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

Pro-forma Response *with ERG responses*

ERG report

Empagliflozin combination therapy for treating type 2 diabetes [ID641]

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

Note from ERG. In the ERG report, on pages 76-79, we raised 10 major and 7 minor concerns about the ECEM model. Boehringer have responded to only one major concern and one minor concern – issues 8 and 10 below.

Issue 1 Absence of Met+TZD throughout ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG RESPONSE
Throughout the report there is an absence of discussion around the metformin and TZD aspect of the	Within section 2 or 3 there should be a statement explaining the exclusion of this aspect of the scope when the analysis was	It seems amiss that part of the scope addressed in the submission has not been considered as part of the ERG	An addendum on the pioglitazone trial (EMPA-REG pio) has been provided by the

decision problem. This is repeated within the discussion of the NMA and also the economic analysis.	provided within the submission. If it is decided this omission is unjustified than an addendum including a comment on this aspect of the decision problem is warranted.	report. Especially given the recent recommendations in relation to canagliflozin.	ERG.

Issue 2 Absence of IMS model validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When discussing the model validation there is an absence of any discussion or mention of the IMS model validation. Given the amount of discussion around validation this seems a significant omission.	There could be a mention of whether the validation analysis is useful or whether it helps to inform the conclusion.	A main issue identified in the ERG report is the validity of the economic analysis it would therefore, seem appropriate to mention this analysis in the overall discussion.	The ERG did not have access to the CORE modelling, and given the timelines of an STA, did not ask for access. We had quite enough to do critiquing one model. If the manufacturer wanted the CORE modelling to be used, they could have provided the submission in CORE and not ECEM. There is a distinction between internal and external validation. The critiques of the ERG suggest a lack of internal validation of the ECEM, which the manufacturer appears to largely accept.

Issue 3 Placebo adjusted weight changes in the EMPA REG MDI study

Description of problem	Description of proposed amendment	Justification for amendment	ERG responses
On page 11, the weight loss in the	The values to weight reduction should be	The values given for the other	Accepted – ERG error between

EMPA REG MDI study is provided as 1.5 kg and 1.6 kg in the 10mg and 25mg treatment groups respectively. It is not clear where these values have been taken from.	amended to 2.39 kg and 2.48 kg respectively as stated in table 7 on page 42 of the ERG report	studies in the section (add on to metformin, add on to metformin plus sulphonylurea and add on to basal insulin) are placebo corrected therefore the reported figures for the MDI study should be also.	body of report and Summary. The figures on page 11 are wrong. The weight losses should have been reported as 1.95 and 2.04 kg, or 2.39 and 2.48 adjusted for placebo change. Replacement text provided.

Issue 4 Background anti-diabetic therapies in the EMPA REG RENAL study

Description of problem	Description of proposed amendment	Justification for amendment	
On page 25 of the ERG report, the authors state that regarding the EMPA REG RENAL study the proportion of patients on monotherapy, dual therapy or insulin is not provided.	The details of the background therapies can be found in table 1 of the Barnett et al 2014 Lancet publication for the EMPA REG RENAL study. The values for the total randomised set are as follows: For CKD 2 Metformin monotherapy 12.8%, insulin monotherapy 9.7%, metformin plus sulphonylurea 23.4%, metformin plus insulin 20.7%, other therapies 33.4% For CKD 3 Metformin monotherapy 7.8%, insulin monotherapy 25.4%, sulphonylurea only 7.5%, metformin plus sulphonylurea 13.9%, metformin plus insulin 13.9%, other therapy 31.6% For CKD 4 Insulin monotherapy 55.4%, sulphonylurea monotherapy 9.5%, metformin plus sulphonylurea 4.1%, metformin plus insulin	Background therapies by treatment arm are provided in the Barnett et al publication and are balanced between treatment arms.	The data were not provided in the manufacturer's submission so the statement on page 25 is correct. However there is an error in line 9 on page 25, where "moderate" should be "mild". The relevance of this trial is reduced by the EMA recommendations against use in moderate renal impairment. .

