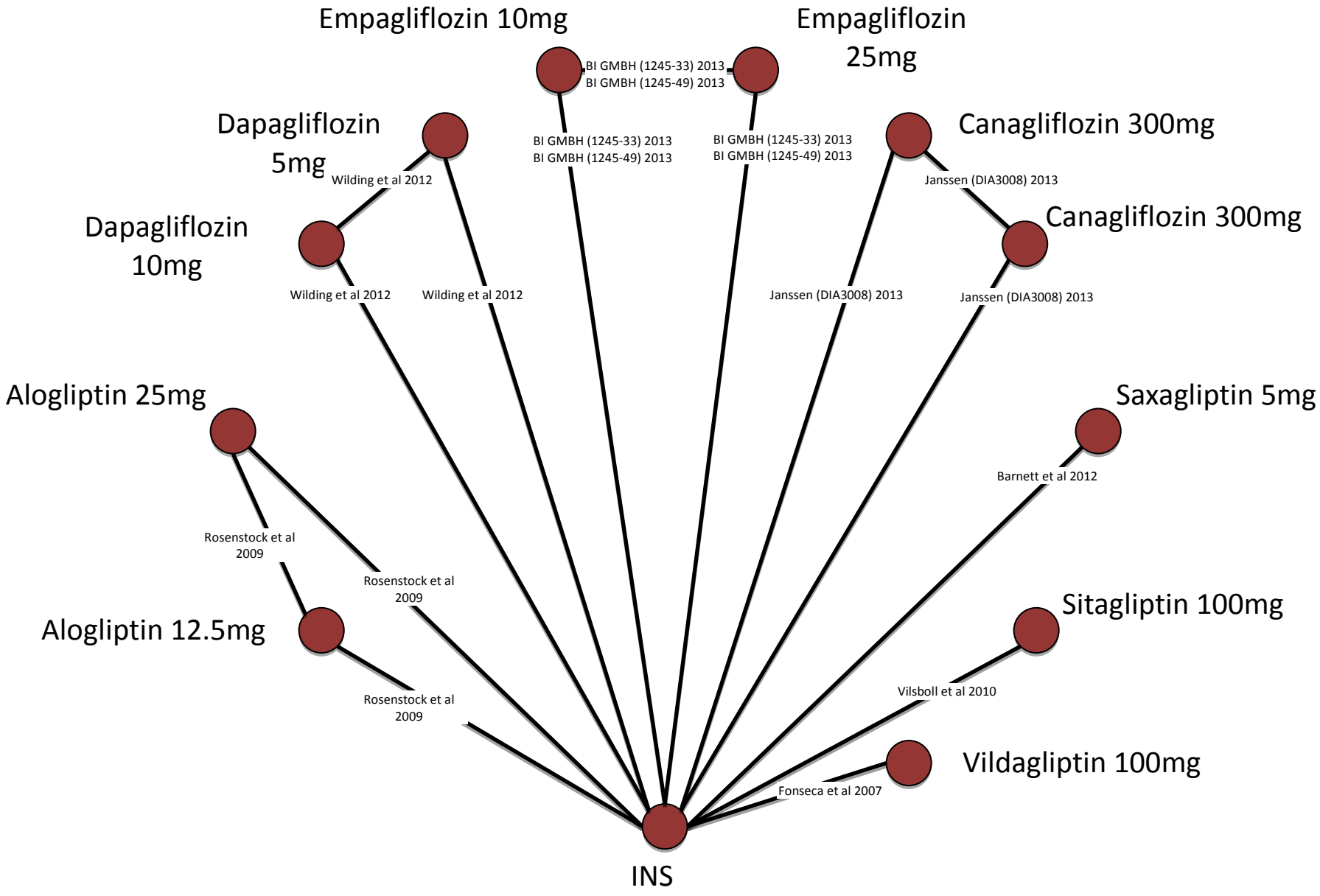

Empagliflozin 10mg
Empagliflozin 25mg
BI GMBH (1245-33) 2013
BI GMBH (1245-49) 2013
Dapagliflozin 5mg
Canagliflozin 300mg
Wilding et al 2012
Janssen (DIA3008) 2013
Dapagliflozin 10mg
Canagliflozin 300mg
Wilding et al 2012
Wilding et al 2012
Janssen (DIA3008) 2013
Janssen (DIA3008) 2013
Alogliptin 25mg
Saxagliptin 5mg
Barnett et al 2012
Rosenstock et al 2009
Rosenstock et al 2009
Alogliptin 12.5mg
Sitagliptin 100mg
Vilsboll et al 2010
Rosenstock et al 2009
Vildagliptin 100mg
Fonseca et al 2007
INS

Table 23: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4 inhibitors for treatment of T2DM patients who are failing insulin therapy plus other OADs (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-0.50 (-0.61 to -0.39)**	--	--	--	--	--	--
Empagliflozin 25mg	**-0.57 (-0.69 to -0.46)**	-0.07 (-0.19 to 0.04)	--	--	--	--	--
Canagliflozin 100mg	**-0.64 (-0.8 to -0.47)**	-0.14 (-0.34 to 0.06)	-0.07 (-0.27 to 0.14)	--	--	--	--
Canagliflozin 300mg	**-0.73 (-0.90 to -0.56)**	**-0.23 (-0.43 to -0.03)**	-0.16 (-0.36 to 0.05)	-0.09 (-0.26 to 0.08)	--	--	--
Dapagliflozin 5mg	**-0.50 (-0.66 to -0.35)**	0.00 (-0.19 to 0.19)	0.07 (-0.12 to 0.27)	0.14 (-0.09 to 0.36)	**0.23 (0.00 to 0.45)**	--	--
Dapagliflozin 10mg	**-0.57 (-0.73 to -0.42)**	-0.07 (-0.26 to 0.12)	0.00 (-0.19 to 0.19)	0.07 (-0.16 to 0.30)	0.16 (-0.07 to 0.38)	-0.07 (-0.21 to 0.07)	--
Alogliptin 12.5mg	-0.5 (-1.06 to 0.06)	0.00 (-0.57 to 0.56)	0.07 (-0.49 to 0.64)	0.14 (-0.45 to 0.72)	0.23 (-0.35 to 0.80)	0.00 (-0.58 to 0.57)	0.07 (-0.50 to 0.65)
Alogliptin 25mg	**-0.59 (-1.14 to -0.03)**	-0.09 (-0.65 to 0.48)	-0.01 (-0.58 to 0.56)	0.05 (-0.53 to 0.64)	0.15 (-0.44 to 0.73)	-0.08 (-0.66 to 0.49)	-0.01 (-0.59 to 0.57)
Saxagliptin 5mg	**-0.41 (-0.58 to -0.24)**	0.09 (-0.11 to 0.29)	0.17 (-0.03 to 0.37)	0.23 (-0.01 to 0.47)	**0.32 (0.08 to 0.56)**	0.10 (-0.14 to 0.32)	0.17 (-0.06 to 0.39)
Sitagliptin 100mg	**-0.60 (-0.80 to -0.41)**	-0.10 (-0.32 to 0.12)	-0.03 (-0.25 to 0.20)	0.04 (-0.22 to 0.29)	0.13 (-0.13 to 0.39)	-0.10 (-0.35 to 0.15)	-0.03 (-0.28 to 0.22)
Vildagliptin 100mg	**-0.31 (-0.58 to -0.03)**	0.20 (-0.10 to 0.50)	0.27 (-0.03 to 0.57)	**0.34 (0.01 to 0.66)**	**0.43 (0.11 to 0.75)**	0.20 (-0.12 to 0.52)	0.27 (-0.04 to 0.58)
Mean reduction in body weight, kg (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-1.36 (-1.81 to -0.91)**	--	--	--	--	--	--
Empagliflozin	**-1.78**	-0.42	--	--	--	--	--

