NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dapagliflozin in triple therapy regimens for treating type 2 diabetes

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dapagliflozin in triple therapy regimens for treating type 2 diabetes

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical

- This is a part-review of TA288:
  - There are currently 3 SGLT2s recommended by NICE in combination therapy regimens for treating type 2 diabetes – dapagliflozin (TA288), canagliflozin (TA315) and empagliflozin (TA336).
  - All 3 SGLT2s are recommended as dual therapy, however dapagliflozin is the only SGLT2 not recommended as triple therapy (because of a lack of evidence).
  - This part-review will consider the negative triple therapy recommendation (taking into account new evidence compared with placebo).
- The scope included people whose disease was not controlled on metformin and SU, **and** people whose disease was not controlled on metformin and DPP4

inhibitors. The company excluded the latter population, citing a lack of evidence. Is this appropriate?

- What are the main comparators for dapagliflozin in triple therapy? The company excluded injectable treatments (insulin and GLP1s, because it stated oral treatments would be used prior to injectable treatments), and pioglitazone (because it stated pioglitazone was rarely used in clinical practice). Are these exclusions appropriate?
- The ERG stated that the company could have included more relevant clinical trial data from the subgroups of other trials. Did the company extract and present all relevant clinical trial data?
- Some of the results of the network meta-analysis were not consistent with the individual trial data feeding into the network. Are the results of the company network meta-analysis plausible?
- Are the efficacy and side effect profiles of the SGLT2s inhibitors sufficiently similar for them to be regarded as a class, and are DPP4 inhibitors the main comparator agents?
- The dapagliflozin trials recruited globally with limited enrolment from the UK. Does the committee consider that the trial data are generalisable to the patient population in England?

Cost

- Dapagliflozin is the only SGLT2 inhibitor not recommended for triple therapy (canagliflozin and empagliflozin are both recommended as triple therapy, but dapagliflozin was not because of a lack of evidence). All SGLT2 inhibitors have the same costs and similar effectiveness. Is there a case for a pragmatic positive recommendation?
- The company used the older UKPDS event equations, rather than using the newer equations which are informed by more follow-up data and have differing rates for certain events. Should the company have used the newer equations?
- Dapagliflozin costs the same as other SGLT2s (all 3 have annual treatments costs of £477), but is more expensive than DPP4 inhibitors (which has an annual treatment cost of £424.50, based on a company estimate using a weighted [by market share] average of several DPP4 inhibitors).

- For the costs of complications, the company used an older version of UKPDS (65), rather than the updated costs from UKPDS 84. Should the company have used the newer source?
- The costs are affected by whether oral treatments are stopped when insulin is started (as assumed in the company base case) or continued indefinitely (as assumed in the ERG base case). Would people continue on SGTL2 inhibitors as part of triple therapy once insulin is started? The company argues that few would continue on dapagliflozin after 10 years because of a decline in renal function.
- The company assumes that the weight loss for dapagliflozin is maintained for 1 year only, however the ERG suggest this is a pessimistic assumption for dapagliflozin. How long is weight loss likely to be maintained?
- The company and the ERG agree that the QALY benefits of dapagliflozin, driven by differences in the incidence of diabetes related complications and weight loss, are modest, but differ in their estimates of relative costs; the company says that dapagliflozin accrues lower costs, the ERG disagrees. What is the committee's view of the different approaches?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of dapagliflozin within its marketing authorisation for treating type 2 diabetes.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: • MET with SU • MET with DPP4	Adults with type 2 diabetes that is inadequately controlled on dual therapy with MET and SU	Not enough evidence for treatments added to MET + DPP4	Company identified 2 trials for MET + DPP4. Triple therapy with both SGLT2+DPP 4 would cost >£900 p.a., (same range as expensive

				GLP1s).
Int.	Dapagliflozin in combination with 2 other oral anti-diabetic agents			
Com.	The following in combination with 2 other oral antidiabetic agents: • other SGLT2 inhibitors • DPP4 inhibitors • pioglitazone • GLP-1 agonists • a sulfonylurea • insulin	MET + SU in combination with: • DPP4 • canagliflozin • empagliflozin	DPP4 is key comparator (62% of patients on MET+SU, add DPP4). Excluded treatments: Pioglitazone - rarely used in UK. Insulin and GLP1s - injectable and used later in treatment pathway.	Injectables not relevant: orals should be tried 1st. Pioglitazone is relevant: its use has declined, but wrong to state rarely used (>1 million prescriptions 2015).
Out.	Mortality; complications of diabetes, including cardiovascular, renal and eye; HbA1c/glycaemic control; body mass index; frequency and severity of hypoglycaemia; changes in cardiovascular risk factors; adverse effects of treatment, including urinary tract infections, genital infections and malignancies; health-related quality of life.	HbA1c; weight; systolic blood pressure	Trials did not typically report data for long-term outcomes	Company did not provide HbA1c data for dapa+ MET+DPP4. ERG agree data not available for long term outcomes e.g. mortality.
Key: DPP4: dipeptidyl peptidase 4 inhibitor; GLP: glucagon-like peptide; HbA1c: glycated haemoglobin; MET: metformin; SU: sulphonylureas				

2 The technology and the treatment pathway

2.1 Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose

levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

2.2 The ERG noted that there are now 2 fixed dose combination tablets for dapagliflozin – dapagliflozin and saxagliptin, and dapagliflozin and extended release metformin.

2.3 In 2014 there were approximately 2.8 million adults in England with diabetes, of whom 90% had type 2 diabetes. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported. The UK prevalence of type 2 diabetes is rising because of increased prevalence of obesity, decreased physical activity and increased life expectancy after diagnosis because of better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin.

2.4 Dapagliflozin (Forxiga, AstraZeneca) is a selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor, which blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine.

2.5 NICE clinical guideline 28 'Type 2 diabetes in adults: management' recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes. NICE has also produced individual guidance for canagliflozin (TA315), dapagliflozin (TA288) and empagliflozin (TA336) as combination therapies. TA315 and TA336 recommended canagliflozin and empagliflozin respectively for triple therapy in combination with metformin and a sulfonylurea (SU), or metformin and a thiazolidinedione. TA288 recommended that dapagliflozin should not be used for triple therapy except as part of a

clinical trial; this recommendation will be the subject of this appraisal (because there is new evidence now available about this recommendation). The company noted that dapagliflozin triple therapy would fit within the existing pathway at second intensification (it is already recommended as an option as dual therapy at first intensification). Figure 1 summarises the current treatment pathway.

Figure 1: Treatment pathway

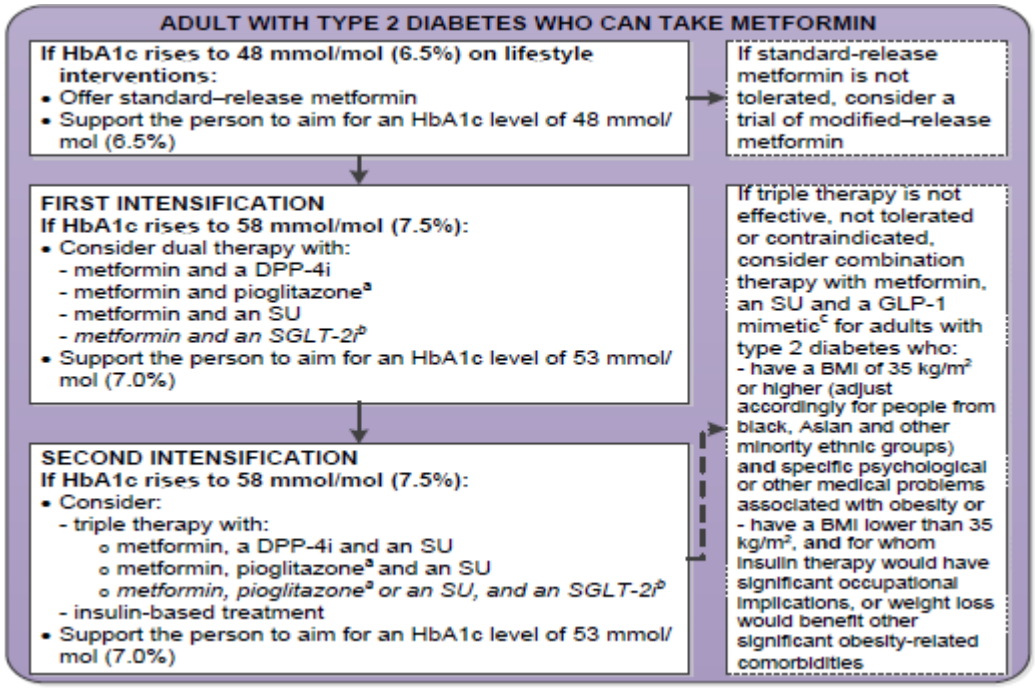

Table 2: Technology

	Dapagliflozin	**SGLT2s**	**DPP4s**
Marketing authorisation (**triple therapy wording only**)	"In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: • add-on combination therapy (in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control)".		*Several DPP4s are available (including sitagliptin, vildagliptin, and saxagliptin); the company considered DPP4s as a class. Sitagliptin (most common DPP4) has an MA as follows*: "For adult patients with type 2 diabetes mellitus, Januvia is indicated to improve glycaemic control: as triple oral therapy in combination with • a sulphonylurea and metformin when diet and

		exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. • a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control".
Administration method	Oral	Oral
Cost	£36.59 per tablet, one daily. Dapagliflozin dose is 10mg. Canagliflozin and empagliflozin have lower starting doses (100mg and 10mg respectively) and can be titrated upwards to 300mg and 25 mg respectively, if people can tolerate the lower dose, have an eGFR of 60 ml/min/1.73 m2 or more, and need tighter glycaemic control. **Annual cost £477**	Price per once-daily tablet ranges from £0.60 (vildagliptin) to £1.19 (sitagliptin and linagliptin). Weighted average (based on market share) **annual cost: £424.50.**
Key: DPP4: dipeptidyl peptidase 4 inhibitor; GLP: glucagon-like peptide; HbA1c: glycated haemoglobin; MET: metformin; PPARy: peroxisome proliferator-activated receptor; SU: sulphonylureas		

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Please see statements from clinical and patient experts.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of dapagliflozin in triple therapy regimens for treating type 2 diabetes. In total the company identified 24 trials of dapagliflozin for all indications, but it considered only 1 trial, 'Study 5' (n=219), to be relevant for this appraisal, which was a 24 week (with 28 week extension) double-blind, parallel-group, phase IIIb

randomised controlled trial comparing dapagliflozin with placebo, both of which were added to metformin and a sulphonylurea (SU). The company also presented primary care observational data from 684 practices for 480 patients who were prescribed dapagliflozin as part of a triple therapy regimen (out of a total of 1,732 patients) from the Clinical Practice Research Datalink (CPRD). As there were no direct comparisons available for people adding a third treatment to metformin and an SU, the company conducted a network meta-analysis (NMA) comparing dapagliflozin with dipeptidyl peptidase 4 (DPP4) inhibitors (as a group) and SGLT2 inhibitors (canagliflozin 100mg and 300mg, and empagliflozin 10mg and 25mg), all of which were in combination with metformin and an SU.

4.2 The company stated that it considered DPP4 inhibitors (added to metformin and an SU) to be the key comparator for this appraisal, citing company data showing 62% of adults taking a dual therapy combination of metformin and SU added DPP4 inhibitors as the third treatment. Furthermore, the company stated the following about the other comparators:

- SGLT2 inhibitors: canagliflozin and empagliflozin have the same costs and similar effectiveness as dapagliflozin, and are already recommended by NICE for triple therapy. The company stated there was a 'pragmatic' case for all 3 SGLT2 inhibitors to have the same recommendation.
- Injectable treatments: although insulin and GLP1s are an option in clinical practice, they are not typically the first addition to dual therapy, because of additional expense and requirement to inject when compared with the oral treatments available. The company therefore did not present any comparative evidence for these treatments.
- Pioglitazone: Not considered because it is rarely used in the UK. The company stated it asked 5 clinical experts about the use of pioglitazone. It reported that the clinicians stated it was rarely used, with issues including several contraindications and fracture risk making

it unsuitable for many patients. One clinical expert stated that when given the choice of treatments, most people would choose either DPP4 inhibitors (weight neutral with few adverse effects) or SGLT2s (weight loss but a risk of genital infection).

4.3 Study 5 was conducted in 46 centres across several European countries (including Germany and Spain, but not the UK) and Canada. The company stated that in general the treatment groups were balanced for baseline characteristics, including age (61 years in both groups), family origin (approximately 95% white both groups), mean HbA1c (around 8%) and mean weight (around 90kg). However it noted there were more female patients in the dapagliflozin arm (57.4%) than the placebo arm (44.4%).

ERG comments

4.4 The ERG considered 'Study 5' to be a good quality trial showing that dapagliflozin improves glycaemic control and weight loss when compared with placebo. However, it stated that the company could have provided more data comparing dapagliflozin with placebo for people whose disease was not adequately controlled on metformin and SU, by extracting data from the subgroups of other trials. Weber et al. (2015, n=449) included patients with uncontrolled diabetes and hypertension, and was not referred to in the company submission. The company stated it had excluded this trial because the population was broader than the scope population (it included people whose disease was uncontrolled on oral antihyperglycaemic drugs, insulin, or both, rather than a specific population failing on metformin and an SU, and also included sub-group data based on type of anti-hypertensive medication rather than type of oral antidiabetic treatment). However, the ERG argued the trial still contained information relevant to the decision problem, and if it had been included it could have approximately doubled the numbers of patients providing evidence for the decision problem (exact figures are not available, but at least 83 patients and probably more were on

dapagliflozin, metformin and an SU). Study 18 and 19 also included patients with uncontrolled diabetes and hypertension, and were included by the company in an appendix but were not discussed in the main submission. The ERG noted the Scottish Medicines Consortium (SMC) had referred to these trials in its appraisal of dapagliflozin combination therapy. The ERG stated these trials could have added data for an additional 441 patients.

4.5 The ERG stated that although it agreed with the exclusion of injectable treatments as comparators (because oral treatments would typically be tried first, and also because of the high costs of GLP1s), the main issue with the company submission was the exclusion of pioglitazone as a comparator. The company had cited a lack of use of pioglitazone in clinical practice as the reason for its exclusion. However, the ERG stated that this was incorrect. Although the use of pioglitazone had declined in clinical practice because it is associated with oedema (which can precipitate congestive heart failure), weight gain, a small increased risk of bladder cancer (although the evidence is inconsistent and recent evidence is "largely reassuring"), and occasional fractures, the ERG cited Prescription Cost Analysis data for England showing more than 1 million prescriptions for pioglitazone in 2015. The ERG also noted that pioglitazone is associated with some cardiovascular benefits (reduced risk of myocardial infarction) and is useful for people with diabetes who also have non-alcoholic fatty liver disease, plus it is generic and substantially cheaper than those of newer drugs (although it noted that there had been a recent large increase, 10-fold compared with previous year, in the costs of pioglitazone). The ERG stated that the company should have included pioglitazone in its analyses, and the ERG included pioglitazone in its own cost-effectiveness analyses.