	2.7%, sulphonylurea plus insulin 8.1%, other therapy 20.3%		

Issue 5 Average BMI range in EMPA REG BASAL and MDI studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG
On page 31 of the ERG report, the BMI for the EMPA REG BASAL and MDI studies is stated as ranging from 31.75 to 34.72 kg/m^2.	The range should be 31.75 to 34.99 kg/m^2.	34.72 kg/m^2 is the average BMI in the empagliflozin 10mg treatment group but it is not the highest average BMI. The highest average BMI in the MDI study is 34.99 kg/m^2 (in the empagliflozin 25mg treatment group).	Accepted but inconsequential

Issue 6 Proportion of patients achieving targets by baseline HbA1c (response to clarification letter)

Description of problem	Description of proposed amendment	Justification for amendment	ERG
On page 33 of the ERG report in table 4, in the EMPA REG MET study the proportion of patients with a baseline HbA1c <8% achieving an HbA1c ≤ 6.5% in the placebo arm is reported as 6.8%. In table 5 on page 35, in the EMPA REG BASAL study the proportion of patients in the placebo treatment group with a baseline HbA1c <8% achieving an HbA1c of ≤ 7% is reported as 4.1%.	In the EMPA REG MET study the proportion of patients treated with placebo with a baseline HbA1c of <8% and achieving an HbA1c ≤ 6.5% is 11.6%. In the EMPA REG BASAL study the proportion of patients in the placebo treatment group with a baseline HbA1c <8% achieving an HbA1c of ≤ 7% is 14.1%.	The figures in the table have been checked against the original data provided to the ERG in response to the clarification letter on 19th May.	Accepted. 6.8% is the figure for all baseline HbA1cs. 4.1% is the figure given in table 18, page 55 of the Boehringer response to clarification questions. 14.1% looks more plausible. In the tables we provided, we simply reported what

			Boehringer had provided. Note that this request by the ERG was not so much for clarification, but for data that had not been provided at all in the submission. We thought it would be useful for the AC.

Issue 7 Extension period for the EMPA REG studies and EMPA REG BASAL study duration

Description of problem	Description of proposed amendment	Justification for amendment	
On page 48 of the ERG report, reference is made to the 24 week data and the 52 week data for EMPA REG studies in the NMA.	The extension period is 52 weeks in addition to 24 weeks, i.e. data at 76 weeks. The EMPA REG MET, MET SU and PIO studies had primary endpoints at 24 weeks with extension for a further 52 weeks resulting in a total duration in the EXTEND studies of 76 weeks.	Clarification is provided on the total duration of the extension periods of the EMPA REG studies.	Page 48 of the ERG report refers to the NMA not the EMPA-REG trials. Page 161 of the MS (line 5) says that "comparisons at 52 +/- 4 weeks were also included".
On page 69 of the ERG report the duration of the EMPA REG BASAL study is incorrect. The proportion of patients completing the 76 weeks in the EMPA REG BASAL study is reported.	The duration of the EMPA REG BASAL study is 78 weeks.	Duration of the EMPA REG BASAL study is clarified.	Accepted but inconsequential.