25mg	**(-2.28 to -1.29)**	(-0.93 to 0.09)					
Canagliflozin 100mg	**-1.85 (-2.44 to -1.26)**	-0.49 (-1.22 to 0.25)	-0.06 (-0.83 to 0.71)	--	--	--	--
Canagliflozin 300mg	**-2.33 (-2.91 to -1.74)**	**-0.97 (-1.70 to -0.24)**	-0.55 (-1.31 to 0.23)	-0.48 (-1.02 to 0.04)	--	--	--
Dapagliflozin 5mg	**-1.43 (-1.97 to -0.89)**	-0.07 (-0.77 to 0.64)	0.35 (-0.38 to 1.08)	0.42 (-0.38 to 1.21)	**0.90 (0.10 to 1.69)**	--	--
Dapagliflozin 10mg	**-2.04 (-2.58 to -1.50)**	-0.67 (-1.39 to 0.02)	-0.26 (-1.00 to 0.47)	-0.19 (-0.99 to 0.60)	0.29 (-0.51 to 1.07)	**-0.61 (-1.15 to -0.07)**	--
Alogliptin 12.5mg	0.09 (-0.47 to 0.65)	**1.45 (0.74 to 2.18)**	**1.88 (1.12 to 2.63)**	**1.94 (1.14 to 2.77)**	**2.43 (1.62 to 3.23)**	**1.52 (0.74 to 2.30)**	**2.13 (1.36 to 2.91)**
Alogliptin 25mg	0.00 (-0.55 to 0.56)	**1.36 (0.65 to 2.07)**	**1.78 (1.05 to 2.53)**	**1.85 (1.05 to 2.66)**	**2.33 (1.53 to 3.13)**	**1.43 (0.66 to 2.20)**	**2.04 (1.28 to 2.81)**
Saxagliptin 5mg	0.21 (-0.29 to 0.71)	**1.57 (0.9 to 2.23)**	**1.99 (1.29 to 2.70)**	**2.06 (1.28 to 2.82)**	**2.54 (1.76 to 3.30)**	**1.63 (0.91 to 2.38)**	**2.25 (1.52 to 2.99)**
Vildagliptin 100mg	0.71 (-0.12 to 1.54)	**2.07 (1.13 to 3.01)**	**2.49 (1.53 to 3.47)**	**2.56 (1.53 to 3.58)**	**3.04 (2.02 to 4.06)**	**2.14 (1.14 to 3.15)**	**2.75 (1.75 to 3.75)**

Mean reduction in SBP, mmHg (95% credible interval)

intervention/ comparator	Placebo (INS+OAD)	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Empagliflozin 10mg	**-2.85 (-4.51 to -1.18)**	--	--	--	--	--	--
Empagliflozin 25mg	**-2.24 (-3.94 to -0.59)**	0.59 (-1.12 to 2.31)	--	--	--	--	--
Canagliflozin 100mg	-2.61 (-5.60 to 0.34)	0.26 (-3.16 to 3.64)	-0.36 (-3.81 to 3.08)	--	--	--	--
Canagliflozin 300mg	**-4.39 (-7.43 to -1.38)**	-1.55 (-5.01 to 1.94)	-2.14 (-5.60 to 1.34)	-1.78 (-4.74 to 1.13)	--	--	--
Dapagliflozin 5mg	-2.38 (-4.98 to 0.24)	0.45 (-2.60 to 3.57)	-0.13 (-3.23 to 3.02)	0.23 (-3.65 to 4.19)	2.01 (-1.92 to 5.98)	--	--
Dapagliflozin 10mg	**-3.12 (-5.76 to -0.42)**	-0.27 (-3.38 to 2.87)	-0.88 (-3.98 to 2.33)	-0.51 (-4.43 to 3.42)	1.27 (-2.76 to 5.28)	-0.74 (-3.32 to 1.84)	--

Hypoglycaemia, RR (95% credible interval)

intervention/ comparator	Placebo (INS+OAD)	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Empagliflozin 10mg	1.09 (0.82 to 1.41)	--	--	--	--	--	--
Empagliflozin 25mg	1.24 (0.95 to 1.59)	1.14 (0.89 to 1.48)	--	--	--	--	--
Canagliflozin 100mg	**1.45 (1.23 to 1.69)**	1.34 (0.99 to 1.82)	1.17 (0.88 to 1.58)	--	--	--	--
Canagliflozin 300mg	**1.42 (1.20 to 1.66)**	1.31 (0.97 to 1.78)	1.15 (0.86 to 1.55)	0.98 (0.84 to 1.15)	--	--	--
Dapagliflozin 5mg	1.12 (0.83 to 1.48)	1.03 (0.70 to 1.53)	0.91 (0.61 to 1.33)	0.77 (0.55 to 1.07)	0.79 (0.56 to 1.09)	--	--
Dapagliflozin 10mg	1.05 (0.77 to 1.40)	0.97 (0.65 to 1.45)	0.85 (0.57 to 1.26)	0.73 (0.52 to 1.01)	0.74 (0.53 to 1.03)	0.94 (0.70 to 1.26)	--
Alogliptin 12.5mg	1.12 (0.72 to 1.64)	1.03 (0.62 to 1.65)	0.90 (0.55 to 1.43)	0.77 (0.48 to 1.17)	0.79 (0.49 to 1.20)	1.00 (0.59 to 1.63)	1.06 (0.63 to 1.73)
Alogliptin 25mg	1.13 (0.73 to 1.67)	1.04 (0.63 to 1.68)	0.91 (0.56 to 1.47)	0.78 (0.49 to 1.19)	0.80 (0.50 to 1.22)	1.01 (0.60 to 1.68)	1.08 (0.64 to 1.78)
Saxagliptin 5mg	1.45 (0.70 to 2.79)	1.33 (0.62 to 2.69)	1.17 (0.54 to 2.32)	1.00 (0.48 to 1.95)	1.02 (0.49 to 2.00)	1.29 (0.59 to 2.62)	1.38 (0.63 to 2.81)
Sitagliptin 100mg	**2.05 (1.68 to 2.46)**	**1.89 (1.38 to 2.62)**	**1.65 (1.22 to 2.26)**	**1.41 (1.10 to 1.80)**	**1.44 (1.13 to 1.84)**	**1.82 (1.31 to 2.59)**	**1.94 (1.38 to 2.77)**
Vildagliptin 100mg	0.75 (0.48 to 1.14)	0.70 (0.41 to 1.14)	**0.61 (0.36 to 0.99)**	**0.52 (0.32 to 0.81)**	**0.53 (0.33 to 0.82)**	0.67 (0.39 to 1.12)	0.72 (0.42 to 1.20)

Hypoglycaemia (non severe), RR (95% credible interval)

intervention/ comparator	Placebo (INS+OAD)	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg
Empagliflozin 10mg	1.06 (0.84 to 1.32)	--	--	--	--	--	--
Empagliflozin 25mg	1.07 (0.85 to 1.33)	1.01 (0.80 to 1.27)	--	--	--	--	--