4.6 For the population of Study 5, the ERG noted that no patients included were from the UK, and only 2 patients were from 'western European' countries. The ERG also noted that there were gender imbalances in Study 5, however that this was unlikely to matter because in a pooled

analysis of 10 dapagliflozin trials (not triple therapy), the effects of dapagliflozin on key outcomes did not vary by gender.

Clinical trial results

4.7 The primary outcome of Study 5 was change from baseline HbA1c at week 24. The company stated there were 4 key secondary outcomes: change from baseline to week 24 in fasting plasma glucose, total body weight, and proportion of people achieving therapeutic glycaemic response (defined as HbA1c <7.0% at week 24), and change from baseline to week 8 in systolic blood pressure. The company also reported these outcomes at 52 weeks, describing these as 'exploratory'.

The primary analysis was done on the full analysis set, which included all randomised randomised subjects (as randomised) who received at least 1 dose of study medication during study medication during the 24-week double-blind treatment period (and had data for both a had data for both a baseline and at least 1 post-baseline efficacy outcome available). Key available). Key outcomes are presented in

4.8 Table 3. The company noted that systolic blood pressure reduced from baseline to week 24 in dapagliflozin and placebo groups but then increased over the following 28 weeks in both groups, which was not consistent with results seen in other trials for dapagliflozin. It stated the increase may have been because of: changes in blood pressure medications and doses; less rigorously tested blood pressure than in a dedicated blood pressure study, and because blood pressure was an exploratory variable and therefore no adjustments were made for type 1 error. The company also noted that at 24 weeks no person receiving dapagliflozin required glycaemic rescue compared with 9% (10 patients) on placebo, and at 52 weeks 9% of people receiving dapagliflozin and 44% receiving placebo required rescue.

Table 3 Summary of primary and secondary outcomes, Study 5

		Dapa (n=108)	Placebo (n=108)
HbA1c (%)			
Week 24	Mean change from baseline (95% confidence interval [CI])	-0.86 (-1.00, -0.72)	-0.17 (-0.31, -0.02)
	Change v placebo (95% CI)	-0.69 (-0.89, -0.49); p<0.0001	
Week 52	Mean value	7.2	7.6
	Mean change from baseline (95% CI)	-0.8 (-1.0, -0.6)	-0.1 (-0.3, 0.1)
Total body weight (kg)			
Week 24	Mean change from baseline (95% CI)	-2.65 (-3.16, -2.14)	-0.58 (-1.09, -0.07)
	Change v placebo (95% CI)	-2.07 (-2.79, -1.35); p<0.0001	
Week 52	Mean	85.0	88.0
	Mean change from baseline (95% CI)	-2.9 (-3.6, -2.2)	-1.0 (-1.8, -0.1)
Fasting plasma glucose (mg/dL)			
Week 24	Mean change from baseline (95% CI)	-34.23 (-40.98, -27.48)	-0.78 (-7.56, 6.01)
	Change vs. placebo (95% CI)	-33.45 (-43.08, -23.82); p<0.0001	
Week 52	Mean	7.8 (1.9)	9.6 (2.1)
	Mean change from baseline (95% CI)	−1.5 (−1.9, −1.1)	0.6 (0.1, 1.1)
Subjects with HbA1c <7%			
Week 24	% adjusted (95% CI)	31.8% (23.3, 40.2)	11.1% (5.4, 16.8)
	Change vs. placebo (95% CI)	20.7% (10.7, 30.6); p<0.0001)	
Seated systolic blood pressure (mmHg)			
Week 8	Mean change from baseline (95% CI)	-4.04 (-6.36, -1.72)	-0.27 (-2.60, 2.05)
	Change vs. placebo (95% CI)	-3.76 (-7.05, -0.48); p=0.0250	
Week 52	Mean	134	138.0
	Mean change from baseline (95% CI)	-1.0 (-3.6, 1.6)	1.1 (-2.2, 4.5)
Note: For week 52 results, mean change from baseline is adjusted for rescue therapy.			

4.9 The company stated that the observational data from CPRD showed that improvements in HbA1c and weight were consistent with those reported in

clinical trials. The addition of dapagliflozin to a dual therapy regimen resulted in an overall reduction in HbA1c of 1.18%, and a decrease in body weight of 4.4kg over a 180 day period.

4.10 Study 5 collected quality of life data using EQ-5D, SHIELD Weight Questionnaire-9 (WQ-9), Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire and the Diabetes Treatment Satisfaction Questionnaire (DTSQ), with measurements for both treatment arms taken at baseline and week 52. The trial results showed:

- EQ5D: Patients receiving both dapagliflozin and placebo (both with metformin plus SU) maintained high health related quality of life scores over the 24 week trial period that were not statistically significantly different in either arm. Index scores for the dapagliflozin arm were 0.84 at baseline and 0.83 at 24 weeks, and for the placebo arm 0.85 at baseline and 0.83 at 24 weeks.
- IWQOL-Lite and DTSQ: In both arms scores improved from baseline to week 52, with no statistically significant differences between groups ($p>0.20$).
- SHIELD: A numerically greater proportion of the dapagliflozin group reported improvement in all nine SHIELD WQ-9 items compared with placebo, and the difference was statistically significant for physical health ($p=0.017$). Over 52 weeks of therapy, patients maintained their health status and health related quality of life when dapagliflozin was added to the treatment.

ERG comments

4.11 For Study 5, the ERG noted that the company had used last observation carried forward (for missing values) for some outcomes. However it stated that this approach may not be appropriate, because the missing results were not missing at random. It also noted that systolic blood pressure had increased from week 24 to week 52. The company explained this was inconsistent with other trials, however the ERG stated it was unclear what evidence the company were basing this explanation on, because the other

trials did not report systolic blood pressure for dapagliflozin at 52 weeks. For the observational data from CPRD, the ERG noted that the HbA1c reductions were higher in absolute terms than the trial data, however the ERG stated this should be considered in the context of higher baseline HbA1c in CPRD (and therefore the relative change in the observational evidence may not be higher than that shown in the trial).

4.12 For a population whose disease was not controlled on metformin and DPP4 inhibitors (a scope population excluded by the company because of a lack of comparative evidence) the ERG stated there are patients with contraindications to pioglitazone and others in whom the risk of hypoglycaemia might be seen as too high with an SU, and therefore there may be a place for triple therapy in this combination. However, it accepted that the costs would mean this combination was unlikely be cost-effective (the combination would probably cost over £900 per year).

Meta-analyses/indirect comparison/MTC

4.13 The company conducted a network meta-analysis comparing dapagliflozin with SGLT2 inhibitors (canagliflozin 100mg and 300mg, and empagliflozin 10mg and 25mg), and DPP4 inhibitors (as a class – the company stated it took this approach because there is published evidence that DPP4 inhibitors are non-inferior to each other), all in combination with metformin and an SU. Outcomes were HbA1c, systolic blood pressure, change in total body weight, and any hypoglycaemic event. The network included 50 trials, with only 1 providing data for dapagliflozin. Not all analyses included all trials. The company presented results for 4 separate network meta-analyses, some using an expanded network (which included all relevant trials in the systematic review) and one using a restricted network (where trials had to include at least one of the key comparators DPP4 inhibitors; canagliflozin and empagliflozin) . The network meta-analyses were: those reporting outcomes at 24 weeks (expanded network), 52 weeks (expanded network), ‘study endpoint’ (expanded network, with studies included irrespective of duration), and ‘base case’ (restricted network, with

studies included irrespective of duration; included 7 to 14 studies depending on outcome). The company stated that the 'base case' network meta-analysis focused only on studies that evaluated comparators directly relevant to UK clinical practice (DPP4 inhibitors and other SGLT2 inhibitors) because of the heterogeneity in the evidence base in terms of the patient populations, study design and study duration. The company performed fixed and random effects analyses for all outcomes, and Table 4 presents the outcomes used in the company model (that is, 'base case' results only, using random effects results for outcomes HbA1c, weight and systolic blood pressure, and fixed effects for hypoglycaemia). Please see company submission pp.81 to 90 for other networks. Mean change in HbA1c, weight and SBP were analysed using the mean difference scale, and the proportion of subjects with any hypoglycaemia used an odds ratio (OR). All results are presented for dapagliflozin 10 mg dose compared with relevant comparators.

Table 4: Network meta-analysis results used in company model

HbA1c	
DPP4 inhibitors	-0.06 (-0.43, 0.33)
Canagliflozin 300mg	0.24 (-0.19, 0.64)
Canagliflozin 100mg	0.02 (-0.44, 0.44)
Empagliflozin 25mg	0 (-0.52, 0.52)
Empagliflozin 10mg	0 (-0.51, 0.52)
Placebo	-0.7 (-1.06, -0.34)
Weight	
DPP4 inhibitors	-2.33 (-4.17, -0.49)
Canagliflozin 300mg	-0.14 (-2.3, 2.02)
Canagliflozin 100mg	-0.42 (-2.78, 1.95)
Empagliflozin 25mg	-0.2 (-2.46, 2.04)
Empagliflozin 10mg	-0.1 (-2.33, 2.15)
Placebo	-1.9 (-3.61, -0.18)
Systolic blood pressure	
DPP4	-4.96 (-17.82, 8.41)
Canagliflozin 300mg	1.05 (-9.27, 11.65)
Canagliflozin 100mg	1.67 (-8.78, 12.07)
Empagliflozin 25mg	0.06 (-11.36, 11.78)
Empagliflozin 10mg	0.19 (-11.31, 11.92)
Placebo	-2.04 (-10.51, 6.45)
Any hypoglycaemic event	

DPP4	1.14 (0.48, 2.92)
Canagliflozin 300mg	0.96 (0.39, 2.5)
Canagliflozin 100mg	0.97 (0.38, 2.59)
Empagliflozin 25mg	1.68 (0.63, 4.67)
Empagliflozin 10mg	1.46 (0.55, 4.01)
Placebo	2.09 (0.9, 5.19)

4.14 The company stated the following as the key findings of the network meta-analysis: there were no statistically significant differences between dapagliflozin and the DPP4 inhibitors in change from baseline in HbA1c and SBP and the incidence of 'any hypoglycaemic event'; there was a significantly greater reduction in total body weight with dapagliflozin compared with DPP4 inhibitors; and dapagliflozin had a similar efficacy and safety to the other SGLT2 inhibitors. The company also noted that the data for comparisons with higher doses of canagliflozin (300mg) and empagliflozin (25mg) were taken from trials where patients could start on these higher doses, rather than titrate to it as would be required in clinical practice, and that these were not licensed starting doses.

4.15 The company conducted sensitivity analyses. The company stated that the results of the sensitivity analysis were consistent with those from the base case with the following exceptions:

- Removing poor quality studies:
  - A statistically significant result for change in total body weight for dapagliflozin compared with placebo was not shown in the random effects model (-1.89, 95% CI -3.91, 0.11)
- Removing sub-group studies:
  - A statistically significant result for change in HbA1c favouring canagliflozin 300mg compared with dapagliflozin was shown in the fixed effects model only
  - A statistically significant result for change in total body weight for dapagliflozin compared with DPP4 inhibitors was not shown in the random effects model (-2.16, 95% CI -4.71, 0.41)

  - A statistically significant result for change in total body weight for dapagliflozin compared with placebo was not shown in the random effects model (-1.89, 95% CI -4.23, 0.45)
- Removing studies increasing heterogeneity:
  - A statistically significant result for change in HbA1c favouring canagliflozin 300mg compared with dapagliflozin was shown in the fixed effects model only.

4.16 The company noted limitations of its network meta-analysis. It stated that the majority of studies were of 24 weeks duration, and there was variation in the longer duration of outcome data (52 weeks for canagliflozin and dapagliflozin studies, and 76 weeks for empagliflozin). However it stated that there is no clinical rationale to expect a different treatment effect for the SGLT2 inhibitors at these different time points. For systolic blood pressure, there were a relatively small number of trials available for the network (7 trials included). For hypoglycaemia, the company stated the evidence base was limited because there were differences in how it was defined across studies, with a lack of adequate definition in many trials.

ERG comments

4.17 The ERG reviewed the trials included in the company networks. It stated that the company should have excluded 1 of the included trials (Nogueira et al.) because it had no metformin and SU arm, and should have included 2 other trials (Charpentier et al. and Home et al.), which included pioglitazone (a comparator excluded by the company but included in the ERG analyses).

4.18 The ERG noted that the company had grouped DPP4 inhibitors as a class in the network. It stated that 'lumping' evidence together in this manner can affect consistency, lead to heterogeneity, cause difficulties in interpreting results, and possibly create conflict between direct and indirect evidence.

4.19 The ERG stated that there were limited data on baseline characteristics for people in the NMA, and the possible effects the trial populations may

have had on the results. The trials included in the NMA had varied characteristics for average age (55 to 62 years), sex (37.5% to 64.1 % male), HbA1c (8.1 to 8.8%) and duration of diabetes (7.3 to 10.9 years), therefore it may have been beneficial to study the effect of these characteristics using meta-regression. The ERG also stated that the company submission was not always clear about the quantity of evidence underpinning some analyses. In some instances, analyses were based on 1 trial only, which highlighted limitations in evidence base for some areas which could have led to wider credible intervals.

4.20 The ERG agreed with the company that when interpreting the results for the higher doses of canagliflozin (300mg) and empagliflozin (25mg), it should be noted that the higher doses are not licensed starting doses.

4.21 The ERG stated it had concerns about the NMA results, because some outcomes were not consistent with the trial data. For example, it was not credible that the risk of severe hypoglycaemia was higher on dapagliflozin (0.04) than intensive insulin therapy (0.022). The ERG stated that it did not regard dapagliflozin as causing hypoglycaemia. The ERG also noted:

- DDP-4 inhibitors: the results for DPP4 inhibitors for HbA1c reduction and weight change in the NMA (-0.79% and +0.12kg respectively) were favourable when compared with other sources (e.g. the sitagliptin trial average was 0.68% HbA1c reduction, and a meta-analysis by Craddy et al. showed a 0.52kg weight gain). Also the NMA showed a systolic blood pressure increase of 1.85mmHg, however none of the individual trials that reported systolic blood pressure had such high estimates.
- Dapagliflozin: The NMA HbA1c reduction was 0.85%, weight reduction 2.2kg, and SBP reduction 3.3mgHG, however the only dapagliflozin trial used in the NMA reported less favourable values (0.70% HbA1c reduction, 1.9kg weight reduction, 1mmHG SBP reduction at 52 weeks). For hypoglycaemia, the NMA figures were generally higher than those seen in the trial.

- Canagliflozin and empagliflozin: HbA1c, weight and systolic blood pressure reductions were all higher than those reported in the trial.

The ERG replaced several company NMA effectiveness assumptions with trial data in its model (see Table 6).