Issue 8 Random sampling for evaluation of events within a PSA iteration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2 (pg. 76): "The ECEM appears to sample one set of random numbers at the start of each probabilistic sensitivity analysis (PSA) iteration. These are used to determine whether events occur for each patient simulated within a PSA iteration. The same set of random numbers appears to be used for each patient. As a consequence, within a PSA iteration two patients who are identical at baseline will be simulated as having the same set of events at the same time and as a consequence the same net costs and net quality adjusted life years (QALYs).This sampling is a key consideration within an individual patient model. If the ERG identified error is confirmed by the manufacturer, this would seem to largely invalidate the modelling of the submission." Section 4.5.1 (pages 83 to 86): "Given the centrality of this to any individual patient modelling the ERG has cross checked this in three ways.	The model considers patients' heterogeneity and therefore does not simulate identical patients for the analyses. To test the impact of using random values drawn at the PSA/sample level on each individual patient pathway is important to consider that patient's characteristics and disease history will differ across patients. There is a second set of random values, at the patient level, so that different baseline characteristics can be generated per patient. It should also be noted that each simulated patient is run across each of the different treatments compared so that both differences in patient characteristics and treatment effects on risk factors will result in different probabilities of developing events across different patients. In the ECEM these different probabilities of experiencing events are compared to the random value per cycle simulated at the PSA/sample level, and will result in different patient pathways.	Based on a discussion with an academic expert (Prof Richard Grieve, LSHTM, London), there is not a standardised/gold-standard method to implement micro-simulation models. It seems to be acceptable to draw the random value to determine whether an event occurs or not at the sample level. Implementing the approach recommended by the ERG results in similar mean estimates but is associated with a lower level of uncertainty (estimated through the 2.5% and 97.5% percentile intervals). As a result one could argue that the approach taken for the ECEM is conservative as it does not underestimate the level of uncertainty.(See Appendix 1)	The manufacturer again appears to conflate the random sampling of patient heterogeneity, i.e.; 1st order uncertainty, with the set of random values that the calculated probabilities of events should be compared against to assess whether an event occurs or not. It is unclear quite what the manufacturer has asked Prof Richard Grieve. It seems possible that the manufacturer may have continued to conflate patient heterogeneity and the set of random values that the calculated probabilities of events should be compared against to assess whether an event occurs or not. It is perfectly reasonable conceptually within a patient level model not to sample patient heterogeneity; i.e. to model a subset of patients who do not differ clinically. But the model should not simulate these patients as having

• Examination of the visual basic code • Simulation of 100 identical patients with no sampling of 2nd order uncertainty • Simulations involving sampling of 1st order and 2nd order uncertainty with additional code inserted into the visual basic to output the calculated probabilities of events and random numbers these are evaluated against by PSA iteration, patient number and cycle number." "At its most extreme, this means that simulating patients who are identical at baseline results in them all following exactly the same path through the model and having the same total costs and QALYs."			identical experiences, costs and QALYs. The manufacturer accepts that the model should be able to be run deterministically; i.e. without sampling of 2nd order uncertainty. Also note that the NICE DSU technical support document only really deals with patient level models being run deterministically as this captures the salient features of the approach, PSA and 2nd order sampling being simply noted as being just as per a cohort modelling approach. So concentrating upon deterministic modelling for simplicity, even with patient heterogeneity it would be perfectly possible for the ECEM to simulate all the heterogeneous patients as having the same experience. For instance, suppose that the random number for the first cycle chance of death from an MI was drawn and was 0.02. Suppose further that the calculated probability of the chance of a fatal MI for each of 15,000 heterogeneous patients simulated ranged between 5% and 10%. The

			ECEM would simulate 100% of the 15,000 as dying from an MI during the first cycle. The correct calculation would result in only somewhere between 5% and 10% being simulated as dying from an MI during the first cycle. This is achieved by drawing a different set of random values for each patient, not by applying a single set across all 15,000 patients simulated. For this reason the ERG disagrees that "*It seems to be acceptable to draw the random value to determine whether an event occurs or not at the sample level*"; i.e. to retain the same random number for the assessment of an event for all patient simulated within a deterministic model run. This sampling issue is also the probable reason behind the results of the ECEM being sensitive to value chosen for the random seed as outlined in table 27 of the ERG report. The manufacturer submits a set of analyses which purport to fix this issue, with little

			overall impact upon model results. The ERG has not had sight of the model underlying these. Fixing this issue would also raises further concerns around the likely convergence of the model over 100 patients and 300 PSA iterations as outlined in the ERG report. If the manufacturer still disputes this point, the simplest means of resolving it might be to ask the authors of the NICE DSU technical support document 15 to arbitrate. No revision required.