Canagliflozin 100mg	**1.44 (1.22 to 1.68)**	**1.36 (1.04 to 1.79)**	**1.35 (1.03 to 1.77)**	--	--	--	--
Canagliflozin 300mg	**1.40 (1.19 to 1.63)**	**1.32 (1.01 to 1.74)**	**1.31 (1.00 to 1.73)**	0.97 (0.83 to 1.13)	--	--	--
Dapagliflozin 5mg	1.10 (0.82 to 1.45)	1.04 (0.72 to 1.49)	1.03 (0.71 to 1.48)	0.77 (0.55 to 1.05)	0.79 (0.57 to 1.08)	--	--
Dapagliflozin 10mg	1.02 (0.74 to 1.35)	0.96 (0.65 to 1.39)	0.95 (0.65 to 1.37)	**0.70 (0.50 to 0.98)**	0.73 (0.52 to 1.01)	0.92 (0.69 to 1.24)	--
Alogliptin 12.5mg	1.29 (0.80 to 1.92)	1.22 (0.72 to 1.93)	1.21 (0.72 to 1.92)	0.90 (0.55 to 1.37)	0.92 (0.56 to 1.41)	1.16 (0.69 to 1.92)	1.27 (0.74 to 2.10)
Alogliptin 25mg	1.34 (0.85 to 1.99)	1.27 (0.77 to 2.00)	1.26 (0.76 to 1.99)	0.93 (0.58 to 1.42)	0.96 (0.60 to 1.47)	1.22 (0.72 to 1.99)	1.32 (0.78 to 2.17)
Saxagliptin 5mg	1.46 (0.71 to 2.79)	1.38 (0.65 to 2.75)	1.37 (0.65 to 2.73)	1.02 (0.49 to 1.94)	1.05 (0.51 to 2.01)	1.33 (0.61 to 2.67)	1.44 (0.67 to 2.93)
Sitagliptin 100mg	0.97 (0.00 to 4.50)	0.92 (0.00 to 4.55)	0.92 (0.00 to 4.51)	0.67 (0.00 to 3.25)	0.69 (0.00 to 3.34)	0.87 (0.00 to 4.55)	0.96 (0.00 to 4.99)
Vildagliptin 100mg	0.99 (0.00 to 4.51)	0.93 (0.00 to 4.53)	0.93 (0.00 to 4.50)	0.69 (0.00 to 3.25)	0.71 (0.00 to 3.32)	0.90 (0.00 to 4.55)	0.97 (0.00 to 5.00)
Hypoglycaemia (severe), RR (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	0.92 (0.07 to 8.16)	--	--	--	--	--	--
Empagliflozin 25mg	2.56 (0.41 to 16.46)	2.73 (0.41 to 33.79)	--	--	--	--	--
Canagliflozin 100mg	0.70 (0.30 to 1.59)	0.77 (0.07 to 12.07)	0.27 (0.04 to 2.04)	--	--	--	--
Canagliflozin 300mg	1.11 (0.54 to 2.30)	1.21 (0.12 to 18.93)	0.43 (0.06 to 3.07)	1.57 (0.72 to 3.64)	--	--	--
Dapagliflozin 5mg	0.91 (0.10 to 8.35)	1.00 (0.04 to 29.76)	0.35 (0.02 to 6.08)	1.30 (0.12 to 13.51)	0.82 (0.08 to 8.30)	--	--
Dapagliflozin 10mg	1.56 (0.24 to 13.03)	1.77 (0.10 to 47.44)	0.62 (0.04 to 9.32)	2.25 (0.29 to 20.75)	1.43 (0.19 to 12.86)	1.72 (0.27 to 14.86)	--

Alogliptin 12.5mg	0.11 (0.00 to 2.00)	0.12 (0.00 to 6.20)	0.04 (0.00 to 1.46)	0.16 (0.00 to 3.26)	0.10 (0.00 to 1.99)	0.11 (0.00 to 4.99)	0.07 (0.00 to 2.32)
Alogliptin 25mg	0.55 (0.04 to 4.55)	0.59 (0.02 to 17.69)	0.21 (0.01 to 3.59)	0.78 (0.05 to 7.60)	0.49 (0.03 to 4.67)	0.58 (0.02 to 13.27)	0.33 (0.01 to 5.90)
Saxagliptin 5mg	0.78 (0.12 to 6.31)	0.87 (0.05 to 24.25)	0.30 (0.02 to 4.86)	1.11 (0.14 to 10.85)	0.70 (0.09 to 6.49)	0.88 (0.05 to 17.95)	0.50 (0.03 to 8.11)
Vildagliptin 100mg	0.06 (0.00 to 0.85)	0.06 (0.00 to 2.96)	**0.02** **(0.00 to 0.61)**	0.09 (0.00 to 1.40)	**0.06** **(0.00 to 0.84)**	0.06 (0.00 to 2.20)	0.04 (0.00 to 1.04)

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).

Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Appendix 3: Corrected tables

Table 24: Characteristics of participants in the RCTs across randomised groups (FAS) (Page 68)

Baseline characteristic	Treatment group			
1245.19 (EMPA-REG PIO) (N=498)	**Placebo (n =165)**	**Empagliflozin 10mg (n=165)**	**Empagliflozin 25mg (n=168)**	
Demographic data				
Age, mean (SD) [years]	54.6 (10.5)	54.7 (9.9)	54.2 (8.9)	
Gender, N (%)				
Male	73 (44.2)	83 (50.3)	85 (50.6)	
Female	92 (55.8)	82 (49.7)	83 (49.4)	
Race, N (%)				
American Indian/Alaska native	1 (0.6)	1 (0.6)	0	
Asian	103 (62.4)	91 (55.2)	94 (56.0)	
Black/African American	1 (0.6)	4 (2.4)	6 (3.6)	
White	60 (36.4)	69 (41.8)	68 (40.5)	
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	85.49 (20.07)	84.26 (20.91)	87.43 (24.36)	
Baseline efficacy variables				
HbA_{1C} [%], mean (SD)	8.16 (0.92)	8.07 (0.89)	8.06 (0.82)	
Time since diagnosis of T2DM, N (%)				
≤1 year	19 (11.5)	29 (17.6)	17 (10.1)	
>1 to 5 years	78 (47.3)	60 (36.4)	76 (45.2)	
>5 to 10 years	42 (25.5)	45 (27.3)	28 (28.6)	
>10 years	26 (15.8)	31 (18.8)	27 (16.1)	
Weight, mean (SD) [kg]	78.1 (20.1)	78.0 (19.1)	78.9 (19.9)	
BMI, mean (SD), [kg/m^2]	29.32 (5.39)	29.15 (5.59)	29.08 (5.54)	
SBP, mean (SD) [mmHg]	125.7 (12.1)	126.5 (13.7)	125.9 (13.9)	
FPG, mean (SD) [mg/dL]	151.9 (40.4)	152.0 (38.2)	151.9 (37.0)	
1245.23 (EMPA-REG MET, EMPA-REG METSU) metformin only (N=706)	**Placebo (n=207)**	**Empagliflozin 10mg (n=217)**	**Empagliflozin 25mg (n=213)**	**Open-label empagliflozin 25mg (n=69)**
Demographic data				
Age, mean (SD) [years]	56.0 (9.7)	55.5 (9.9)	55.6 (10.2)	49.8 (11.5)
Gender, N (%)				
Male	116 (56.0)	125 (57.6)	120 (56.3)	41 (59.4)
Female	91 (44.0)	92 (42.4)	93 (43.7)	28 (40.6)
Race, N (%)				
American Indian/Alaska native	0	2 (0.9)	2 (0.9)	2 (2.9)