Adverse effects of treatment

4.22 The company presented data on adverse events. It stated that the adverse events reviewed in the dapagliflozin trials were similar to those observed in clinical practice. The dapagliflozin studies specifically monitored for hypoglycaemia and showed a low incidence, and no major events. In addition to hypoglycaemia, adverse events of special interest included urinary and genital tract infection. These were monitored because it was hypothesised that increasing urinary glucose through the SGLT2 mechanism of action may promote microbial growth. The company noted a higher incidence of urinary and genital tract infection in the trials, however it stated that overall the incidence was modest, and mild or moderate in severity. The company stated that dapagliflozin was well tolerated, with a similar proportion of adverse events in both groups, however there were more serious adverse events in the placebo group. Please see pp.95-102 in the company submission for more information about adverse events.

4.23 The company also presented data it had previously presented to the US Food and Drug Administration (FDA). This included a cardiac event meta-analysis (21 trials, n=9,000) presented to the FDA's Endocrinologic & Metabolic Drug Advisory Committee (EMDAC) in December 2013. This showed that dapagliflozin was not associated with an increased risk of cardiovascular events for a composite of cardiovascular death, myocardial infarction, stroke and hospitalisation for unstable angina. It also presented data about malignancy risk, which showed no statistically significant increases in risk between dapagliflozin and control group.

ERG comments

4.24 The ERG agreed with the company comments that dapagliflozin is associated with an increase in urinary and genital tract infections that were mild or moderate in severity, which usually occurred within the first 6 months of treatment, were more common in women, and were amenable to standard treatment.

4.25 The ERG noted that the US FDA had issued a warning about acute kidney injury with dapagliflozin and canagliflozin (but not empagliflozin) after reports of 101 cases (73 canagliflozin, 28 dapagliflozin) where 4 patients died. The warning was recently (June 2016) "strengthened" by the FDA, who recommended that health professionals should consider if there are any factors that would predispose patients to acute kidney injury before starting treatment with canagliflozin or dapagliflozin.

4.26 The ERG stated there were reports of diabetic ketoacidosis with SGLT2 inhibitors, however the European Medicines Agency (EMA, Feb 2016) stated that DKA should be seen as a rare adverse event associated with SGLT2 inhibitors (affecting approximately 1 in 1,000 patients).

5 Cost-effectiveness evidence

Model structure

5.1 The company did a literature search to identify studies evaluating the cost effectiveness of dapagliflozin and comparator drug triple therapy for type 2 diabetes. It identified 10 relevant economic evaluations that reported cost per QALY outcomes in a UK healthcare setting for people adding a third treatment to metformin and an SU. The company summarised all 10 economic evaluations as follows: all studies used a lifetime horizon, all used risk equations from the UK Prospective Diabetes Study (UKPDS) to estimate long term outcomes associated with the incidence of complications, several different economic models were used (including CORE, ECHO and the Cardiff model), and 7 of the studies were used as part of a health technology assessment. Two of the economic evaluations

were cost-utility studies of dapagliflozin triple therapy in the Scottish healthcare system, comparing dapagliflozin with DPP4 inhibitors (both in combination with metformin and an SU). These studies used the same economic model as that used in this NICE appraisal submission. The studies both showed an ICER of £10,995 per QALY gained (incremental costs £253, incremental QALYs 0.023).

5.2 The company presented a new health economic analysis, using the Cardiff diabetes model with a Microsoft Excel 'front end'. It stated that its cost-effectiveness model only included a population whose disease was not controlled on dual therapy with metformin and SU, because there was not enough evidence to compare treatments for the other population in the scope (people whose disease was not controlled on metformin and DPP4 inhibitors). It also stated that DPP4 inhibitors are the most commonly used comparator. Patients entered the model on dual therapy with metformin and SU and received the addition of either dapagliflozin, SGLT2 inhibitors (canagliflozin 100mg and 300mg, and empagliflozin 10mg and 25mg) or DPP4 inhibitors (as a class). This treatment then determined the initial change in "intermediate" outcomes HbA1c, total body weight, total cholesterol, high density lipoprotein (HDL) cholesterol and systolic blood pressure. These outcomes progressively worsened over time and when HbA1c rose above 7.5%, it triggered the initiation of another treatment (which improved the outcome, followed by another progressive worsening of disease). The model also included health states for "final" outcome measures, for micro- and macro-vascular disease. Microvascular health states were amputation, nephropathy and blindness. Macro-vascular health states were ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure. The model also accounted for hypoglycaemia, urinary tract infections (UTIs), and genital tract infections (GIs). The time horizon was 40 years, the cycle length was 6 months, and costs and benefits were discounted at 3.5%.

5.3 The company assumed that patients received a pre-specified treatment sequence after triple therapy, which was the same in all arms. Modelled

patients first switched to metformin and insulin, followed by metformin and intensified insulin (defined as a 50% increase in the original dose of insulin). Patients could discontinue treatment because of adverse events. The company assumed that after discontinuation patients moved to the next line of treatment, but modelled patients could not discontinue the third (final) line of therapy, and were assumed to receive this treatment for the remainder of the model.

5.4 Table 5 shows baseline variables in the company model. The base case included a mixture of data from Study 5 and the THIN database (UK primary care data used in NG28). Scenario analyses replaced some base-case values with values from THIN.

Table 5: Summary of patient baseline variables in company model

	Base case (Study 5)	Scenario (THIN)
Demographics		
Current Age (years)	61.0	65.4
Proportion female	0.51	0.44
Duration diabetes (years)	9.45	8.5
Height (m)	1.68	
Proportion smokers	0.1900	
Modifiable risk factors		
HbA1c (%)	8.15	7.9
Total-Cholesterol (mg/dL)	211.97	
HDL Cholesterol (mg/dL)	46.72	
Systolic blood pressure (mmHg)	135.40	143.2
Weight (kg)	89.35	86.7
Clinical event history		
Atrial fibrillation	0.0063	
Peripheral vascular disease	0.0047	
Ischaemic heart disease	0.097	
Myocardial infarction	0.025	
Congestive heart failure	0.023	
Stroke	0.018	
Amputation	0.004	
Blindness	0.022	
End-stage renal disease	0.01	

ERG comments

5.5 The ERG noted that the model used by the company (C++) has been used for previous NICE appraisals, and was checked by the NICE decision support unit (DSU) during a previous dapagliflozin appraisal. However, the ERG was unable to validate all analyses conducted by the company because the model lacked transparency and took a long time to run.

5.6 The ERG stated there was an error in the model in switching therapies, because when HbA1c rose above 7.5%, people remained on dapagliflozin for 1 cycle before moving to the next line of treatment, whereas people remained on DPP4 inhibitors for 2 cycles. The ERG stated that this may exaggerate differences in treatment costs.

5.7 The ERG noted that the model had a 6 month cycle length, however patients could only intensify at the end of a year. The ERG stated that typically, a 6 month cycle would be used to allow patients to intensify treatment more promptly, therefore the ERG was unclear why the company had chosen this cycle frequency. It stated that this increased the risk of error with no gain in model accuracy.

Model details

Clinical effectiveness

5.8 The company used the results of its network meta-analysis for the treatment effect of all modelled interventions (other than metformin plus insulin and intensified insulin which were taken from the literature) on HbA1c, weight, systolic blood pressure and symptomatic hypoglycaemia. Progressive worsening of intermediate outcomes over time was modelled using UKPDS68 for HbA1c, systolic blood pressure, and TC:HDL (the ratio of total cholesterol to HDL cholesterol), and the company assumed weight gain of 0.1kg per year. UKPDS was also used for all-cause mortality, and for the 10 year risk of micro- or macro-vascular events in the model, which also varied over time according to patient age, duration of diabetes, gender, ethnicity, smoking status, and intermediate outcomes (HbA1c etc.). Because of a lack of trial data for dapagliflozin, the company derived the treatment effect for severe hypoglycaemia, UTIs and GTIs from canagliflozin trial data, and did not include a treatment effect for total or HDL cholesterol. Table 6 shows the treatment effect assumptions used in the company model, and also the ERG model (who changed several assumptions, see section 4.21).

Table 6: Clinical effectiveness assumptions used in company and ERG base cases

	Change from baseline			Prob. Disc.	No. of hypo (sympt)	Prob. Hypo (severe)	Prob. UTI	Prob.GI
	HbA1c (%)	Weight (kg)	SBP (mmHg)					
Company base case model assumptions								
DPP4	-0.79	0.12	1.85	0.029	0.181	0.034	0.021	0.056
Dapagliflozin	-0.85	-2.20	-3.13	0.053	0.202	0.04	0.119	0.04
Empa 10mg	-0.85	-2.10	-3.30	0.053	0.148	0.04	0.119	0.04
Empa 25mg	-0.85	-2.00	-3.19	0.053	0.131	0.04	0.119	0.04
Cana 100mg	-0.87	-1.78	-4.82	0.053	0.208	0.04	0.119	0.04
Cana 300mg	-1.09	-2.06	-4.16	0.053	0.208	0.04	0.119	0.04
MET+ insulin	-1.1	1.08	0.00	0	0.0108	0.037	0.00	0.00
Int insulin	-1.11	1.90	0.00	0	0.616	0.022	0.00	0.00
ERG base case model assumptions								
DPP4	-0.76	+0.52	0.5	0.015	0.270	0.013	0.056	0.021
Dapa	-0.70	-1.90	-2.00	0.019	0.073	0.00	0.101	0.101
Empa 10mg	-0.70	-1.75	-2.20	0.053	0.148	0.00	0.119	0.04
Empa 25mg	-0.70	-1.75	-2.20	0.053	0.131	0.00	0.119	0.04
Cana 100mg	-0.62	-1.25	-2.90	0.053	0.208	0.08	0.119	0.04
Cana 300mg	-0.77	-2.50	-2.50	0.053	0.208	0.05	0.119	0.04
MET+ insulin	-1.11	1.80	0.00	0.10	0.610	0.013	0.00	0.00
Int insulin	-0.66	+0.80	0.00	-	0.380	0.007	0.00	0.00
SA insulin	-0.66	+ 0.80	0.00	-	0.380	0.007	0.00	0.00
Pioglitazone	-0.87	+2.20	-0.50	-	0.116	0.00	0.00	0.00

Key: Cana: canagliflozin; Empa: empagliflozin; GI: genital tract infection; Int: intensified; MET: metformin; prob: probability; SA: short acting; sympt: symptomatic; UTI: urinary tract infection

ERG comments

5.9 The ERG stated that the weight loss assumption used in the model (that any weight loss only lasted for 1 year) was a conservative assumption. It would have been reasonable for the company to assume weight loss was maintained for a longer period, with evidence from a pooled analysis by Fioretto et al. showing weight loss was maintained at 104 weeks.

5.10 The ERG noted that the company had used UKPDS 68 equations in its model to predict the incidence of specific macro and micro-vascular complications. However, UKPDS 68 has been partially updated by UKPDS 82, which includes more follow-up data, and so may better reflect the current management of diabetes. Also, the newer equations show a lower incidence of myocardial infarction, renal failure and deaths. The ERG stated using the older equations may therefore overestimate patient gains and reduce costs for the more effective treatment (because the more effective treatment will be less affected by the overestimated incidence of adverse events and death in UKPDS68). In addition, the ERG noted that some equations in UKPDS 68 make a distinction between values at baseline, and values at diagnosis (for outcomes such as HbA1c). However the company assumed these values were both the same, which was not likely to be correct. The ERG stated that the impact of this would be to overestimate complication rates and deaths. It attempted to explore this in a scenario analysis, however changing the values so that values at baseline and at diagnosis were different for outcomes HbA1c, SBP and cholesterol ratio had no effect on results, suggesting that this assumption could not be modified in the model.

5.11 The ERG noted that for baseline patient characteristics, baseline continuous values such as HbA1c were not sampled (all patients entered the model with approximately the same baseline patient characteristics). The ERG stated this may polarise the analyses, because all patients receiving a particular treatment will intensify at a similar time. The ERG

stated that sampling baseline HbA1c could reduce this, and that it explored the impact of doing this in a scenario analysis.

5.12 The ERG noted that each treatment in the model had different discontinuation rates. However, an NMA of discontinuation rates provided by the company showed wide, overlapping confidence intervals for the discontinuation rate of each treatment. In addition, the company assumed that after discontinuation, patients moved directly to receive insulin rather than attempting another triple therapy regimen. The ERG stated therefore that it may be preferable to assume no discontinuations in the model.

5.13 The company used its network meta-analysis for the effectiveness of treatments in the model. The ERG explored alternative values in its own base case by replacing some values taken from the NMA with trial data, because of concerns about the lack of consistency between trial and NMA data for some outcomes (see section 4.21).

Utility

5.14 The company presented quality of life data from its pivotal trial, Study 5 (section 4.10). However, it did not use the results in the model, stating that it had identified a non-significant difference between treatments arms, and also because it considered that the quality of life data from a 52 week period would not be suitable for a model with a 40 year time horizon.

5.15 The company did a systematic literature search to identify health related quality of life studies for people with type 2 diabetes. It identified 13 relevant studies that reported utility values. The company summarised the studies identified as follows: many of the studies used the EQ-5D (tariff and visual analogue score), and the studies reported utility or disutility values for the complications of type 2 diabetes, the relationship between weight or BMI and utility (and found a significant correlation between increased BMI or weight and disutility using EQ5D and other recognised methods), and the disutility associated with hypoglycaemia or further hypoglycaemic episodes.

5.16 Patients entered the model with a baseline utility of 0.87, derived from age-adjusted Health Survey for England data for a person aged 61. Baseline utility declined as patients got older in the model, based on EQ5D data by age. Modelled patients also experienced event-specific utility decrements. For patients experiencing more than one complication, the disutility was additive. For complication events (micro and macrovascular health states) the disutility was applied in the cycle of the event and all cycles thereafter, whereas those associated with adverse events (hypoglycaemia and urinary and genital tract infections) were only applied in the event cycle. The incidence of events influenced future disutility values. In addition, a change in utility was assumed when there were changes in body weight. Table 7 lists utility values and sources.

Table 7: Utility decrements in company model

Type 2 diabetes related complications	Utility decrements	Source:
Ischemic Heart Disease	-0.09	UKPDS62
Myocardial infarction	-0.055	
Congestive Heart Failure	-0.108	
Stroke	-0.164	
Blindness	-0.074	
Amputation	-0.28	
End stage renal disease	-0.263	Currie (2005), using HODAR, a Welsh T2DM database
For each unit decrease in BMI	±0.0061	Bagust (2005), observational database (n=4,600) using TTO
Urinary tract infection	-0.00283	Barry (1997), cost-utility study of office based strategies
Genital tract infection	-0.00283	
Hypoglycaemic event	Not stated	Currie (2006), statistical model for fear of hypoglycaemia (n=1,305)
Key: HODAR: health outcomes data repository; TTO: time trade off		

ERG comments

5.17 The ERG stated that the utility values from Currie et al. (2006, used for the disutility for fear of hypoglycaemia) had major caveats, including that values were based on results from two surveys with a response rate of 31%, 45% of respondents were on insulin, that respondents may have

been more likely to have been concerned about hypoglycaemia than non-respondents, and around one third of respondents had type 1 diabetes.