Issue 9 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Pg. 81 (section 4.3) “Treatment failures relate to when the patient’s HbA1c has risen above 7.5%. At this point the patient is assumed to switch to insulin therapy, and to experience the clinical effects associated with it in terms of changes to HbA1c,	“Treatment failures relate to when the patient’s HbA1c has risen above 7.5%. At this point the patient is assumed to receive add-on insulin in the case of dual and triple therapies, or to switch to insulin rescue therapy in the case of receiving a therapy with insulin as background, and to experience the clinical effects associated with it in terms of changes to HbA1c, SBP,	The initial statement could be changed to reflect the recommended treatment pathway. This was also clarified in question B11 of the document the ‘Response to NICE clarification questions’.	Point accepted, except there is no explanation of “insulin rescue therapy”. In people on MDI, the only insulin rescue would be to increase the dose. Proposed clarification accepted

SBP, lipids and weight.”	lipids and weight.”		

Issue 10 Dying twice

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Pg. 107 (section 4.6.6.5) “It appears that within a cycle a patient may die twice.”	“It appears that within a cycle the death of a patient may be related to more than one cause.”	The interpretation is to consider that a patient may experience more than one complication in a cycle each of them associated with a cost, before dying. However, the model does not allow a patient to die twice within the same cycle. The model selects the cause of death based on the random value used to assess the occurrence of death.	This is to a degree semantics, but in the opinion of the ERG a patient should not be modelled as incurring both the costs of e.g. a fatal stroke and a fatal amputation. The ECEM does just this, and the ERG offered to supply the manufacturer with a parsed run of the ECEM that outlined this happening for a patient number 54 in footnote 9 of the ERG report. See table below wherein a patient incurs the costs of two fatal conditions. In the opinion of the ERG the ECEM should simulate which events occur during a cycle in random order, with some logical constraints around these. If one of these is a fatal event, no fatal events subsequent to this should be simulated; i.e. a patient should not be modelled as incurring the costs of both a fatal stroke and a fatal amputation.

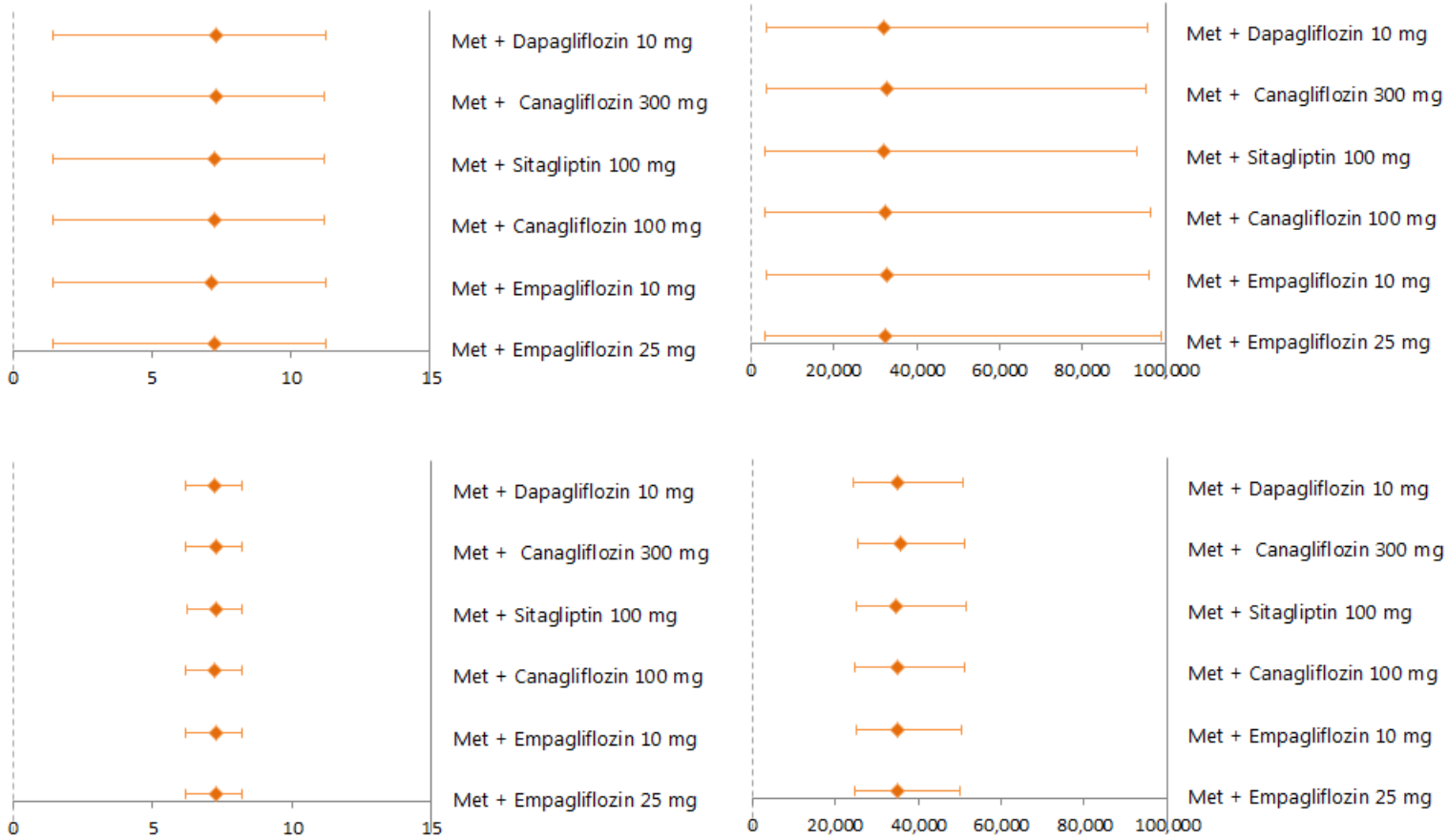
			No revision required.