Baseline characteristic	Treatment group			
Asian	92 (44.4)	99 (45.6)	98 (46.0)	14 (20.3)
Black/African American	2 (1.0)	4 (1.8)	0	4 (5.8)
White	113 (54.6)	112 (51.6)	113 (53.1)	49 (71.0)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	89.7 (21.4)	89.5 (19.6)	87.7 (19.3)	95.5 (20.7)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	7.90 (0.88)	7.94 (0.79)	7.86 (0.87)	11.07 (1.29)
Time since diagnosis of T2DM, N (%)				
≤1year	19 (9.2)	20 (9.2)	19 (8.9)	5 (7.2)
>1 to 5years	83 (40.1)	78 (35.9)	69 (32.4)	28 (40.6)
>5 to 10 years	65 (31.4)	68 (31.3)	74 (34.7)	19 (27.5)
>10 years	40 (19.3)	51 (23.5)	51 (23.9)	17 (24.6)
Weight, mean (SD) [kg]	79.73 (18.57)	81.59 (18.51)	82.21 (19.29)	85.07 (21.96)
BMI, mean (SD), [kg/m^2]	28.70 (5.22)	29.12 (5.48)	29.72 (5.72)	30.37(5.51)
SBP, mean (SD) [mmHg]	128.6 (14.7)	129.6 (14.1)	130.0 (15.1)	126.2 (11.4)
MDG, mean (SD) [mg/dL]	169.53 (37.77)	168.03 (32.14)	167.87 (34.14)	226.32 (54.14)
1245.23 (EMPA-REG MET, EMPA-REG METSU) metformin plus SU (N=767)	**Placebo (n=225)**	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Demographic data				
Age, mean (SD) [years]	56.9 (9.2)	57.0 (9.2)	57.4 (9.3)	53.4 (10.5)
Gender, N (%)				
Male	112 (49.8)	113 (50.2)	114 (52.8)	54 (53.5)
Female	113 (50.2)	112 (49.8)	102 (47.2)	47 (46.5)
Race, N (%)				
American Indian/Alaska native	3 (1.3)	4 (1.8)	3 (1.4)	2 (2.0)
Asian	127 (56.4)	129 (57.3)	125 (57.9)	48 (47.5)
Black/African American	7 (3.1)	3 (1.3)	3 (1.4)	1 (1.0)
White	88 (39.1)	89 (39.6)	85 (39.4)	50 (49.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.9 (20.1)	86.5 (21.8)	88.3 (22.6)	93.1 (23.7)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	8.15 (0.83)	8.07 (0.81)	8.10 (0.83)	11.18 (1.25)
Time since diagnosis of T2DM, N (%)				
≤1 year	2 (0.9)	3 (1.3)	7 (3.2)	4 (4.0)
>1 to 5 years	36 (16.0)	59 (26.2)	43 (19.9)	26 (25.7)
>5 to 10 years	94 (41.8)	74 (32.9)	79 (36.6)	33 (32.7)
>10 years	93 (41.3)	89 (39.6)	87 (40.3)	38 (37.6)
Weight, mean (SD) [kg]	76.23 (16.88)	77.08 (18.34)	77.50 (18.81)	76.93 (18.00)
BMI, mean (SD), [kg/m^2]	27.90 (4.93)	28.32 (5.43)	28.32 (5.45)	28.70 (5.49)
SBP, mean (SD) [mmHg]	128.8 (14.3)	128.7 (13.9)	129.3 (14.2)	126.4 (12.4)

Baseline characteristic	Treatment group			
MDG, mean (SD) [mg/dL]	170.45 (30.38)	170.28 (29.06)	172.72 (37.79)	233.07 (63.34)
1245.28 (EMPA-REG H2H-SU) (N=1,545)		**Empagliflozin 25mg (n=765)**		**Glimepiride 1-4mg (n=780)**
Demographic data				
Age, mean (SD) [years]		56.2 (10.3)		55.7 (10.4)
Gender, N (%)				
Male		432 (56.5)		421 (54.0)
Female		333 (43.5)		359 (46.0)
Race, N (%)				
American Indian/Alaska native		0		0
Asian		254 (33.2)		253 (32.4)
Black/African American		12 (1.6)		8 (1.0)
Hawaiian/pacific Islander		1 (0.1)		0
White		498 (65.1)		519 (66.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]		87.94 (16.82)		88.11 (17.85)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]		7.92 (0.81)		7.92 (0.86)
Time since diagnosis of T2DM, N (%)				
≤1 year		79 (10.3)		93 (11.9)
>1 to 5 years		341 (44.6)		336 (43.1)
>5 to 10 years		214 (28.0)		211 (27.1)
>10 years		131 (17.1)		140 (17.9)
Weight, mean (SD) [kg]		82.52 (19.16)		83.03 (19.22)
BMI, mean (SD), [kg/m^2]		29.95 (5.28)		30.27 (5.3)
SBP, mean (SD) [mmHg]		133.4 (15.9)		133.5 (16.0)
DBP, mean (SD) [mmHg]		79.5 (9.6)		79.4 (9.2)
1245.31 (EMPA-REG EXTEND) monotherapy (1245.20 roll-over)	**Placebo (n=228)**	**Empagliflozin 10mg (n=224)**	**Empagliflozin 25mg (n=224)**	**Sitagliptin 100mg (n=223)**
Demographic data				
Age, mean (SD) [years]	54.9 (10.9)	56.2 (11.6)	53.8 (11.6)	55.1 (9.9)
Gender, N (%)				
Male	123 (53.9)	142 (63.4)	145 (64.7)	141 (63.2)
Female	105 (46.1)	82 (36.6)	79 (35.3)	82 (36.8)
Race, N (%)				
American Indian/Alaska native	0	0	0	1 (0.4)
Asian	146 (64.0)	143 (63.8)	144 (64.3)	143 (64.1)
Black/African American	6 (2.6)	3 (1.3)	7 (3.1)	3 (1.3)
Hawaiian/pacific Islander	0	1 (0.4)	0	0
White	76 (33.3)	77 (34.4)	73 (32.6)	76 (34.1)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.76 (17.94)	87.70 (19.16)	87.61 (18.28)	87.57 (17.30)
Baseline efficacy variables				

Baseline characteristic	**Treatment group**			
HbA_{1C}, mean (SD) [%]	7.91 (0.78)	7.87 (0.88)	7.86 (0.85)	7.85 (0.79)
Time since diagnosis of T2DM, N (%)				
≤1 year	72 (31.6)	87 (38.8)	91 (40.6)	93 (41.7)
>1 to 5 years	104 (45.6)	92 (41.1)	83 (37.1)	86 (38.6)
>5 to 10 years	33 (14.5)	29 (12.9)	37 (16.5)	32 (14.3)
>10 years	19 (8.3)	16 (7.1)	13 (5.8)	12 (5.4)
Weight, mean (SD) [kg]	78.23 (19.86)	78.35 (18.67)	77.80 (17.96)	79.31 (20.40)
BMI, mean (SD), [kg/m^2]	28.73 (6.15)	28.31 (5.46)	28.17 (5.52)	28.23 (5.21)
SBP, mean (SD) [mmHg]	130.4 (16.3)	133.0 (16.6)	129.9 (17.5)	132.5 (15.8)
1245.31 (EMPA-REG EXTEND) background of pioglitazone (1245.19 roll-over)	**Placebo (n=165)**	**Empagliflozin 10mg (n=165)**		**Empagliflozin 25mg (n=165)**
Demographic data				
Age, mean (SD) [years]	54.6 (10.5)	54.7 (9.9)		54.2 (8.9)
Gender, N (%)				
Male	73 (44.2)	83 (50.3)		85 (50.6)
Female	92 (55.8)	82 (49.7)		83 (49.4)
Race, N (%)				
American Indian/Alaska native	1 (0.6)	1 (0.6)		0
Asian	103 (62.4)	91 (55.2)		94 (56.0)
Black/African American	1 (0.6)	4 (2.4)		6 (3.6)
White	60 (36.4)	69 (41.8)		68 (40.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	85.49 (20.07)	84.26 (20.91)		87.43 (24.36)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	8.16 (0.92)	8.07 (0.89)		8.06 (0.82)
Time since diagnosis of T2DM, N (%)				
≤1 year	19 (11.5)	29 (17.6)		17 (10.1)
>1 to 5 years	78 (47.3)	60 (36.4)		76 (45.2)
>5 to 10 years	42 (25.5)	45 (27.3)		48 (28.6)
>10 years	26 (15.8)	31 (18.8)		27 (16.1)
Weight, mean (SD) [kg]	78.10 (20.11)	77.97 (19.15)		78.93 (19.93)
BMI, mean (SD), [kg/m^2]	29.32 (5.39)	29.15 (5.59)		29.08 (5.54)
SBP, mean (SD) [mmHg]	125.7 (12.1)	126.5 (13.7)		125.9 (13.9)
1245.31 (EMPA-REG EXTEND) metformin background (1245.23 roll-over)	**Placebo (n=207)**	**Empagliflozin 10mg (n=217)**		**Empagliflozin 25mg (n=213)**
Demographic data				
Age, mean (SD) [years]	56.0 (9.7)	55.5 (9.9)		55.6 (10.2)
Gender, N (%)				
Male	116 (56.0)	125 (57.6)		120 (56.3)
Female	91 (44.0)	92 (42.4)		93 (43.7)
Race, N (%)				
American Indian/Alaska	0	2 (0.9)		2 (0.9)