Costs

5.18 Table 8 outlines the drug costs used in the model. The company used BNF (2015) for drug costs. For DPP4 inhibitors, the company used a weighted average (based on market share of those added to metformin and SU) of 5 DPP4 inhibitors used in clinical practice in England and Wales. Sitagliptin had the highest market share with 71%. The company stated it used the lowest non-proprietary cost for metformin, and used the cost of gliclazide as the cost for SU (although the ERG stated the company had omitted the costs of metformin and SU from its base case, see section 5.25). For NPH (human neutral protamine Hagedorn) insulin regimen, the company used the lowest cost available (Insuman Basal). The cost of insulin in the model was applied as a cost per kg per day based on the estimated baseline weight of 86.7 kg from the THIN NG28 second intensification data.

5.19 The company assumed that oral treatments were ceased when intensifying to insulin. The company asked 5 clinical experts about this assumption. One of the clinical experts stated that the retention of oral therapies when intensifying to insulin would depend on the insulin regimen. If using a basal only insulin then the clinical expert stated they would continue using metformin and an SU but stop the DPP4 or SGLT2, and consider reintroducing either drug if the insulin dose reached 40+ units, or if the patient was overweight. If using a twice daily biphasic insulin then the clinical expert stated they would continue using metformin but reduce the SU by 50%, with the aim of stopping treatment as the insulin dose was titrated upwards. DPP4s or SGLT2s would also be stopped but again consideration would be given to reintroducing it if the insulin dose reached more than1 unit/kg or if the patient was overweight.

Table 8: Drug costs in company model

Therapy	Price per tablet	Dose per tablet	Daily dose	Annual cost
Dapagliflozin	£1.31	10 mg		£476.92
DPP4 inhibitors:				
Sitagliptin	£1.19	100 mg		£433.57
Saxagliptin	£1.13	5 mg		£411.92
Vildagliptin	£0.60	50 mg		£434.74
Linagliptin	£1.19	5 mg		£433.57
Alogliptin	£0.95	25 mg		£346.75
Weighted average	**-**	**-**	**-**	**£424.50**
SGLT2 inhibitors				
Canagliflozin	£1.31	100/300 mg		£476.93
Empagliflozin	£1.31	10/25 mg		£476.98
Other:				
SU (Gliclazide)	£0.04	80 mg	160 mg	£29.46
MET	£0.03	850 mg	1900 mg	£25.29

5.20 The company assumed there were no costs of administration for any treatment in the model, as most therapies were oral, other than insulin, which was assumed to be self-administered. The company included additional costs of renal monitoring for dapagliflozin and other SGLT2 inhibitors, because its effectiveness is dependent on renal function and it is not recommended for people with renal impairment. This included one GP visit of £45 and a 24 hour urine creatine clearance test (£2, NHS reference costs). A one-off GP visit (cost £45) was assumed when patients discontinued treatment. Table 9 shows the health state costs.

Table 9: Health state costs

Event	Fatal	Non-fatal	Maintenance
No complication	NA	£465	NA
Ischaemic heart disease	NA	£3,346	£1,105
Myocardial infarction	£1,695	£6,451	£1,062
Congestive heart failure	£3,731	£3,731	£1,308
Stroke	£4,977	£3,946	£746
Amputation	£12,847	£12,847	£742
Blindness	NA	£1,685	£714
End stage renal disease	£35,715	£35,715	£35,631

5.21 The company included costs for adverse events. Costs associated with hypoglycaemia were £380 for a severe episode, taken from Hammer et al (UK non-random sample of people with type 2 diabetes on insulin based treatment). This cost was inclusive of a wide range of direct health care costs including primary care visits, hospital costs, and out of hospital health care professional contacts, ambulance services and drug treatment. UTI and GI adverse event and treatment discontinuation costs: £45 (for GP visit).

ERG comments

5.22 The ERG stated that in clinical practice, patients tend to retain oral therapies when intensifying to insulin, however the company assumed that patients discontinued oral therapies when starting insulin.

5.23 The ERG noted that the UKPDS cost equations had been based on an older version (UKPDS65), rather than using the more recent data available (UKPDS84).

5.24 The company included insulin and intensified insulin, which was defined as an increase of 50% in original dose. However, the ERG stated that in clinical practice, the dose of insulin would be titrated upwards to achieve glycaemic control. The ERG preference was to assume that basal insulin will be titrated to achieve target, and if that cannot be done, short-acting insulin will be added at mealtimes.

5.25 The ERG noted that the company submission listed annual costs of metformin £25.29 and of sulfonylurea £29.46, however these did not appear to have been applied in the company model. The ERG also noted that the company had excluded the costs of needles and self-monitoring of blood glucose, and had stated that the impact of this would be small because all treatments intensify at the same time, other than canagliflozin 300mg. However the ERG stated that this meant that the canagliflozin 300mg treatment arm avoided the costs of needles and blood glucose

monitoring for 1 year, because in the model people receiving canagliflozin intensified to insulin 1 year later.

Company's base-case results and sensitivity analysis

5.26 The company presented its original cost effectiveness results (hereafter referred to as the original base case). In response to a request for clarification, the company identified 3 errors (2 transcription errors, for costs and hypoglycaemia rates, and a miscalculation of drug costs), which had a minor impact on cost-effectiveness results. The company therefore presented an updated base case (hereafter referred to as base case A) – this pre-meeting briefing document only presents the results of base case A (see Table 10), please see company submission p.159 for original base case results.

Table 10: Company base case A

Treatment	Costs (£)	QALYs	ICER (£/QALY)
Absolute results (per patient)			
Dapagliflozin (dapa)	20,910	9.62	
DPP4 inhibitors	21,028	9.58	
Canagliflozin 100mg	20,844	9.62	
Canagliflozin 300mg	21,096	9.61	
Empagliflozin 10mg	20,899	9.61	
Empagliflozin 25mg	20,902	9.61	
Incremental results (per patient) (Dapagliflozin vs treatment)			
DPP4 inhibitors	-118	0.032	Dapa dominates
Canagliflozin 100mg	66	-0.001	Cana 100 dominates
Canagliflozin 300mg	-187	0.003	Dapa dominates
Empagliflozin 10mg	10	0.005	£1,965
Empagliflozin 25mg	8	0.006	£1,354
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

5.27 The company stated that the QALY gain for dapagliflozin compared with DPP4 inhibitors (0.032) is because of the superior weight reduction of dapagliflozin and its impact on health related quality of life. Compared with SGLT2 inhibitors, which cost exactly the same with no significant differences in efficacy and safety results, results showed negligible cost and QALY differences, with cost-effectiveness results a mixture of dapagliflozin dominant, cost-effective (at a maximum ICER of £20,000 per

QALY gained), and dominated. The company stated that care should be taken when interpreting these results because the small incremental results made the ICERs unstable (incremental costs ranged from -£187 to £66, and incremental QALYs ranged from -0.001 to 0.006).

ERG comments

5.28 The ERG stated that the QALY differences between SGLT2 inhibitors were so small that they should be regarded as showing no differences between the treatments.

5.29 The ERG stated that it had several differences of the opinion with the company about assumptions used in the model:

- Oral treatments when intensifying to insulin: the ERG believed that these should continue; the company assumed they ceased.
- UKPDS event equations: The ERG believed that the newer UKPDS (82) event equations should have been used; the company used UKPDS 68.
- UKPDS 68 values at diagnosis: the ERG believed the values at baseline and the values at diagnosis in UKPDS 68 event equations should be different; the company assumed they were the same
- UKPDS costs: The ERG believed that the costs of diabetes should have been taken from UKPDS 84; the company used UKDS 65
- Pioglitazone: the ERG believed that pioglitazone was a relevant comparator; the company excluded it.

5.30 The ERG stated that because the company assumed that oral therapies are discontinued when patients intensify to insulin, and because it used the more dated UKPDS 68 event equations rather than the UKPDS 82 event equations, the company submission may not provide accurate estimates of the cost effectiveness of dapagliflozin.

Company scenarios

5.31 The company did a number of sensitivity and scenario analyses. The company did not repeat the sensitivity and scenario analyses conducted for its original base case because it stated the changes were negligible and therefore the original conclusions of these analyses still held. However, it presented additional sensitivity and scenario analyses based on base case A, in response to requests from the ERG compared with DPP4 inhibitors only:

- Original base case: In scenarios including varying baseline patient characteristics and HbA1c, dapagliflozin either remained dominant or ICERs were less than £20,000 per QALY gained (the maximum ICER was £13,514, when assuming oral treatments are continued instead of ceased when intensifying to insulin). In univariate sensitivity analyses, results were most sensitive to assumptions about smoking status (this had the highest ICER, the only univariate analysis to increase the ICER to over £30,000 per QALY gained), baseline hbA1c and age. In probabilistic sensitivity analyses, when assuming a maximum ICER of £20,000 per QALY gained, dapagliflozin had a probability of cost effectiveness of approximately 50% when compared with other SGLT2 inhibitors, and 56.98% compared with DPP4 inhibitors.
- Base case A: Using alternate insulin hypoglycaemia rates, a different baseline utility value (0.85), different percentages of smokers, alternative UKPDS assumptions, adding an additional insulin disutility, and alternative costings for renal function for SLGT2s, the impacts on results were negligible. Please see clarification response tables 18 to 24.

ERG exploratory analyses

5.32 The ERG revised the company model to create its own base case, using the following new assumptions:

- Used updated clinical effectiveness estimates (some company NMA results were replaced with results taken from trial data, see section 4.21)
- Assumed patients retained oral treatments when intensifying to insulin.
- Added costs of:
  - metformin and sulfonylurea to triple therapies and insulin
  - metformin to intensified insulin.
  - self-monitoring of blood glucose costs of £51 for insulin and £119 for intensified insulin (taken from a recent NICE technology appraisal for SGLT2 inhibitors as monotherapy).
  - needle costs of £32 for insulin and an additional £32 for intensified insulin (also taken from recent NICE TA).
  - hypoglycaemia events for the insulin containing regimes.
- Included values at diagnosis in UKPDS 68 equations 11, 12 and 13 (although the ERG stated it was unclear if this had actually carried through into the main model).
- Used the more up to date UKPDS 82 event equations.
- Used THIN database values for patient characteristics complete with standard deviations.
- Added hypoglycaemia event rates for insulin plus metformin and intensified insulin plus metformin.
- Subtracted the ongoing costs for a patient with no complications from those of the costs of complications (the ERG stated this was imperfect because for patients who had multiple complications, the amount would be subtracted more than once).
- Removed standard errors from treatment costs for the DPP4 inhibitors and dapagliflozin.
- Used the UTI and GTI cost and QALY decrement estimates from the recent NICE MTA of SGLT2 inhibitors as monotherapy.
- Added pioglitazone as a comparator (the ERG noted that there had been a recent 10-fold increase in the cost of pioglitazone in eMIMS. It therefore used the BNF costs in its base case [£20.99] and the eMIMs

costs [£225] in a sensitivity analysis). The ERG also included an annual monitoring cost of £72 for BNP monitoring.

Table 11: ERG base case (dapagliflozin vs treatment)

	Incremental cost	Incremental QALY	Incremental cost-effectiveness ratio
DPP4 inhibitors	£651	0.017	£37,997
Empagliflozin 10	-£35	0.004	Dominant
Empagliflozin 25	-£35	0.003	Dominant
Canagliflozin 100	-£124	0.017	Dominant
Canagliflozin 300	£110	0.009	£12,875
Pioglitazone	£4,834	0.009	£558,000

5.33 Table 11 shows the ERG base case. The ERG stated that dapagliflozin was virtually equivalent to empagliflozin, and there were small cost and QALY differences when compared with canagliflozin 100mg and 300mg. When compared with DPP4 inhibitors, the ERG stated that it should be borne in mind that both weight gains (for DPP4 inhibitors) and losses (for dapagliflozin) were assumed to rebound to natural history after 1 year. The ERG stated that if weight gains and losses were maintained, the ICER would be £28,374 per QALY gained. Table 12 shows further scenario analyses compared with DPP4 inhibitors only, and Table 13 shows scenarios compared with all other comparators.

Table 12: ERG scenario analyses, dapagliflozin vs DPP4 inhibitors

	Δ Cost	Δ QALY	ICER
Base case	£651	0.017	£37,997
Orals discontinued	£143	0.017	£8,351
Remove placebo/natural history effect	£650	0.017	£38,147
UKPDS 68 event equations	£495	0.02	£25,329
No BMI quality of life	£651	0.012	£53,642
No patient heterogeneity sampling	£651	0.017	£37,997
PSA patient characteristics sampling	£930	0.104	£8,933
No discontinuations	£647	0.018	£36,818
Not subtracting no complication costs	£639	0.017	£37,294
No triple therapy hypoglycaemia	£651	0.01	£68,210
Company NMA: Base case random effects	£677	0.017	£40,735
Company NMA: Base case fixed effects	£677	0.017	£40,792
Company NMA: End point random effects	£681	0.015	£45,499
Company NMA: End point fixed effects	£680	0.015	£44,371
Company NMA: 24 week random effects	£694	0.003	£242k
Company NMA: 24 week fixed effects	£697	0.000	£27mn
Key: see Table 13			

Table 13: ERG scenario analyses, dapagliflozin vs SGLT2s and pioglitazone

	Empa 10	Empa 25	Cana 100	Cana 300	Pio
Base case	DomT	DomT	DomT	£12,875	£558k
Orals discontinued	£2,721	£3,261	DomT	DomT	£133k
Remove placebo/natural history effect	DomT	DomT	DomT	DomT	£440k
UKPDS 68 event equations	DomT	DomT	DomT	£8,201	£239k
No BMI quality of life	DomT	DomT	DomT	£11,940	DomD
No patient heterogeneity sampling	DomT	DomT	DomT	£12,875	£558k
PSA patient characteristics sampling	DomT	DomT	DomT	£3,284	£123k
No discontinuations	£3,729	£6,409	DomT	£27,828	£1.8mn
Not subtracting no complication costs	DomT	DomT	DomT	£12,441	£557k
No triple therapy hypoglycaemia	DomT	DomT	DomT	£80,301	£784k
Pioglitazone £225 per year	n.a.	n.a.	n.a.	n.a.	£270k
Company NMA: Base case random effects	DomD	DomD	DomD	DomD	£501k
Company NMA: Base case fixed effects	DomD	DomD	DomD	DomD	£503k
Company NMA: End point random effects	DomD	£246 SW	DomD	DomD	£454k
Company NMA: End point fixed effects	DomD	DomD	DomD	DomD	£400k
Company NMA: 24 week random effects	£18,870	DomT	DomT	DomD	DomD
Company NMA: 24 week fixed effects	£22,603	DomT	DomT	DomD	DomD

Cana: canagliflozin; DomD: dapagliflozin dominated by comparator; DomT: dapagliflozin dominant; empa: empagliflozin; k: thousand; mn: million; n.a.: not applicable; NMA: network meta-analysis; pio: pioglitazone; PSA: probabilistic sensitivity analysis

6 Equality issues

6.1 No relevant issues have been identified.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002322/WC500136024.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Dapagliflozin in triple therapy regimens for treating type 2 diabetes

Final scope

Remit

To appraise the clinical and cost effectiveness of dapagliflozin within its marketing authorisation for treating type 2 diabetes.