Table showing costs of death applied within the ECEM for patient number 54

	1	2	3	4	5	6	7	8	9	10	11	12.00
MatSumDirC_MI_fatal(i)	0	0	0	0	0	0	0	0	0	0	0	0.00
MatSumDirC_stroke_fatal(i)	0	0	0	0	0	0	0	0	0	0	0	6773.98
MatSumDirC_CHF_fatal(i)	0	0	0	0	0	0	0	0	0	0	0	0.00
MatSumDirC_Amp_fatal(i)	0	0	0	0	0	0	0	0	0	0	0	6280.48
MatSumDirC_Renal_fatal(i)	0	0	0	0	0	0	0	0	0	0	0	0.00
MatSumDirC_Diab_death(i)	0	0	0	0	0	0	0	0	0	0	0	0.00
MatSumDirC_CVdeaths(i)	0	0	0	0	0	0	0	0	0	0	0	0.00
MatSumDirC_Deaths(i)	0	0	0	0	0	0	0	0	0	0	0	13054.46
MatSumDirC_Cum_costs_Deaths(i)	0	0	0	0	0	0	0	0	0	0	0	13054.46

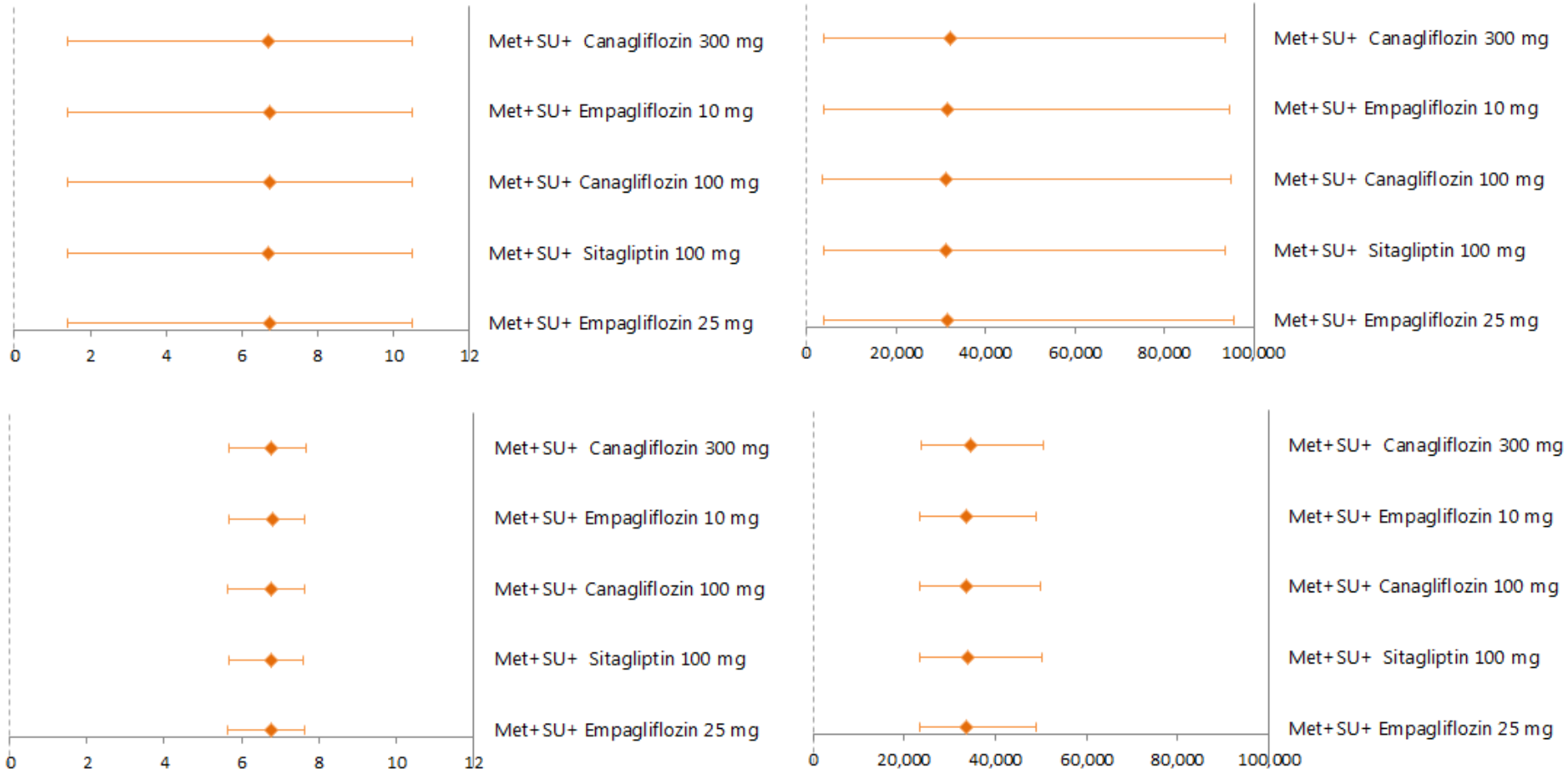
Appendix 1

Figure 1. QALYs* and costs (and corresponding 95% percentile confidence intervals) obtained with 2nd line therapies (metformin background) based on ECEM approach (top graphs) vs. suggested ERG approach (bottom graphs)