Baseline characteristic	Treatment group		
native			
Asian	92 (44.4)	99 (45.6)	98 (46.0)
Black/African American	2 (1.0)	4 (1.8)	0
White	113 (54.6)	112 (51.6)	113 (53.1)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	89.70 (21.40)	89.48 (19.63)	87.71 (19.26)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	7.90 (0.88)	7.94 (0.79)	7.86 (0.87)
Time since diagnosis of T2DM, N (%)			
≤1 year	19 (9.2)	20 (9.2)	19 (8.9)
>1 to 5 years	83 (40.1)	78 (35.9)	69 (32.4)
>5 to 10 years	65 (31.4)	68 (31.3)	74 (34.7)
>10 years	40 (19.3)	51 (23.5)	51 (23.9)
Weight, mean (SD) [kg]	79.79 (18.57)	81.59 (18.51)	82.21 (19.29)
BMI, mean (SD), [kg/m^2]	28.70 (5.22)	29.12 (5.48)	29.72 (5.72)
Waist circumference, mean (SD) [cm]	99.3 (12.8)	99.1 (13.8)	100.0 (14.5)
SBP, mean (SD) [mmHg]	128.6 (14.7)	129.6 (14.1)	130.0 (15.1)
DBP, mean (SD) [mmHg]	78.1 (7.9)	79.6 (8.0)	78.4 (8.4)
Blood pressure controlled (SBP <130 and DBP <80mmHg), N (%)	71 (34.3)	75 (34.6)	75 (35.2)
History of hypertension, N (%)	107 (51.7)	124 (57.1)	124 (58.2)

1245.31 (EMPA-REG EXTEND) metformin plus SU background (1245.23 roll-over)	**Placebo (n=225)**	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**
Demographic data			
Age, mean (SD) [years]	56.9 (9.2)	57.0 (9.2)	57.4 (9.3)
Gender, N (%)			
Male	112 (49.8)	113 (50.2)	114 (52.8)
Female	113 (50.2)	112 (49.8)	102 (47.2)
Race, N (%)			
American Indian/Alaska native	3 (1.3)	4 (1.8)	3 (1.4)
Asian	127 (56.4)	129 (57.3)	125 (57.9)
Black/African American	7 (3.1)	3 (1.3)	3 (1.4)
White	88 (39.1)	89 (39.6)	85 (39.4)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.91 (20.11)	86.49 (21.79)	88.33 (22.63)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.15 (0.83)	8.07 (0.81)	8.10 (0.83)
Time since diagnosis of T2DM, N (%)			
≤1 year	2 (0.9)	3 (1.3)	7 (3.2)
>1 to 5 years	36 (16.0)	59 (26.2)	43 (19.9)
>5 to 10 years	94 (41.8)	74 (32.9)	79 (36.6)

Baseline characteristic	Treatment group		
>10 years	93 (41.3)	89 (39.6)	87(40.3)
Weight, mean (SD) [kg]	76.23 (16.88)	77.08 (18.34)	77.50 (18.81)
BMI, mean (SD), [kg/m^2]	27.90 (4.93)	28.32 (5.43)	28.32 (5.45)
SBP, mean (SD) [mmHg]	128.8 (14.3)	128.7 (13.9)	129.3 (14.2)
1245.33 (EMPA-REG BASAL) (N=494)	**Placebo (n =170)**	**Empagliflozin 10mg (n=169)**	**Empagliflozin 25mg (n=155)**
Demographic data			
Age, mean (SD) [years]	58.1 (9.4)	58.6 (9.8)	59.9 (10.5)
Gender, N (%)			
Male	90 (52.9)	93 (55.0)	93 (60.0)
Female	80 (47.1)	76 (45.0)	62 (40.0)
Race, N (%)			
Asian	33 (19.4)	37 (21.9)	28 (18.1)
Black/African American	21 (12.4)	12 (7.1)	15 (9.7)
Other	3 (1.8)	1 (0.6)	1 (0.6)
White	113 (66.5)	119 (70.4)	111 (71.6)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	83.89 (22.73)	85.01 (23.63)	82.88 (25.46)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.18 (0.79)	8.27 (0.83)	8.27 (0.84)
Time since diagnosis of diabetes, N (%)			
≤1 year	4 (2.4)	0	1 (0.6)
>1 to 5 years	20 (11.8)	15 (8.9)	12 (7.7)
>5 years	146 (85.9)	154 (91.1)	142 (91.6)
Weight, mean (SD) [kg]	90.46 (22.47)	91.59 (20.05)	94.71 (20.70)
BMI, mean (SD), [kg/m^2]	31.75 (5.98)	32.13 (5.77)	32.65 (5.90)
SBP, mean (SD) [mmHg]	133.9 (16.3)	132.4 (15.5)	132.8 (15.1)
1245.36 (EMPA-REG RENAL) (All renal impairment categories N=738)	**Placebo (n=319)**	**Empagliflozin 10mg (n=98)**	**Empagliflozin 25mg (n=321)**
Demographic data			
Age, mean (SD) [years]	64.1 (8.7)	63.2 (8.5)	63.9 (9.0)
Gender, N (%)			
Male	181 (56.7)	60 (61.2)	189 (58.9)
Female	138 (43.3)	38 (38.8)	132 (41.1)
Race, N (%)			
American Indian/Alaska native	1 (0.3)	0	0
Asian	119 (37.3)	25 (25.5)	122 (38.0)
Black/African American	6 (1.9)	3 (3.1)	13 (4.0)
Hawaiian/Pacific Islander	2 (0.6)	1 (1.0)	1 (0.3)
White	191 (59.9)	69 (70.4)	185 (57.6)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	49.90 (18.62)	70.77 (10.34)	51.12 (18.39)
Efficacy variables			