Appraisal objective

This appraisal is a part-review of NICE technology appraisal (TA) 288, dapagliflozin combination treatment. It will only consider recommendation 1.3 in TA288, dapagliflozin triple therapy. The other recommendations in TA288 remain extant.

Background

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy

In 2014 there were approximately 2.8 million adults in England with diabetes, of whom 90% had type 2 diabetes[i]. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported (it is estimated that there are around 590,000 people in the UK who have diabetes but have not been diagnosed[i]). The UK prevalence of type 2 diabetes is rising because of increased prevalence of obesity, decreased physical activity and increased life expectancy after diagnosis because of better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin[i].

NICE guideline (NG) 28 ‘Type 2 diabetes in adults: management’ recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes. It recommends beginning with dietary advice and increasing physical activity for all people with type 2 diabetes. If blood glucose is not adequately controlled by lifestyle interventions alone, the guideline recommends one or more oral anti-diabetic drugs, beginning with metformin. If blood glucose is not adequately controlled

following monotherapy, dual therapy should be considered followed by either the addition of insulin or triple therapy. For triple therapy, NG28 recommends considering a combination of metformin with: a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sulfonylurea, and; pioglitazone and a sulfonylurea. If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, NG28 recommends considering combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) agonist for some people with type 2 diabetes. NICE technology appraisals (TA) 315 and 336 recommended canagliflozin and empagliflozin respectively for triple therapy in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione. TA288 recommended that dapagliflozin should not be used for triple therapy except as part of a clinical trial; this recommendation will be the subject of this appraisal (because there is new evidence now available about this recommendation).

The technology

Dapagliflozin (Forxiga, AstraZeneca) is a selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor, which blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. Through this mechanism, dapagliflozin may help control glycaemia independently of insulin pathways. It is administered orally.

Dapagliflozin has a UK marketing authorisation in "adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

- Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control"

Intervention(s)	Dapagliflozin in combination with 2 other oral anti-diabetic agents
Population(s)	Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: • metformin with a sulfonylurea • metformin with a DPP-4 inhibitor
Comparators	The following in combination with 2 other oral antidiabetic agents: • other SGLT2 inhibitors • DPP-4 inhibitors • pioglitazone

	• GLP-1 agonists • a sulfonylurea • insulin
Outcomes	The outcome measures to be considered include: • mortality • complications of diabetes, including cardiovascular, renal and eye • HbA1c/glycaemic control • body mass index • frequency and severity of hypoglycaemia • changes in cardiovascular risk factors • adverse effects of treatment, including urinary tract infections, genital infections and malignancies • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Empagliflozin in combination therapy for treating type 2 diabetes' (2015). NICE Technology Appraisal 336. Review proposal date March 2018. 'Canagliflozin in combination therapy for treating type 2 diabetes' (2014). NICE Technology Appraisal 315. Review proposal date May 2017. 'Dapagliflozin in combination therapy for treating type 2

	diabetes' (2013). NICE Technology Appraisal 288. Review Proposal Date TBC. Appraisals in development (including suspended appraisals) 'Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes'. NICE technology appraisals guidance [ID756]. Publication expected May 2016. Related Guidelines: 'Type 2 diabetes in adults: management' (2015). NICE guideline 28. Review date December 2017. 'Diabetic foot problems: prevention and management' (2015). NICE Guideline 19. Review date February 2017. 'Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period' (2015). NICE guideline 3. Review date TBC. 'Diabetes in adults' (2011). NICE quality standard 6. Related NICE Pathways: Diabetes (2011). NICE pathway
Related National Policy	NHS England (2014) 'Manual for Prescribed Specialised Services'. Chapter 67. Department of Health (2001) 'National Service Framework: Diabetes'. Department of Health (2014) 'NHS Outcomes Framework 2015-16'. Domains 1 to 5.

References

[i] Diabetes UK (2015) 'Diabetes: Facts and Stats'. Accessed December 2015.

APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • AstraZeneca (dapagliflozin) Patient/carer groups • BEMDA: Black and Ethnic Minority Diabetes Association • Black Health Agency • Diabetes Research and Wellness Foundation • Diabetes UK • Equalities National Council • InDependent Diabetes Trust • INPUT • Insulin Pumpers UK • Muslim Council of Britain • Network of Sikh Organisations • South Asian Health Foundation • Specialised Healthcare Alliance • Surya Foundation Professional groups • Association for the Study of Obesity • Association of British Clinical Diabetologists • British Geriatrics Society • Primary Care Diabetes Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for Endocrinology • TREND UK • UK Health Forum • United Kingdom Clinical Pharmacy Association	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Diabetes UK Cymru • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Accord healthcare (gliclazide, glimepiride, pioglitazone) • Actavis UK (gliclazide, pioglitazone, tolbutamide) • Almus Pharmaceuticals (glibenclamide) • AstraZeneca (exenatide, saxagliptin) • Aurobindo Pharma (glibenclamide) • Boehringer Ingelheim (empagliflozin, linagliptin) • Bristol laboratories (gliclazide, glimepiride) • Consilient Health (gliclazide, pioglitazone) • Dr Reddy's laboratories (pioglitazone) • GlaxoSmithKline (albiglutide) • Janssen (canagliflozin) • Kent Pharmaceuticals (tolbutamide) • Lilly UK (dulaglutide, empagliflozin,

Others • Department of Health • NHS England • NHS West Hampshire CCG • NHS West Kent CCG • Welsh Government	insulin, linagliptin) • Merck Sharp and Dohme (sitagliptin) • Morningside Healthcare (pioglitazone) • Mylan UK (gliclazide, glipizide) • Novartis Pharmaceuticals (vildagliptin) • Novo Nordisk (insulin, liraglutide) • Pfizer (glipizide) • Sandoz (glimepiride, glipizide, pioglitazone) • Sanofi (glimepiride, insulin, lixisenatide) • Servier Laboratories (gliclazide) • Takeda UK (alogliptin, pioglitazone) • Teva UK (glibenclamide, gliclazide, glimepiride, glipizide, pioglitazone, tolbutamide) • Tillomed Laboratories (pioglitazone) • Wockhardt UK (glibenclamide, gliclazide, insulin) • Zentiva UK (glimepiride, pioglitazone) Relevant research groups • Cochrane Metabolic & Endocrine Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research Associated Public Health Groups • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology are invited to prepare a submission dossier, can respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).
All non-manufacturer/sponsor consultees are invited to prepare a submission dossier respond to consultations on the draft scope, the Assessment Report and the Appraisal Consultation Document. They can nominate clinical specialists and/or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but are not asked to prepare a submission dossier. Commentators are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.
All non-manufacturers/sponsors commentator organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

AstraZeneca Submission for Dapagliflozin in Triple Therapy Regimens for Treating Type 2 Diabetes [ID 962]

Company evidence submission

April 2016

File name	*Version*	*Contains confidential information*	*Date*
Dapagliflozin triple therapy_ID962_FINAL_without appendices	Final	No	12th April 2016

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Abbreviations

AC	Afro-Carribean
ACD	Appraisal consultation document
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse event
AHA	Anti-hyperglycaemic agent
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BGR	Brooks and Gelman Ratio
BID	Bis in die (Twice daily)
BMI	Body mass Index
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane® Central Register of Controlled Trials
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
CrI	Credible interval
CSR	Clinical study report
CUA	Cost-utility analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DM	Diabetes mellutis
DPP4-i	Dipeptidyl peptidase-4 inhibitor
DTSQ	Diabetes Treatment Satisfaction Questionnaire

EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMDAC	Endocrinologic & Metabolic Drug Advisory Committee
EQ-5D	Five-dimension EuroQol questionnaire
ERG	Evidence Review Group
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed Effect
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
GI	Genital infection
GLP-1	Glucagon-like peptide-1 analogues
GP	General practioner
GTI	Genital tract infection
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HFS	Hypoglycaemia fear survey
HIV	Human immunodeficiency virus
HODAR	Health Outcomes Data Repository
HOMA	Homeostasis model assessment
HRQoL	Health related quality of life
HR	Hazard ratio
HRU	Health related utility
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IDF	International Diabetes Federation
IHD	Ischaemic heart disease
ITT	Intention to treat
IU	International unit
IV	Intravenous
IVRS	Interactive voice response system
IWQOL	Impact of weight on quality of life
JADE	Januvia diabetes economic
LDL	Low-density lipoprotein

LOCF	Last observation carried forward
LRM	Longitudinal Repeated Measures
LT	Long term
LYG	Life years gained
MACE	Major adverse cardiovascular event
MCMC	Markov Chain Monte Carlo
MD	Maximum dose
MEDLINE	Medical Literature Analysis and Retrieval System Online
MET	Metformin
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MRD	Maximum recommended dose
MTA	Multiple technology appraisal
MTC	Mixed Treatment Comparison
MTD	Maximum tolerated dose
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NPH	Neutral protamine hagedorn
NPL	Neutral protamine lispro
NR	Not reported
NYHA	New York Heart Association
OAD	Oral antidiabetic
OD	Once daily
OLS	Ordinary least squares
OR	Odds ratio
PAS	Patient access scheme
PPG	Postprandial plasma glucose
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality adjusted life year
QD	Quaque die (once a day)
QoL	Quality of life
RE	Random Effects
RCT	Randomised, controlled trial
RWE	Real world evidence

SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2-i	Sodium-glucose cotransporter 2 inhibitors
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish medicines consortium
SoC	Standard of care
SPC	Summary of Product Characteristics
ST	Short term
STA	Single technology appraisal
SU	Sulphonylurea
TC	Total cholesterol
TG	Triglyceride
THIN	The Health Improvement Network
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedione
UA	Unstable angina
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	Upper limit of normal
US	United States
USA	United States of America
UTI	Urinary tract infection
VAT	Value-added tax
vs	versus
WBDC	Web based data capture
WQ-9	Weight questionnaire-9

1 Executive summary

Dapagliflozin, an oral anti-diabetic medicine, was the first sodium glucose cotransporter 2 inhibitor (SGLT2-i) to launch in the United Kingdom (UK) in 2012. It is licensed to improve glycaemic control in adults with type 2 diabetes; and can be used alone or in combination with other oral treatments, or with insulin.

Dapagliflozin received a recommendation from the National Institute for Health and Care Excellence (NICE) in 2013 for use as dual therapy (add-on to metformin [MET]) and add-on to insulin. At the time of this initial appraisal, the key clinical study for dapagliflozin used in a triple regimen was not available; and therefore NICE was unable to recommend its use in a triple regimen. The key triple study was later reviewed by the European Medicines Agency (EMA) and subsequently included in the dapagliflozin licence in December 2013. This appraisal will only assess dapagliflozin when used in a triple therapy regimen: other patterns of use are not considered: the other NICE recommendations remain extant.

When used as part of a triple regimen with metformin and a sulfonylurea (MET + SU), dapagliflozin provides glycated haemoglobin (HbA1c) lowering in line with dipeptidyl peptidase 4 inhibitors (DPP4-is) as well as greater weight loss compared to DPP4-is, the key comparator in this submission. Results from economic modelling show that dapagliflozin provides higher quality adjusted life years (QALYs) at lower cost compared with the DPP4-is.

The other SGLT2-is licensed in the UK (canagliflozin and empagliflozin) are also used in triple therapy regimens. The daily cost of dapagliflozin is exactly the same as that of the other SGLT2-is. The three SGLT2-is have a similar efficacy and safety profile as demonstrated in this submission, and in previous NICE appraisals. Further, canagliflozin and empagliflozin have received positive NICE recommendations for use in a triple therapy regimen based on similar economic results as those presented in this submission for dapagliflozin. For these reasons, this appraisal presents a pragmatic case for dapagliflozin to be recommended as an option for treating type 2 diabetes in combination with MET + SU as part of a triple therapy regimen.

Diabetes mellitus is a long-term (chronic) metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. Type 2 diabetes specifically is where there is reduced tissue sensitivity to insulin (known as insulin resistance) as well as a failure of insulin secretion to compensate for this. The prevalence of type 2 diabetes in

England and Wales is estimated to be 3.4 million in 2016 and is expected to rise to 3.7 million in 2020. Diabetes presents a high and increasing burden to the National Health Service (NHS). It is often associated with being overweight and in the UK, it is estimated that 90% of patients with type 2 diabetes are overweight or obese.

Type 2 diabetes is a progressive disease with the need for step-wise treatment to maintain HbA1c to target as the disease advances. Weight gain is also an important consideration in treatment choice due to reduced patient quality of life, and the link to long term cardiovascular (CV) complications. The recent NICE guideline for type 2 diabetes (NG28) recommends treatment initiation with the oral antidiabetic metformin. As the disease progresses, the guideline presents a number of options for first intensification (dual therapy) with SU, DPP4-i, SGLT2-i or pioglitazone (which is less commonly used) recommended in combination with metformin. Second intensification (triple therapy) options in the guideline include DPP4-i, SGLT2-i or pioglitazone on a background of MET and SU. The guideline algorithm recommends that choice of drug treatment should include consideration of a person's individual clinical circumstances, preferences, and needs. One key factor regarding individualised treatment choice is the effect of certain drugs on patients' weight with some treatments, such as SUs and pioglitazone being associated with weight gain.

Due to lower cost and greater patient satisfaction, oral regimens are typically used in advance of injectables (insulin and glucagon-like peptide-1 analogues [GLP-1s]) in the treatment of type 2 diabetes. Specifically regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy IMS data (Patient Data, IMS Information Solutions UK Ltd, December 2015) show that 62% of patients are prescribed metformin plus SU plus a DPP4-i. Therefore, DPP4-is are considered the key comparator in this submission. The DPP4-is provide HbA1c lowering yet are weight neutral; and as such do not address the importance of reducing weight for type 2 diabetes patients.

Dapagliflozin (Forxiga®) is a selective SGLT2-i, and was the first in this novel class of insulin independent, glucose-lowering medications (SGLT2-is also include canagliflozin and empagliflozin). SGLT2-is are associated with a low risk of hypoglycaemia and have demonstrated weight reduction. As SGLT2-is act independently of insulin they can be used at varying stages of the Type 2 diabetes treatment pathway, as monotherapy or as add-on therapy to other oral glucose-lowering medicinal products and to insulin, thereby providing flexibility in their use.