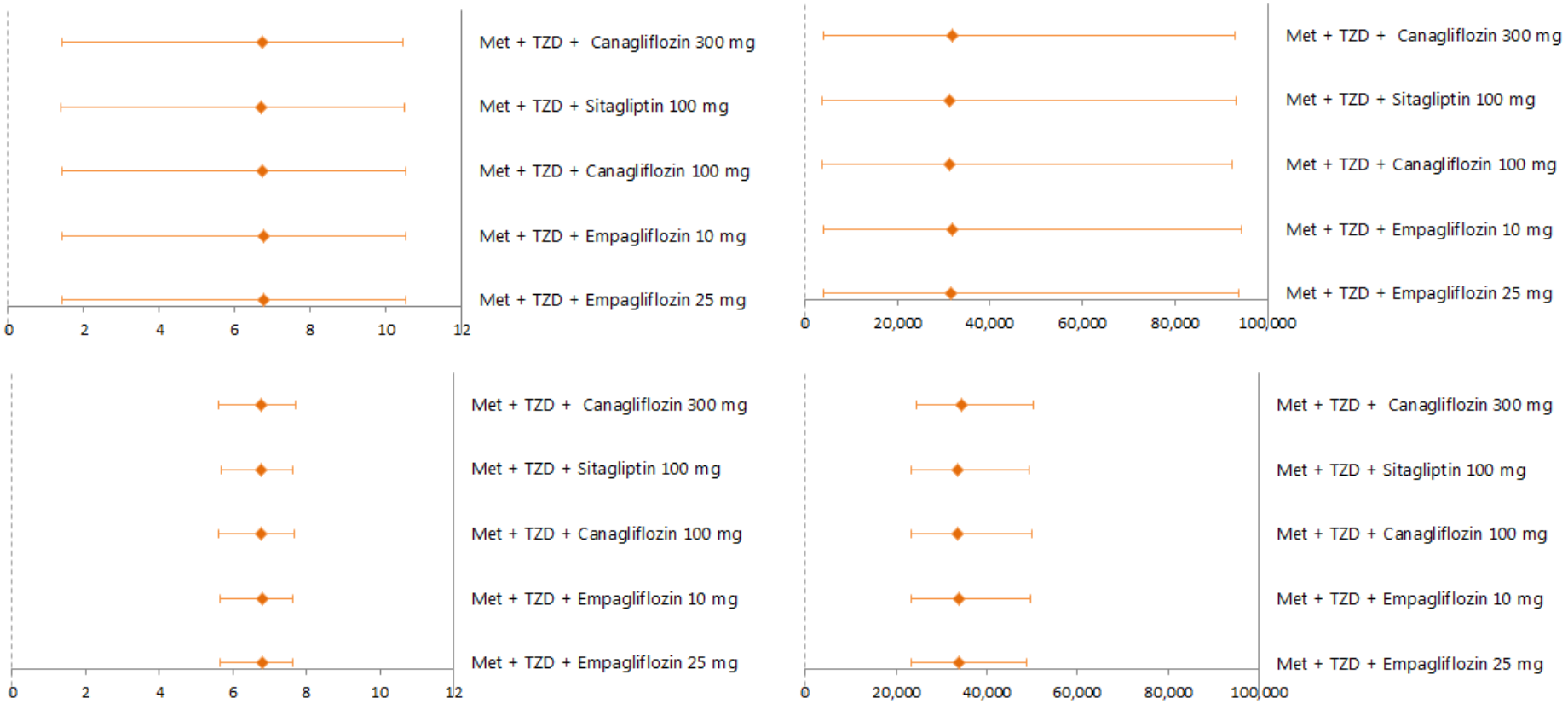
*After adjusting QALYs following ERG's comments in section 4.5.7 of the document 'ERG report – factual error check'.

Figure 2. QALYs and costs (and corresponding 95% percentile confidence intervals) obtained with 3rd line therapies (metformin+SU background) based on ECEM approach (top graphs) vs. suggested ERG approach (bottom graphs)