Baseline characteristic	**Treatment group**		
HbA_{1C}, mean (SD) [%]	8.07 (0.82)	8.02 (0.84)	8.01 (0.81)
Time since diagnosis of diabetes, N (%)			
≤1 year	2 (0.6)	0	4 (1.2)
>1 to 5 years	50 (15.7)	18 (18.4)	39 (12.1)
>5 to 10 years	75 (23.5)	22 (22.4)	74 (23.1)
>10 years	192 (60.2)	58 (59.2)	204 (63.6)
Weight, mean (SD) [kg]	83.7 (19.0)	92.1 (21.4)	84.1 (20.1)
BMI, mean (SD), [kg/m^2]	30.60 (5.47)	32.41 (5.43)	30.38 (5.45)
SBP, mean (SD) [mmHg]	137.0 (18.7)	137.4 (15.0)	136.7 (18.5)
1245.48 (EMPA-REG BP) (N=823)	**Placebo (n=271)**	**Empagliflozin 10mg (n=276)**	**Empagliflozin 25mg (n=276)**
Demographic data			
Age, mean (SD) [years]	60.3 (8.8)	60.6 (8.5)	59.9 (9.7)
Gender, N (%)			
Male	168 (62.0)	171 (62.0)	156 (56.5)
Female	103 (38.0)	105 (38.0)	120 (43.5)
Race, N (%)			
American Indian/Alaska native	0	1 (0.4)	1 (0.4)
Asian	1 (0.4)	3 (1.1)	4 (1.4)
Black/African American	13 (4.8)	14 (5.1)	14 (5.1)
Hawaiian/ Pacific islander	1 (0.4)	0	0
White	256 (94.5)	258 (93.5)	257 (93.1)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	84.96 (16.97)	83.41 (16.71)	83.50 (17.80)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	7.90 (0.72)	7.87 (0.77)	7.92 (0.72)
Time since diagnosis of T2DM, N (%)			
≤1 year	7 (2.6)	9 (3.3)	12 (4.3)
>1 to 5 years	70 (25.8)	62 (22.5)	73 (26.4)
>5 to 10 years	83 (30.6)	92 (33.3)	90 (32.6)
>10 years	111 (41.0)	113 (40.9)	101 (36.6)
SBP, 24h mean [mmHg] (ABPM)	131.7 (11.8)	131.3 (13.0)	131.2 (12.1)
DBP, 24h mean [mmHg] (ABPM)	75.2 (7.5)	75.1 (8.3)	74.6 (7.5)
SBP, mean (SD) [mmHg] (office measurement)	142.0 (12.4)	142.3 (12.1)	141.9 (12.5)
DBP, mean (SD) [mmHg] (office measurement)	83.7 (7.1)	84.1 (7.3)	83.8 (6.8)
SBP, daytime mean [mmHg] (ABPM)	136.1 (12.0)	135.3 (13.0)	135.1 (12.2)
DBP, daytime mean [mmHg] (ABPM)	78.7 (7.7)	78.4 (8.4)	77.9 (7.9)
SBP, night-time mean (SD) [mmHg] (ABPM)	123.1 (13.7)	123.5 (14.7)	123.3 (13.8)
DBP, night-time mean (SD) [mmHg] (ABPM)	68.2 (8.8)	68.7 (9.6)	68.0 (8.3)
Orthostatic BP test positive, N (%)	47 (17.3)	43 (15.6)	55 (19.9)
BP controlled (SBP <130 and DBP <80 mmHg) (office measurement), N (%)	30 (11.1)	25 (9.1)	29 (10.5)

Baseline characteristic	**Treatment group**		
Weight, mean (SD) [kg]	95.22 (17.47)	94.71 (19.77)	95.59 (17.37)
BMI, mean (SD), [kg/m^2]	32.43 (4.93)	32.36 (5.32)	33.00 (4.97)
1245.49 (EMPA-REG MDI) (N=563)	**Placebo (n=188)**	**Empagliflozin 10mg (n=186)**	**Empagliflozin 25mg (n=189)**
Demographic data			
Age, mean (SD) [years]	55.3 (10.1)	56.7 (8.7)	58.0 (9.4)
Gender, N (%)			
Male	75 (39.9)	97 (52.2)	84 (44.2)
Female	113 (60.1)	89 (47.8)	105 (55.6)
Race, N (%)			
American Indian/Alaska native	4 (2.1)	3 (1.6)	2 (1.1)
Asian	2 (1.1)	0	1 (0.5)
Black/African American	8 (4.3)	7 (3.8)	4 (2.1)
Hawaiian/ Pacific islander	0	1 (0.5)	0
White	174 (92.6)	175 (94.1)	182 (96.3)
eGFR (MDRD), mean (SD) [ml/min/1.73m^2]	83.41 (15.40)	84.14 (17.76)	84.35 (16.59)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.33 (0.72)	8.39 (0.74)	8.29 (0.72)
Time since diagnosis of T2DM, N (%)			
≤1 year	1 (0.5)	0	0
>1 to 5years	17 (9.0)	22 (11.8)	11 (5.8)
>5 to 10 years	40 (21.3)	44 (23.7)	38 (20.1)
>10 years	130 (69.1)	120 (64.5)	140 (74.1)
Weight, mean (SD) [kg]	95.5 (17.5)	96.7 (17.9)	95.9 (17.3)
BMI, mean (SD) [kg]	34.65 (4.30)	34.72 (3.83)	34.99 (4.04)
SBP, mean (SD) [mmHg]	132.6 (15.8)	134.2 (16.4)	132.9 (14.2)

Efficacy section

Table 25: Summary of primary and secondary endpoints in study 1245.19 (Page 109)

Efficacy Results			
	Placebo (n=165)	**Empagliflozin 10 mg (n=165)**	**Empagliflozin 25 mg (n=168)**
Mean baseline HbA_{1C} (%) ± SE	8.16 ± 0.07	8.07 ± 0.07	8.06 ± 0.06
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF)	8.02 ± 0.09	7.50 ± 0.07	7.36 ± 0.07
Adjusted mean change from baseline (%) ± SE	−0.11 ± 0.07	−0.59 ± 0.07	−0.72 ± 0.07
Adjusted mean difference vs placebo (%) ± SE		−0.48 ± 0.09	−0.61 ± 0.09
[97.5% CI]		[−0.69, −0.27]	[−0.82, −0.40]
P value		<0.0001	<0.0001
	Placebo (n=165)	**Empagliflozin 10mg (n=163)**	**Empagliflozin 25mg (n=168)**
Mean baseline FPG (mg/dL) ± SE	151.93 ± 3.14	152.01 2.99	151.86 ± 2.86
Mean FPG at week 24 (mg/dL) ± SE – FAS (LOCF)	158.56 ± 3.59	134.85 ± 3.36	129.86 ± 2.15
Adjusted mean change from baseline (mg/dL) ± SE	6.47 ± 2.61	-17.00 ± 2.63	-21.99 ± 2.59
Adjusted mean difference vs placebo (mg/dL) ± SE		-23.48 ± 3.71	-28.46 ± 3.68
[97.5% CI]		[-31.81, -15.15]	[-36.73, -20.19]
P value		<0.001	<0.001
	Placebo (n=165)	**Empagliflozin 10 mg (n=165)**	**Empagliflozin 25 mg (n=168)**
Mean baseline body weight (kg) ± SE	78.10 ± 1.57	77.97 ± 1.49	78.93 ± 1.54
Mean body weight at week 24 (kg) ± SE – FAS (LOCF)	78.45 ± 1.54	76.37 ± 1.46	77.44 ± 1.51
Adjusted mean change from baseline (kg) ± SE	0.34 ± 0.21	−1.62 ± 0.21	−1.47 ± 0.21
Adjusted mean difference vs placebo (kg) ± SE		−1.95 ± 0.30	−1.81 ± 0.30
[97.5% CI]		[−2.64, −1.27]	[−2.49, −1.13]