As described above, this appraisal will assess the use of dapagliflozin in a triple oral regimen only; the other NICE recommendations for dapagliflozin (add-on to MET; and add-on to insulin) remaining extant.

The primary data used in this submission are derived from study 5, a 24-week placebo controlled phase III randomised, controlled trial (RCT) of dapagliflozin with

MET + SU with a 28-week blinded extension period. In this population inadequately controlled on MET + SU:

- Dapagliflozin, compared to placebo, was superior in improving glycaemic control based on the reduction in HbA1c from baseline to week 24 of -0.86% vs. -0.17% for placebo (p-value <0.0001), and -0.8% (95% CI: −1.0, −0.6) vs. placebo: -0.1% (95% CI: −0.3, 0.1) at 52 weeks
- Dapagliflozin showed a significant difference in body weight change from baseline versus placebo with weight loss of -2.7 kg vs -0.6 kg for placebo (p <0.0001) at 24 weeks, and -2.9 kg (95% CI: −3.6, −2.2) vs. -1.0 kg (95% CI: −1.8, −0.1) for placebo at 52 weeks

The dapagliflozin licence also includes data from a placebo-controlled trial demonstrating that dapagliflozin is effective as add on therapy to sitagliptin (a DPP4-i) with or without MET. Whilst the scope of this appraisal includes the use of dapagliflozin on a background of MET + DPP4-i, the systematic review has revealed a lack of data for the relevant comparators (on a background of MET + DPP4-i) meaning that robust estimates of comparative effectiveness or cost effectiveness are not possible at this time. This submission therefore focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET + SU.

Dapagliflozin versus DPP4-is

Given that there are no head to head trials of dapagliflozin versus an active comparator on a background of MET+ SU, a network meta-analysis (NMA) has been carried out. This shows no significant differences between dapagliflozin and the DPP4-is with regard to change from baseline in HbA1c or Systolic Blood Pressure (SBP), or hypoglycaemia rates. There were significant differences in favour of dapagliflozin with regard to reduction in total body weight versus the DPP4-is. This clinical benefit of greater weight loss drives a dominant result from the economic modelling showing that dapagliflozin in a triple therapy regimen provides higher QALYs at lower cost than the DPP4-is.

Dapagliflozin versus other SGLT2-is

The three SGLT2-is have a similar mode of action with evidence indicating similar efficacy and safety from comparable trials against a background of MET + SU. In the UK, there are no price differences between the SGLT2-is (including all doses).

Conclusion: Dapagliflozin in combination with MET + SU as part of a triple therapy regimen provides an additional treatment option. Treatment with dapagliflozin in a triple therapy regimen provides higher QALYs at lower cost than the DPP4-is. In addition, there are no meaningful differences in safety or efficacy between dapagliflozin and the other SGLT2-is (canagliflozin and empagliflozin) used in triple therapy regimens. We propose all three SGLT2-is should have the same NICE recommendation in

triple therapy with dapagliflozin now recommended as a treatment option for treating type 2 diabetes in combination with MET + SU alongside the other already recommended SGLT2-is.

1.1 *Statement of the decision problem*

Table 1: The decision problem

	Final scope issued by NICE	***Decision problem addressed in the company submission***	***Rationale if different from the final NICE scope***
Population	Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: • MET with a SU • MET with a DPP4-i	Adults with type 2 diabetes that is inadequately controlled on dual therapy with MET and a SU	Within this submission AstraZeneca have focused on patients who are inadequately controlled on MET and a SU only. Clinical data for dapagliflozin versus placebo supports its use in patients inadequately controlled on MET with a DPP4-i, however, results of the systematic review show that it is not possible to conduct comparative analyses due to a lack of available evidence for comparators in the scope in combination with MET + DPP4-is. Therefore, this submission focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET with a SU
Intervention	Dapagliflozin in combination with 2 other oral antidiabetic agents	As per scope	
Comparator (s)	The following in combination with 2 other oral antidiabetic agents: • other SGLT2-is • DPP4-is • pioglitazone • GLP-1 agonists • a SU • insulin	In the base case analysis dapagliflozin in combination with MET and SU is compared to DPP4-i class, canagliflozin and empagliflozin in combination with MET and SU	In line with the manufacturer submission in the empagliflozin STA: • Pioglitazone has not been considered in this submission as it is used rarely in the UK • Insulin and GLP-1s have not been considered in this submission as these are injectables, and used later in the treatment pathway Triple therapy with MET and a SU

			• Regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy, IMS data (Patient Data, IMS Information Solutions UK Ltd, December 2015) show that 62% of patients are prescribed metformin plus SU plus a DPP4-i. The DPP4-is are therefore the key comparator for this submission • Since the launch of dapagliflozin, two other SGLT2-is, canagliflozin and empagliflozin have launched in the UK; and are also comparators in this submission Triple therapy in combination with MET and DPP4-i • As described above, due to the current lack of evidence on a background of MET + DPP4-i for the comparators in the scope, this submission focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET + SU
Outcomes	The outcome measures to be considered include: • mortality • complications of diabetes, including • cardiovascular, renal and eye • HbA1c/glycaemic control • body mass index (BMI)	Dapagliflozin provides reductions of HbA1c with the additional secondary clinical benefits of weight loss and systolic blood pressure lowering Change from baseline in total body weight; and change from baseline in SBP has therefore been assessed in addition to these outcomes Further, it should be noted that the RCTs	

	• frequency and severity of hypoglycaemia • changes in cardiovascular risk factors • adverse effects of treatment, including urinary tract infections (UTIs), genital infections and malignancies • Health-related quality of life	included in the systematic review carried out for this appraisal did not typically report data for long-term outcomes	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	The time horizon is 40 years as used within most type 2 diabetes economic analyses including those within the recent canagliflozin STA; dapagliflozin STA and SGLT2-is as monotherapy multiple technology appraisal (MTA). The starting mean age of patients in the model is 61 years; therefore 40 years translates into a lifetime Following discussion at the decision problem meeting, we have presented a rationale for use of the UK Prospective Diabetes Study (UKPDS) 68 version of the UKPDS equations in the base case in section 5	
Subgroups to be considered	No subgroups were included in the scope		
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator		

1.2 *Description of the technology being appraised*

Dapagliflozin (Forxiga®), a selective inhibitor of SGLT2, was the first in this novel class of insulin independent, glucose-lowering medications. In contrast to existing therapies, SGLT2-i (dapagliflozin, canagliflozin and empagliflozin) remove glucose through the kidneys and do not directly influence insulin secretion resulting in a low risk of hypoglycaemia. In addition, the excretion of glucose/calories in the urine with SGLT2-i can lead to weight loss. The SGLT2-i may also cause a mild diuretic effect, with potential for modest blood pressure (BP) lowering in hypertensive patients through the inhibition of sodium and glucose transport in the proximal tubule. Furthermore, the SGLT2-i can be used at varying stages of the type 2 diabetes mellitus treatment pathway providing renal function is adequate, as they act independently of insulin secretion and insulin action.

Please see Section 2 for further detail regarding dapagliflozin including its mechanism of action, marketing authorisation; prior health technology assessment (HTA) and cost.

1.3 *Summary of the clinical effectiveness analysis*

Summary of the dapagliflozin trial programme

The dapagliflozin trial programme is one of the largest diabetes trial programmes to date, comprised of 24 Phase IIb and III studies, including a single RCT evaluating the efficacy of dapagliflozin as a part of a triple therapy treatment regimen. Overall, the trials have included both placebo-controlled and active comparator designs, with durations ranging from 12 weeks to 4 years. More than 11,000 patients were randomised in these studies, with over 6,000 receiving dapagliflozin. These studies have demonstrated the durable efficacy, safety and tolerability of dapagliflozin across the spectrum of disease, ranging from monotherapy in early disease to add-on to insulin in advanced disease. Treatment with dapagliflozin is associated with prompt and sustained improvements in HbA1c, weight reduction, lowered BP, and a low intrinsic propensity to cause hypoglycaemia.

Dapagliflozin triple regimen key study

Clinical efficacy of dapagliflozin in a triple regimen is derived from Study 5, a placebo controlled phase III RCT of dapagliflozin with MET plus SU. This study demonstrates significantly greater reductions in HbA1c, weight, and SBP for dapagliflozin compared to placebo (with MET+ SU).

- HbA1c: dapagliflozin: -0.86% vs. -0.17% for placebo (p-value <0.0001) at 24 weeks, and dapagliflozin:-0.8% (95% CI: −1.0, −0.6) vs. placebo: -0.1% (95% CI: −0.3, 0.1) at 52 weeks
- Weight loss: dapagliflozin: -2.7 kg vs -0.6 kg for placebo (p <0.0001) at 24 weeks, and dapagliflozin: -2.9 kg (95% CI: −3.6, −2.2) vs. -1.0 kg (95% CI: −1.8, −0.1) for placebo at 52 weeks
- Clinically and statistically significant reduction in placebo-corrected SBP at 8 weeks that was maintained up to 24 weeks

There are no head-to-head trials of dapagliflozin versus an active comparator in a triple therapy regimen. An NMA has been carried out to inform this submission: this shows no significant differences between dapagliflozin and the other SGLT2-i based on a comparison versus each individual dose (canagliflozin 300mg; canagliflozin 100mg; empagliflozin 10mg;

empagliflozin 25mg) in the key outcomes of change from baseline in HbA1c; SBP; and total body weight; and any hypoglycaemic event (Section 4.10).

In addition, UK real world evidence from a retrospective observational study conducted using the Clinical Practice Research Datalink (n=1732), which contains records from 684 primary care practices in the UK) (Wilding 2015b), demonstrated improvements in HbA1c and weight that are consistent with those reported in clinical trials.

1.4 *Summary of the cost-effectiveness analysis*

Dapagliflozin + MET+ SU:

A cost-utility model demonstrates the cost-effectiveness of dapagliflozin compared to DPP4-is (Table 2). The incremental cost of dapagliflozin versus DPP4-i was -£112 (i.e. a saving of £112) with an incremental QALY gain of 0.03, resulting in dapagliflozin being a dominant treatment option compared to DPP4-i.

Although the cost of therapy of SGLT2-is is exactly the same with no significant differences in efficacy and safety results, cost effectiveness analyses were also performed for the comparison of dapagliflozin versus empagliflozin (10mg and 25mg regimens) and canagliflozin (100mg and 300mg regimens). Results of these analyses demonstrate negligible cost and QALY differences with ICER estimates resulting in a mix of dominant, cost-effective and dominated outcomes. However, care should be taken when interpreting these results, due to the tendency of small incremental outcomes to significantly affect ICER estimates.

Table 2: Incremental cost-effectiveness results – base case

Treatment	Costs (£)	QALYs	ICER (£/QALY)
Absolute results (per patient)			
MET + SU + Dapagliflozin	20,417	9.62	
MET + SU + DPP4-i	20,529	9.58	
Canagliflozin (100mg)	20,351	9.62	
Canagliflozin (300mg)	20,610	9.61	
Empagliflozin (10mg)	20,456	9.61	
Empagliflozin (25mg)	20,410	9.61	
Incremental results (per patient)			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-112	0.032	Dapagliflozin Dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	66	-0.001	Canagliflozin 100mg Dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-192	0.003	Dapagliflozin Dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	-38	0.005	Dapagliflozin Dominates

MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.006	£1,354 Cost-effective

DPP4-i: dipeptidyl peptidase-4 inhibitor; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; MET: metformin; SU: sulphonylurea

2 The technology

- Dapagliflozin (Forxiga®), a selective inhibitor of SGLT2, was the first in this novel class of insulin independent, glucose-lowering medications to launch in the UK in November 2012
- The SGLT2-i (dapagliflozin; canagliflozin and empagliflozin) provide reductions of HbA1c with the additional secondary clinical benefits of weight loss and SBP lowering
- Dapagliflozin gained a NICE recommendation in 2013 for use as add onto MET and add-on to insulin. At the time of the initial NICE submission in 2012, the key RCT for dapagliflozin used in a triple regimen (with MET + SU) was not available and therefore dapagliflozin was not recommended for use as part of a triple therapy regimen. The key triple RCT (dapagliflozin + MET + SU) was then included in the dapagliflozin licence in December 2013
- This appraisal will assess the use of dapagliflozin in a triple oral regimen only; the other NICE recommendations for dapagliflozin remaining extant

2.1 *Description of the technology*

Brand name: Forxiga®

UK approved name: Dapagliflozin

Therapeutic class: Dapagliflozin is an antidiabetic, blood glucose lowering drug and is a selective and reversible inhibitor of SGLT2.

Anatomical Therapeutic Chemical (ATC) code: A10BX09

Brief overview of the mechanism of action

Dapagliflozin (Forxiga®) is a highly potent, selective and reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2) and was the first SGLT2-i to launch in the UK. Subsequently, two SGLT2s inhibitors (canagliflozin and empagliflozin) have been launched and approved in the indication sought in this submission. SGLT2-is have an insulin independent mechanism of action which is different but complementary to other anti-diabetic medications. The SGLT2 is selectively expressed in the kidney and is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of an excess of sugar in the blood (hyperglycaemia) in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin improves glycaemic control in patients with type 2 diabetes mellitus by reducing glucose reabsorption in the kidneys and leading to urinary glucose excretion (glucuresis). As dapagliflozin does not directly influence insulin secretion, there is a low risk of hypoglycaemia, as these agents selectively target renal glucose transporters, without

affecting the counter-regulatory hormones. Furthermore, dapagliflozin has the potential to induce weight loss due to excretion of associated calories.

Glucose excretion is observed after the first dose of dapagliflozin, is continuous over the 24-hour dosing interval, and is sustained for the duration of dapagliflozin treatment. The amount of glucose excreted via the kidney through this mechanism is not only dependent upon the blood glucose concentration but also the kidney's glomerular filtration rate (GFR). Dapagliflozin lowers both fasting and post-prandial plasma glucose levels.

In healthy patients, with normal blood glucose concentration, dapagliflozin has a low propensity to cause an abnormal decrease in blood sugar (hypoglycaemia); furthermore, dapagliflozin does not impair normal body glucose production in response to hypoglycaemia. Because dapagliflozin acts independently of insulin secretion and insulin action, it may be used at any stage of type 2 diabetes. Finally, dapagliflozin causes mild increased excretion of urine (diuresis) and as a consequence it is associated with modest reductions in BP.

Interestingly, most oral antidiabetic therapies rely on insulin-secreting cells (β-cell) function for their activity, but because type 2 diabetes mellitus is characterised by a steady decline in pancreatic β-cell function, the effectiveness of these anti-diabetic agents diminishes over time. In contrast, dapagliflozin does not rely on β-cell function. Furthermore, improvement in the homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

Importantly, the urinary glucose excretion induced by dapagliflozin is associated with calorie loss and associated reduction in body weight. The majority of the weight reduction has been observed to be loss of body fat, including visceral fat rather than lean tissue or fluid loss, as demonstrated by dual X-ray absorptiometry and magnetic resonance imaging.