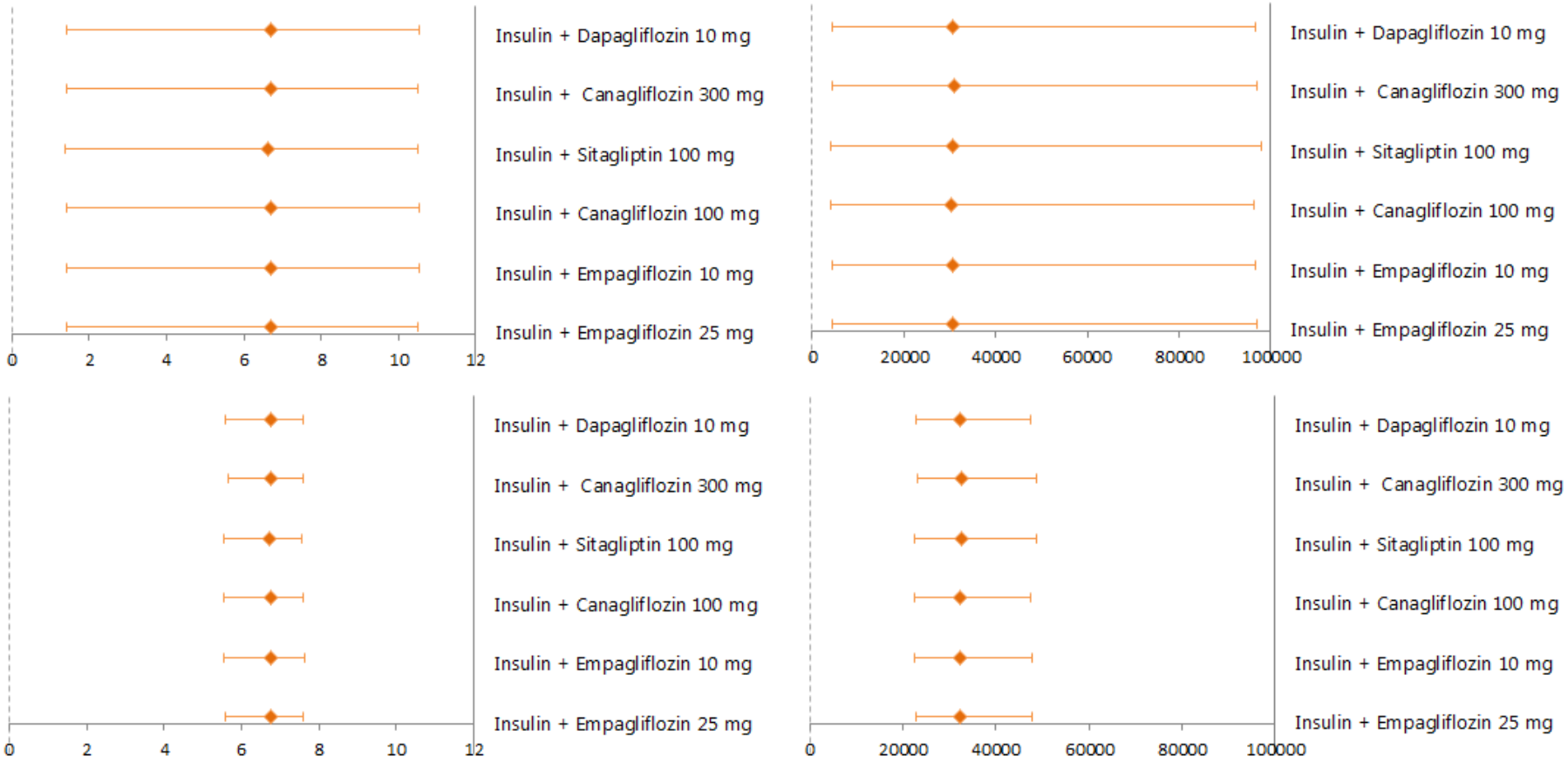
*After adjusting QALYs following ERG's comments in section 4.5.7 of the document 'ERG report – factual error check'.

Figure 3. QALYs and costs (and corresponding 95% percentile confidence intervals) obtained with 3rd line therapies (metformin+TZD background) based on ECEM approach (top graphs) vs. suggested ERG approach (bottom graphs)



*After adjusting QALYs following ERG's comments in section 4.5.7 of the document 'ERG report – factual error check'.

Figure 4. QALYs and costs (and corresponding 95% percentile confidence intervals) obtained with insulin add-on therapies based on ECEM approach (top graphs) vs. suggested ERG approach (bottom graphs)



*After adjusting QALYs following ERG's comments in section 4.5.7 of the document 'ERG report – factual error check'.