P value		<0.0001	<0.0001
	Placebo (n=165)	**Empagliflozin 10 mg (n=165)**	**Empagliflozin 25 mg (n=168)**
Mean baseline SBP (mmHg) ± SE	125.71 ± 0.94	126.51 ± 1.06	125.95 ± 1.07
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF)	126.58 ± 1.15	123.28 ± 1.03	121.89 ± 1.01
Adjusted mean change from baseline (mmHg) ± SE	0.72 ± 0.85	−3.14 ± 0.85	−4.00 ± 0.84
Adjusted mean difference vs placebo (mmHg) ± SE		−3.86 ± 1.20	−4.73 ± 1.20
[95% CI]		[−6.23, −1.50]	[−7.08, −2.37]
P value		0.0014	<0.0001

Table 26: Summary of primary and secondary endpoints in study 1245.23 (metformin plus SU) (Page 115)

Efficacy Results				
	Placebo (n=225)	**Empagliflozin 10 mg (n=225)**	**Empagliflozin 25 mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline HbA_{1C} ± SE	8.15 ± 0.06	8.07 ± 0.05	8.10 ± 0.06	11.18 ± 0.12
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF), OLS (LOCF)	7.97 ± 0.07	7.26 ± 0.05	7.33 ± 0.06	8.65 ± 0.14
Adjusted mean change from baseline (%) ± SE	-0.17 ± 0.05	-0.82 ± 0.05	-0.77 ± 0.05	-2.53 ± 0.15†
Adjusted mean difference vs placebo (%) ± SE		-0.64 ± 0.07	-0.59 ± 0.07	
[97.5% CI]		[-0.79, -0.49]	[-0.74, -0.44]	
P value		<0.001	<0.001	
	Placebo (n=225)	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline body weight (kg) ± SE	76.23 ± 1.13	77.08 ± 1.22	77.50 ± 1.28	76.43 ± 1.81
Mean body weight at week 24 (kg) ± SE – FAS (LOCF), OLS (LOCF)	75.86 ± 1.12	74.91 ± 1.22	75.10 ± 1.26	75.15 ± 1.78
Adjusted mean change from baseline (kg) ± SE	-0.39 ± 0.15	-2.16 ± 0.15	-2.39 ± 0.16	-1.29 ± 0.30†
Adjusted mean difference vs placebo (kg) ± SE		-1.76 ± 0.22	-1.99 ± 0.22	
[97.5% CI]		[-2.25, -1.28]	[-2.48, -1.50]	
P value		<0.0001	<0.0001	
	Placebo (n=151)	**Empagliflozin 10mg (n=148)**	**Empagliflozin 25mg (n=117)**	**Open-label empagliflozin 25mg (n=52)**
Mean baseline MDG (mg/dL) ± SE	170.45 ± 2.47	170.28 ± 2.39	172.72 ± 3.49	233.07 ± 8.78
Mean MDG at week 24 (mg/dL) ± SE – FAS (LOCF), OLS (LOCF)	170.95 ± 2.48	160.53 ± 2.66	158.68 ± 3.15	203.72 ± 8.36
Adjusted mean change from baseline (mg/dL) ± SE	0.00 (1.78)	-10.01 ± 1.80	-13.06 ± 2.03	-29.34 ± 6.58†
Adjusted mean difference vs placebo (mg/dL) ± SE		-10.02 ± 2.53	-13.06 ± 2.70	

[97.5% CI]		[-15.72, -4.32]	[-19.15, -6.98]	
P value		<0.001	<0.001	
	Placebo (n=225)	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline SBP (mmHg) ± SE	128.8 ± 1.0	128.7 ± 0.9	129.3 ± 1.0	126.4 ± 1.2
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF), OLS (LOCF)	127.4 ± 0.9	124.7 ± 1.0	125.7 ± 0.8	122.7 ± 1.3
Adjusted change from baseline (mmHg) ± SE	-1.4 ± 0.7	-4.1 ± 0.7	-3.5 ± 0.7	-3.6 ± 1.0[†]
Adjusted difference vs placebo (mmHg) ± SE		-2.7 ± 1.0	-2.1 ± 1.0	
[95% CI]		[-4.6, -0.8]	[-4.0, -0.2]	
P value		0.0049	0.0321	

Table 27: Summary of efficacy endpoints in 1245.31 extension study (Page 122)

Efficacy Results				
Monotherapy (1245.20 roll-over)				
	Placebo (N=228)	**Empagliflozin 10mg (N=224)**	**Empagliflozin 25mg (N=224)**	**Sitagliptin 100ng (N=223)**
Mean baseline HbA_{1C} (%) ± SE	7.91 ± 0.05	7.87 ± 0.06	7.86 ± 0.06	7.85 ± 0.05
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.03 ± 0.07	7.22 ± 0.06	7.11 ± 0.06	7.33 ± 0.07
Adjusted mean change from baseline (%) ± SE	0.13 ± 0.06	-0.65 ± 0.06	-0.76 ± 0.06	-0.53 ± 0.06
Adjusted mean difference *vs* placebo (%) ± SE		-0.78 ± 0.08	-0.89 ± 0.08	-0.66 ± 0.08
[95% CI]		[-0.94, -0.63]	[-1.04, -0.73]	[-0.82, -0.51]
P value		<0.0001	<0.0001	<0.0001
Adjusted mean difference *vs* sitagliptin (%) ± SE		-0.12 ± 0.08	-0.22 ± 0.08	
[95% CI]		[-0.28, 0.04]	[-0.38, -0.07]	
P value		0.1310	0.0050	
	Placebo (N=228)	**Empagliflozin 10mg (N=224)**	**Empagliflozin 25mg (N=224)**	**Sitagliptin 100ng (N=223)**
Mean baseline body weight (kg) ± SE	78.23 ± 1.32	78.35 ± 1.25	77.80 ± 1.20	79.31 ± 1.37
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	77.79 ± 1.29	76.10 ± 1.21	75.36 ± 1.17	79.41 ± 1.37
Adjusted mean change from baseline (kg) ± SE	-0.43 ± 0.20	-2.24 ± 0.20	-2.45 ± 0.20	0.10 ± 0.20
Adjusted mean difference *vs* placebo (kg) ± SE		-1.81 ± 0.28	-2.02 ± 0.28	0.54 ± 0.28
[95% CI]		[-2.35, -1.26]	[-2.56, -1.48]	[-0.01, 1.08]
P value		<0.0001	<0.0001	0.0546
Adjusted mean difference *vs* sitagliptin (kg) ± SE		-2.34 ± 0.28	-2.56 ± 0.28	
[95% CI]		[-2.89, -1.80]	[-3.10, -2.01]	
P value		-	-	