As dapagliflozin acts independently of insulin secretion and insulin action it can be used at any stage of the type 2 diabetes mellitus treatment pathway, providing renal function is adequate, thus allowing flexibility in its use.

2.2 *Marketing authorisation/CE marking and health technology assessment*

Marketing authorisation

Regulatory approval for dapagliflozin was filed with EMA via the centralised procedure; the UK is part of this procedure. Dapagliflozin (Forxiga®) received EMA marketing authorisation on 12th November 2012. Committee for Medicinal Products for Human Use (CHMP) positive opinion for the 'Triple Combination' variation to include the combination treatment option dapagliflozin in combination with MET plus SU to the European Union (EU) licence was granted on 18th December 2013, with the data relating to this combination being incorporated in Section 5.1 of the Summary of Product Characteristics (SPC) as part of a Type 2 variation.

Dapagliflozin is indicated for the treatment of adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

- Monotherapy
    - When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of MET is considered inappropriate due to intolerance
- Add-on combination therapy

- In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

The SmPC is included in the reference pack.

Health Technology Assessment

- Dapagliflozin received a NICE recommendation in 2013 for use as an add-on therapy to MET or insulin. At the time of this appraisal, data for the use of dapagliflozin as part of a triple therapy regimen (MET + SU) were not available and therefore NICE was unable to recommend its use in a triple regimen at this time. Clinical data supporting the use of dapagliflozin as a triple therapy treatment regimen are now available, and were incoportaed into the licence in 2013. AstraZeneca is now seeking a NICE recommendation for the use of dapagliflozin in a combination with MET and SU with the existing recommendations for dapagliflozin remaining extant
- Other HTA bodies already recommend the use of dapagliflozin in a triple therapy regimen. For example, the Scottish Medicines Consortium (SMC) has provided advice recommending the use of dapagliflozin in such a regmien (with MET and SU) in NHS Scotland
- NICE is currently evaluating dapagliflozin monotherapy along with canagliflozin and empagliflozin for the treatment of type 2 diabetes as part of a multiple technology appraisal (MTA), (ID756) with guidance publication expected later this year (May 2016)

Costs of the technology being appraised

Table 3: Costs of the technology being appraised

	Cost	***Source***
Pharmaceutical formulation	Film-coated tablet	SmPC
Acquisition cost (excluding value-added tax [VAT]) *	5mg tablets (28 tablets): £36.59 per pack 10mg tablets (28 tablets): £36.59 per pack	
Method of administration	Oral tablet formulation	SmPC
Doses	5mg per day (starting dose in patients with severe hepatic impairment), 10mg per day	SmPC
Dosing frequency	Once daily (OD)	SmPC
Average length of a course of treatment	Due to the chronic nature of the disease and the stepwise addition of treatments; the duration of treatment is hard to quantify. For dapagliflozin a clear stopping rule would be the development of moderate renal impairment, which is a common feature of patients with diabetes. Although this varies considerably between patients. The UKPDS showed that at 10 years 5% of patients developed macroalbuminuria or worse nephropathy and 24% will develop microalbuminuria after diagnosis (Adler 2003) suggesting that a substantial proportion	SmPC

	of patients would no longer be eligible for dapagliflozin at 10 years.	
Average cost of a course of treatment	Not applicable (see above)	
Anticipated average interval between courses of treatments	Not applicable	
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	**Renal impairment** No dosage adjustment is indicated in patients with mild renal impairment. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2). **Hepatic impairment** No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg. **Elderly (≥ 65 years)** In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended. **Patients at risk for volume depletion, hypotension and/or electrolyte imbalances** Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, and laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.	SmPC
Anticipated care setting	Primary care	

No patient access scheme (PAS) is being proposed

Comparative price of dapagliflozin

- Dapagliflozin 10 mg has the same drug price as canagliflozin 100 mg; 300 mg and empagliflozin 10 and 25 mg (£1.31 per day). All of the SGLT2-i have a slightly higher price than the DPP4s (£0.95-£1.19 per day) (BNF 2015). Further details on the drug acquisition costs of the therapies included in the economic evaluation are provided in the cost-effectiveness section of this submission (see Section 5).

2.3 *Changes in service provision and management*

Dapagliflozin is already being prescribed within NHS England. Therefore, no additional resources will be associated with the use of dapagliflozin as part of a triple therapy treatment regimen other than drug acquisition costs.

2.4 *Innovation*

- Unlike other therapies, the SGLT2-is remove glucose via the kidney. In contrast, other agents move glucose from the circulation to various compartments (muscle, fat etc.)
- The action of the SGLT2-is is insulin independent, meaning they do not rely on underlying beta-cell function to exert its effect. In diabetes, beta-cell function wanes over time and therefore exogenous insulin (insulin injections) is/are eventually required
- Dapagliflozin is associated with weight loss, as a result of the calorie loss induced by glucuresis (glucose excretion). Other oral agents are often associated with weight gain (Thiazolidinedione [TZD] or SU) or are weight neutral (DPP4-is)
- As SGLT2-is do not directly influence insulin secretion, there is a low risk of hypoglycaemia, as these agents selectively target renal glucose transporters without affecting the counter-regulatory hormones (Wright 2001)
- Dapagliflozin can be added to insulin and exerts a clinically meaningful insulin sparing effect while reducing HbA1c and weight
- Dapagliflozin is also associated with moderate BP reductions

3 Health condition and position of the technology in the treatment pathway

- Type 2 diabetes is a progressive disease with the need for step-wise treatment to maintain HbA1c to target as the disease advances. Weight gain is also an important consideration in treatment choice due to reduced patient quality of life, and the link to long term CV complications with approximately 90% of type 2 diabtes patients being overweight in the UK
- The recent NICE guideline for type 2 diabetes (NG28) recommends treatment initiation with the oral antidiabetic metformin. As the disease progresses, the guideline presents a number of options for first intensification (dual therapy) with SU, DPP4-i, SGLT2-i or pioglitazone (which is less commonly used) recommended in combination with metformin. Second intensification (triple therapy) options in the guideline include DPP4-i, SGLT2-i or pioglitazone on a background of MET and SU
- Due to lower cost and greater patient satisfaction, oral regimens are typically used in advance of injectables (insulin and GLP-1s). Specifically regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy, IMS data (Patient Data, IMS Information Solutions UK Ltd, December 2015) show that 62% of patients are prescribed metformin plus SU plus a DPP4-i. Therefore, the DPP4-i are considered the key comparator in this submission. The DPP4-i provide HbA1c lowering yet are weight neutral; and as such do not address the importance of reducing weight for type 2 diabetes patients
- Dapagliflozin, a selective SGLT2-i meets this unmet need in providing HbA1c lowering with a low risk of hypoglycaemia and demonstrated weight reduction in a population with inadequate control on MET + SU. Used within a triple regimen, dapagliflozin could increase the options available in the Primary Care setting and so could delay the progression to an injectable GLP-1 analogue or insulin, which usually requires Secondary Care referral for initiation

3.1 *Disease background*

Diabetes mellitus

Diabetes mellitus is a long-term (chronic) metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action.

Type 2 diabetes specifically is where there is reduced tissue sensitivity to insulin (known as insulin resistance) as well as a failure of insulin secretion to compensate for this. Type 2 diabetes is often associated with being overweight. In the UK, it is estimated that 90% of patients with type 2 diabetes are overweight or obese (Diabetes UK 2014).

Complications of diabetes mellitus

If not managed effectively, diabetes can lead to serious, early microvascular complications including kidney failure, blindness, limb amputation, as well as damage to the nervous system, peripheral vasculature and skin (ulcers). Macrovascular complications, including cardiovascular disease (CVD), may follow, which can result in myocardial infarction (MI) or stroke (Table 4).

Between 2006 and 2012, all complications due to diabetes increased in the UK, with a 33% increase in retinopathy, 106% increase in stroke, 95% increase in renal replacement therapy, 130% increase in cardiac failure, 67% increase in angina and 60% increase in amputations (Diabetes UK 2014). In fact, limb amputations due to the vascular effects of type 2 diabetes mellitus are still very common, the majority of which are preventable (RightCare 2011) with proper medical/nursing care and this is despite the availability of modern foot care management and current anti-diabetic medications.

Table 4: Complication prevalence in people with type 2 diabetes mellitus and the general population

	Additional risk of complication among people with diabetes (England and Wales)
Complications	
Angina	135.1
MI	87.6
Cardiac failure	121.1
Stroke	59.1
Renal replacement therapy	220.9
Minor amputation	686.8
Major amputation	338.5
These figures are based on the number of people who appeared in the 2011-2012 audit with one or more complication event during the year 1 April 2012 to 31 March 2013	

MI, myocardial infarction
Reference: (HSCIC 2015)

Treatment

Early diagnosis and effective treatment of diabetes mellitus can minimise the risk of developing serious complications. Type 2 diabetes may be controlled initially by eating a healthy diet, losing weight (if overweight) and monitoring blood glucose levels. As diabetes cannot be cured, anti-diabetic treatments aim to keep blood glucose levels as normal as possible, and to control symptoms to prevent health problems developing later in life. Weight gain is also an important consideration in treatment choice due to reduced patient quality of life, and the link to long term CV complications.

Some existing treatments, such as SUs, and TZDs can cause weight gain, which is an issue especially in patients who are already overweight. This in turn may lead to greater NHS expenditure on weight-loss programmes and/or anti-obesity drugs. Hypoglycaemia can also be a concern with some medications (especially SUs). This may manifest clinically as major episodes requiring hospitalisation, ambulance call outs or other emergency attention for the resulting complications such as falls, fractures, acute confusion. Minor episodes whilst not requiring third party assistance may still result in increased general practitioner (GP) or nurse visits or decreased medication compliance (Amiel et al 2008). As type 2 diabetes mellitus progresses, worsening β-cell function will often ultimately require additional anti-diabetic medication and/or insulin treatment and at increasingly higher doses as the benefits of treatment reduce over time (Kahn 2006).

Due to lower cost and greater patient satisfaction, oral regimens are typically used in advance of injectables (insulin and GLP-1s). Specifically regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy IMS data show that 62% of patients are prescribed metformin plus SU plus a DPP4-i. (Patient Data, IMS Information Solutions UK Ltd, December 2015). Therefore, the DPP4-is are considered the key comparator in this submission. The DPP4-is provide HbA1c lowering yet are weight neutral; and as such do not address the importance of reducing weight for type 2 diabetes patients.

3.2 *Clinical pathway of care*

Please see Section 3.4.

3.3 *Life expectancy, prevalence and incidence of the disease*

The UK, like the rest of the world, has continued to see a steady increase in the prevalence of Type 2 diabetes mellitus. In 2016 there are an estimated 3.7 million people diagnosed with diabetes in England and Wales (YHPHO 2015) of which type 2 diabetes mellitus accounts for ~90% of all cases.

People with type 2 diabetes in England and Wales are 32 per cent more likely to die earlier than their peers (HSCIC 2015). In Type 2 diabetes, the average reduced life expectancy for someone diagnosed with type 2 diabetes in their 50s is about 6 years (Seshasai 2011).

3.4 *Clinical Guidance and guidelines*

NICE guidance

The NICE Single Technology Appraisals (STAs) of the other SGLT2-is are described below, both of which recommend canagliflozin and empaglflozin for use in a triple regimen in combination with MET and a SU. These decisions for canagliflozin and empagliflozin have been based on a similar evidence base; and similar cost effectiveness results (showing lower costs and greater QALYs compared to DPP4-is) as that described in this submission for dapagliflozin.

It should also be noted that in NICE TAGs, the three SGLT2-is have been considered to have similar efficacy and safety:

- Specifically, the evidence considered in the Empagliflozin STA showed that the clinical effectiveness of the SGLT2-i is similar (FAD, January 2015)
- The ongoing MTA for all SGLT2-i in monotherapy has not identified any differences in effectiveness between the SGLT2-i (FAD, March 2016)

Canagliflozin in combination therapy for treating type 2 diabetes (NICE TA315 2014):

Canagliflozin in a dual therapy regimen in combination with MET is recommended as an option for treating type 2 diabetes, only if:

- a SU is contraindicated or not tolerated, or
- the person is at significant risk of hypoglycaemia or its consequences

Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- MET and a SU, or
- MET and a TZD

Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

Empagliflozin in combination therapy for treating type 2 diabetes (NICE TA336 2015):

Empagliflozin in a dual therapy regimen in combination with MET is recommended as an option for treating type 2 diabetes, only if:

- a SU is contraindicated or not tolerated, or
- the person is at significant risk of hypoglycaemia or its consequences

Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- MET and a SU, or
- MET and a TZD

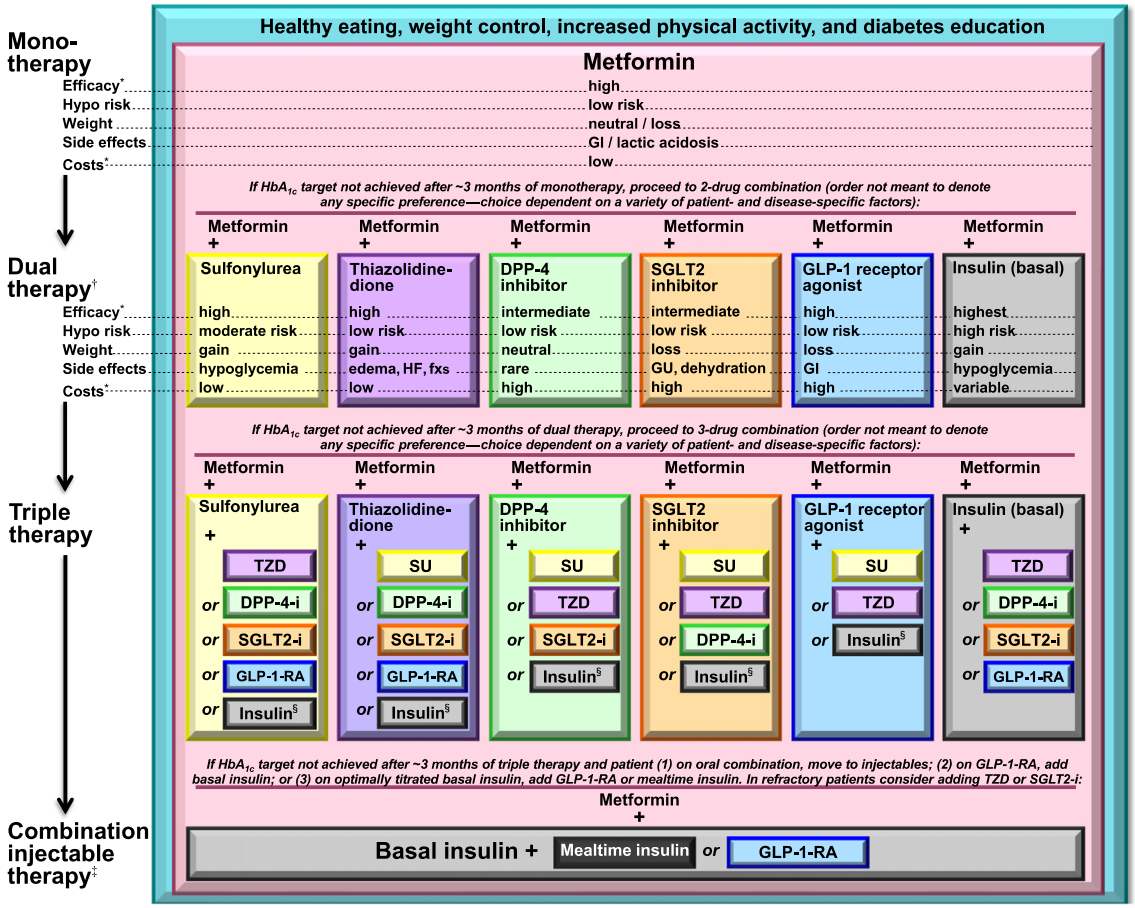
Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

It should also be noted that NICE is currently evaluating dapagliflozin monotherapy along with canagliflozin and empagliflozin for the treatment of type 2 diabetes as part of a MTA (ID756) with publication of this guidance expected later this year (May 2016).