	Placebo (N=228)	Empagliflozin 10mg (N=224)	Empagliflozin 25mg (N=224)	Sitagliptin 100ng (N=223)
Mean baseline SBP (mmHg) ± SE	130.4 ± 1.1	133.0 ± 1.1	129.9 ± 1.2	132.5 ± 1.1
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	130.0 ± 1.1	128.2 ± 1.0	126.4 ± 1.0	131.8 ± 1.1
Adjusted mean change from baseline (mmHg) ± SE	-0.7 ± 0.8	-4.1 ± 0.8	-4.2 ± 0.8	-0.3 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.4 ± 1.1	-3.4 ± 1.1	0.4 ± 1.1
[95% CI]		[-5.5, -1.2]	[-5.6, -1.2]	[-1.8, 2.6]
P value		0.025	0.0021	0.7241
Adjusted mean difference *vs* sitagliptin (mmHg) ± SE		-3.7 ± 1.1	-3.8 ± 1.1	
[95% CI]		[-5.9, -1.6]	[-6.0, -1.6]	
P value		-	-	
Background of pioglitazone (1245.19 roll-over)				
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**	
Mean baseline HbA_{1C} (%) ± SE	8.16 ± 0.07	8.07 ± 0.07	8.06 ± 0.06	
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.11 ± 0.09	7.47 ± 0.08	7.37 ± 0.07	
Adjusted mean change from baseline (%) ± SE	-0.01 ± 0.07	-0.61 ± 0.07	-0.70 ± 0.07	
Adjusted mean difference *vs* placebo (%) ± SE		-0.59 ± 0.10	-0.69 ± 0.10	
[95% CI]		[-0.79, -0.40]	[-0.88, -0.50]	
P value		<0.0001	<0.0001	
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**	
Mean baseline body weight (kg) ± SE	78.10 ± 1.57	77.97 ± 1.49	78.93 ± 1.54	
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	78.60 ± 1.57	76.52 ± 1.47	77.71 ± 1.50	
Adjusted mean change from baseline (kg) ± SE	0.50 ± 0.26	-1.47 ± 0.26	-1.21 ± 0.26	
Adjusted mean difference *vs* placebo (kg) ± SE		-1.97 ± 0.37	-1.71 ± 0.37	

[95% CI]		[-2.69, -1.24]	[-2.43, -0.99]
P value		<0.0001	<0.0001
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**
Mean baseline SBP (mmHg) ± SE	125.7 ± 0.9	126.5 ± 1.1	125.9 ± 1.1
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	126.2 ± 1.1	124.7 ± 1.1	122.6 ± 1.0
Adjusted mean change from baseline (mmHg) ± SE	0.3 ± 0.9	-1.7 ± 0.9	-3.4 ± 0.9
Adjusted mean difference *vs* placebo (mmHg) ± SE		-2.0 ± 1.2	-3.7 ± 1.2
[95% CI]		[-4.5, 0.4]	[-6.1, -1.3]
P value		0.0987	0.0028
Background of metformin (1245.23 roll-over)			
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline HbA_{1C} (%) ± SE	7.90 ± 0.06	7.94 ± 0.05	7.86 ± 0.06
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	7.89 ± 0.07	7.30 ± 0.05	7.14 ± 0.06
Adjusted mean change from baseline (%) ± SE	-0.01 ± 0.05	-0.62 ± 0.05	-0.74 ± 0.05
Adjusted mean difference *vs* placebo (%) ± SE		-0.61 ± 0.07	-0.73 ± 0.07
[95% CI]		[-0.75, -0.46]	[-0.88, -0.58]
P value		<0.0001	<0.0001
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline body weight (kg) ± SE	79.73 ± 1.29	81.59 ± 1.26	82.21 ± 1.32
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	79.34 ± 1.30	79.19 ± 1.20	79.49 ± 1.25
Adjusted mean change from baseline (kg) ± SE	-0.46 ± 0.22	-2.39 ± 0.21	-2.65 ± 0.21
Adjusted mean difference *vs* placebo (kg) ± SE		-1.93 ± 0.30	-2.19 ± 0.30
[95% CI]		[-2.52, -1.34]	[-2.79, -1.60]

P value		<0.0001	<0.0001
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline SBP (mmHg) ± SE	128.6 ± 1.0	129.6 ± 1.0	130.0 ± 1.0
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	128.1 ± 1.0	124.2 ± 0.9	125.3 ± 1.1
Adjusted mean change from baseline (mmHg) ± SE	-0.8 ± 0.8	-5.2 ± 0.8	-4.5 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-4.4 ± 1.1	-3.7 ± 1.1
[95% CI]		[-6.6, -2.3]	[-5.9, -1.5]
P value		<0.0001	0.0008
Background of metformin plus SU (1245.23 roll-over)			
	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline HbA_{1C} (%) ± SE	8.15 ± 0.06	8.07 ± 0.05	8.10 ± 8.10
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.11 ± 0.08	7.34 ± 0.06	7.38 ± 0.06
Adjusted mean change from baseline (%) ± SE	-0.03 ± 0.06	-0.74 ± 0.06	-0.72 ± 0.06
Adjusted mean difference *vs* placebo (%) ± SE		-0.72 ± 0.08	-0.69 ± 0.08
[95% CI]		[-0.87, -0.56]	[-0.85, -0.53]
P value		<0.0001	<0.0001
	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline body weight (kg) ± SE	76.23 ± 1.13	77.08 ± 1.22	77.50 ± 1.28
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	75.63 ± 1.12	74.62 ± 1.22	75.20 ± 1.27
Adjusted mean change from baseline (kg) ± SE	-0.63 ± 0.19	-2.44 ± 0.19	-2.28 ± 0.20
Adjusted mean difference *vs* placebo (kg) ± SE		-1.81 ± 0.27	-1.64 ± 0.27
[95% CI]		[-2.34, -1.27]	[-2.18, -1.11]
P value		<0.0001	<0.0001

	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline SBP (mmHg) ± SE	128.8 ± 1.0	128.7 ± 0.9	129.3 ± 1.0
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	127.3 ± 0.9	125.0 ± 0.9	125.4 ± 0.9
Adjusted mean change from baseline (mmHg) ± SE	-1.6 ± 0.7	-3.8 ± 0.7	-3.7 ± 0.7
Adjusted mean difference *vs* placebo (mmHg) ± SE		-2.2 ± 1.0	-2.1 ± 1.0
[95% CI]		[-4.1, -0.3]	[-4.1, -0.2]
P value		0.0213	0.0288

Safety section

Table 28: Summary of AEs in study 1245.28 (Page 203)

	Empagliflozin 25mg (n=765)	Glimepiride (n=780)
One or more AE(s), n (%)	661 (86.4)	673 (86.3)
One or more drug-related AE(s), n (%)	190 (24.8)	252 (32.3)
AEs leading to discontinuation, n (%)	39 (5.1)	34 (4.4)
One or more serious AE(s), n (%)	119 (15.6)	89 (11.4)
Deaths, n (%)	5 (0.7)	5 (0.6)
AEs with frequency of ≥5% in any randomised group		
UTI, n (%)	95 (12.4)	99 (12.7)
Nasopharyngitis, n (%)	76 (9.9)	89 (11.4)
URTI, n (%)	79 (10.3)	74 (9.5)
Influenza, n (%)	51 (6.7)	51 (6.5)
Hyperglycaemia, n (%)	105 (13.7)	168 (21.5)
Hypoglycaemia, n (%)	32 (4.2)	197 (25.3)
Dyslipidemia, n (%)	41 (5.4)	39 (5.0)
Headache, n (%)	48 (6.3)	55 (7.1)
Dizziness, n (%)	49 (6.4)	49 (6.3)
Hypertension, n (%)	41 (5.4)	77 (9.9)
Cough n (%)	42 (5.5)	47 (6.0)
Diarrhoea, n (%)	39 (5.1)	51 (6.5)
Arthralgia, n (%)	44 (5.8)	66 (8.5)
Back pain, n (%)	63 (8.2)	64 (8.2)
Pain in extremity, n (%)	39 (5.1)	32 (4.1)
Special interest categories		
Hypoglycaemia, n (%)	19 (2.5)	189 (24.2)
AEs belonging to BICMQ 'UTI', n (%)	105 (13.7)	102 (13.1)
AEs belonging to BICMQ 'genital infection', n (%)	90 (11.8)	17 (2.2)
AEs belonging to BICMQ 'volume depletion', n (%)	11 (1.4)	8 (1.3)
AEs belonging to BICMQ 'bone fractures', n (%)	19 (2.5)	17 (2.2)
AEs belonging to BICMQ 'malignancies', n (%)	15 (2.0)	9 (1.2)

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