EASD/ADA clinical guidelines

The EASD/ADA guidelines recommend SGLT2-is as reasonable second- or third-line treatment options (Figure 1).

Figure 1: ADA/EASD treatment algorithm for the pharmacotherapy of glucose lowering in patients with type 2 diabetes mellitus (Inzucchi 2015)



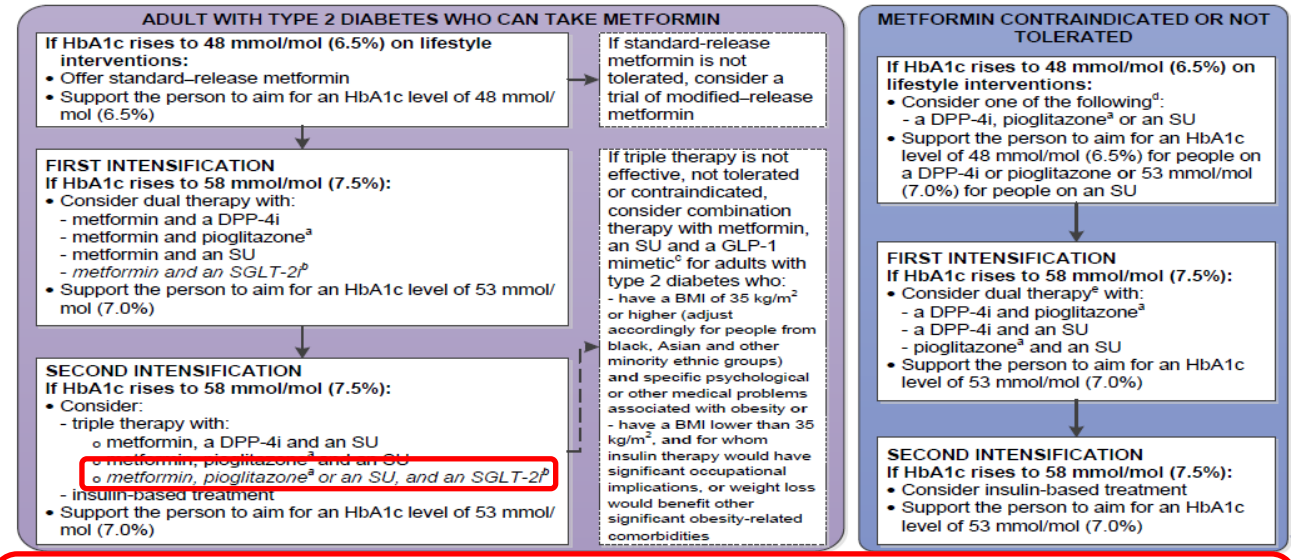
NICE clinical guideline: NG28: Type 2 diabetes in adults: management

The NICE clinical guideline for type 2 diabetes was updated and recently published in December 2015 (NG28: Type 2 diabetes in adults: management). The treatment algorithm is summarised below (Figure 2).

It recommends treatment initiation with the oral antidiabetic metformin. As the disease progresses, the guideline presents a number of options for first intensification (dual therapy) with SU, DPP4-i, SGLT2-i or pioglitazone (which is less commonly used) recommended in combination with metformin. Second intensification (triple therapy) options in the guideline include DPP4-i, SGLT2-i or pioglitazone on a background of MET and SU. Regarding the recommendation for SGLT2-is, there is a footnote reference to the existing TAGs as well as this appraisal now in progress, which is highlighted in Figure 2.

The guideline algorithm recommends that choice of drug treatment should include consideration of a person's individual clinical circumstances, preferences, and needs. As decribed in Section 3.1, one key factor regarding individualised treatment choice is the effect of certain drugs on patients' weight with some treatments, such as SUs and pioglitazone being associated with weight gain.

Figure 2: Treatment Algorithm for blood glucose lowering therapy in adults with type 2 diabetes (NICE 2015)



b. **Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT2-is are recommended as options in dual therapy regimens with MET under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288.**

Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT2-is (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT2-i. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

Please see the NICE guideline for additional footnotes to this algorithm

Clinical pathway of care

The use of dapagliflozin would fit into the NICE pathway for diabetes under the second intensification with MET combination therapy along with other SGLT2-is within a triple regimen section. The text below should be added to bring the NICE pathway in line with the NICE guideline (NICE 2015):

In adults with type 2 diabetes, if dual therapy with MET and another oral drug (see first intensification with MET combination therapy in this pathway) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:

- triple therapy with:
    - MET, a DPP4-i and a SU or
    - MET, pioglitazone and a SU, or
    - MET, pioglitazone or an SU, and an SGLT2-i

3.5 *Issues relating to current clinical practice*

With the exponential rise in the prevalence of diabetes, a variety of models for the delivery of care have emerged across the UK, with a preference for Primary Care led services. However, the majority of complex patients are managed by Intermediate or Secondary Care, although there is a wide variation in the threshold for referral of patients to Secondary Care.

Used within a triple regimen, dapagliflozin could increase the options available in the Primary Care setting and so could delay the progression to an injectable GLP-1 analogue or insulin, which usually requires Secondary Care referral for initiation.

The variations in standards of care of patients with diabetes across the UK include:

- Postcode lottery of care (NDA 2014/2015)
- Integration of primary and secondary care services, which is currently only available in certain areas
- The recent national diabetes audit demonstrating that only 66% of type 2 diabetes mellitus patients achieved a HbA1c target that is recommended by NICE (≤7.5% or ≤58mmol/mol) and only 41% of patients achieving all three key measurements (HbA1c of 58mmol/mol or less, BP 140/80 or less and cholesterol levels of 5 mmol/L or less). This varies considerably by age with patients aged under 65 years less likely to achieve these treatment targets. Currently less than 27% of patients aged 40 years or younger achieved all three targets (HSCIC 2016)(National Diabetes Audit 2003-2015)

Last spring Diabetes UK, and more recently the Public Health Committee (Dec 2015), have stressed that reducing local variation is key and have called for CCGs to:

- Develop and implement performance improvement plans for all of the recommended care processes and treatment targets
- Set themselves performance improvement targets and implement plans of action. In particular, CCGs in the bottom 25 per cent need to take steps to achieve levels of performance similar to the middle 50 per cent, as a matter of urgency

3.6 *Assessment of equality issues*

No equality or equity issues are envisaged with the introduction of dapagliflozin as a triple therapy treatment regimen.

4 Clinical effectiveness

- Dapagliflozin as part of a triple regimen (with MET plus SU) is an effective and well tolerated treatment in type 2 diabetes patients inadequately controlled with MET plus SU, reducing HbA1c, weight, and seated SBP, whilst hypoglycaemic events remain uncommon
- The primary data for this appraisal is from Study 5, a 24-week placebo controlled phase III RCT of dapagliflozin with MET plus SU with a 28-week blinded extension period, which demonstrated:
    - Dapagliflozin, compared to placebo, was superior in improving glycaemic control based on the reduction in HbA1c from baseline to week 24 of -0.86% vs. -0.17% for placebo (p-value <0.0001) at 24 weeks, and -0.8% (95% CI: −1.0, −0.6) vs. placebo: -0.1% (95% CI: −0.3, 0.1) at 52 weeks
    - Dapagliflozin showed a significant difference in body weight change from baseline versus placebo with weight loss of -2.7 kg vs -0.6 kg for placebo (p <0.0001) at 24 weeks, and -2.9 kg (95% CI: −3.6, −2.2) vs. -1.0 kg (95% CI: −1.8, −0.1) for placebo at 52 weeks
    - Consistent with the rest of the Phase III dapagliflozin clinical programme, there was a clinically and statistically significant reduction in placebo-correct SBP. Seated SBP in the dapagliflozin and placebo groups had declined from baseline by week 24 (−5.4 vs −1.3 mmHg, respectively), though this difference was attenuated at week 52 for reasons that will be outlined in Section 4.7
    - Furthermore, despite stringent glycaemic rescue parameters, no subject receiving dapagliflozin required glycaemic rescue during the 24 week study period vs 9% on placebo. At 52 weeks, only 9% of subjects on dapagliflozin had required rescue versus 44% on placebo
- The evidence from this study corresponds with the findings of other Phase III studies of dapagliflozin (e.g. in dual therapy), thereby showing that the efficacy of dapagliflozin remains similar regardless of the drugs it is combined with in order to achieve glycaemic control
- UK real-world evidence (n=1,732) from a retrospective, Clinical Practice Research Datalink (CPRD) observational study showed improvements in HbA1c and weight that are consistent with those reported in clinical trials. In this observational study, approximately one third of patients received dapagliflozin as part of a triple regimen demonstrating the clinical need for the use of dapagliflozin as part of a triple therapy regimen in the UK
- In the absence of head to head trials comparing dapagliflozin with an active comparator in a triple regimen a NMA has been carried out. This demonstrates:
    - No statistically significant differences between dapagliflozin and the DPP4-is in change from baseline in HbA1c and SBP; and the incidence of 'any hypoglycaemic event'
    - A significantly greater reduction in total body weight with dapagliflozin compared with DPP4-is
    - No significant differences between dapagliflozin and the other SGLT2-i based on a comparison versus each individual dose (Canagliflozin 300mg; Canagliflozin 100mg; Empagliflozin 10mg; Empagliflozin 25mg) in the key outcomes of

HbA1c; SBP; change in total body weight; and any hypoglycaemic event

4.1 *Identification and selection of relevant studies*

A systematic review of the published and unpublished literature was conducted to identify information from RCTs that presented efficacy and/or safety data for anti-diabetic agents used within a triple therapy regimen in combination with MET and SU or MET and DPP4-i in adult patients with type 2 diabetes mellitus.

The search terms comprised disease terms, a study design filter and drug terms for anti-diabetic agents licensed for use in the UK. The study design filter was adapted from the Scottish Intercollegiate Guidelines Network (SIGN) guidelines to identify RCTs using a combination of MeSH and free text terms. The disease facet was adapted from the NG28 NICE type 2 diabetes guideline and a diabetes Cochrane review (Swinnen 2011). Searches of the electronic databases and relevant conference proceedings were carried out on 15 December 2015 (Table 5). All literature databases were searched from database inception to search date. Clinicaltrials.gov was searched for only the previous year (2015). The full search strategy is given in Appendix 2.

Table 5: Summary of data sources for the systematic review

Search strategy component	Sources
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL) Clinicaltrials.gov (searched for the last one year for studies with results)

Embase®: Excerpta Medica Database; HTA: health technology assessment; MEDLINE® : Medical Literature Analysis and Retrieval System Online; MTA: multiple technology appraisal

In addition to the database searches, conferences were searched for the last 3 years (2013, 2014, 2015) (Table 6).

Table 6: Conferences searched for the systematic review and the service provider used

Conference name	Link	Year
American Diabetes Association (ADA)	http://professional.diabetes.org/content/previous-scientific-sessions-abstracts-posters-and-webcasts	2013, 2014, 2015
European Association for the study of Diabetes (EASD)	http://www.easd.org/index.php?option=com_content&view=article&id=69&Itemid=509	2013, 2014, 2015

The eligibility criteria used in the clinical systematic review are listed in Table 7.

Abstracts of citations identified through the searches were reviewed for inclusion based on title and abstract alone. Full-text copies of studies that potentially met the inclusion criteria were obtained. Full-text papers were screened and included or excluded accordingly. Relevant systematic reviews (Mearns 2015; Schroeder 2015); and the recent NICE guideline in type 2 diabetes (NG28 (NICE 2015)) were used to cross-validate the included studies.

Data from the studies were extracted by two analysts and any discrepancies were reconciled by a third independent analyst. A critical appraisal of the study, using the assessment criteria recommended in the NICE manufacturer's template, was also conducted in a similar manner.

Table 7: Inclusion and exclusion criteria of the systematic review

	Criteria	Rationale
Inclusion criteria	Population • Age: Adults (≥18 years) • Gender: Any • Race: Any • Disease: Adult patients with inadequately controlled type 2 diabetes mellitus (HbA1c >6.5%, FPG > 7mmol/L or 2-hour PPG > 10 mmol/L) despite dual therapy with MET and SU or MET and a DPP4-i	The patient population has been restricted to match that stated in the decision problem for dapagliflozin
	Intervention • Dapagliflozin	Intervention defined by the NICE decision problem for treatment of patients with inadequately controlled type 2 diabetes mellitus
	The following interventions on top of MET and SU: • DPP4-is ○ Alogliptin ○ Linagliptin ○ Saxagliptin ○ Sitagliptin ○ Vildagliptin • GLP-1 analogues ○ Albiglutide ○ Exenatide ○ Liraglutide ○ Lixisenatide ○ Dulaglutide • AGIs ○ Acarbose ○ Miglitol • Insulin ○ Long-acting insulin ○ Intermediate-acting insulin ○ Short-acting insulin or fast/rapid-acting insulin ○ Premix insulin ○ Combination of insulins ○ Intermediate-acting insulin • SGLT2-is ○ Empagliflozin ○ Canagliflozin ○ Dapagliflozin • Meglitinides ○ Repaglinide ○ Nateglinide • TZDs	Potentially enable both direct and indirect comparisons between the interventions of interest; and ensure the broadest possible network of evidence All anti-diabetic agents used in the UK for the treatment of type 2 diabetes were included in the search

	○ Pioglitazone The following interventions on top of MET and DPP4-i will be of interest to the review • SUs ○ Tolbutamide ○ Glipizide ○ Gliclazide ○ Glibenclamide ○ Glyburide ○ Glibornuride ○ Glimepiride • GLP-1 analogues ○ Albiglutide ○ Exenatide ○ Liraglutide ○ Lixisenatide ○ Dulaglutide • SGLT2-is ○ Empagliflozin ○ Canagliflozin ○ Dapagliflozin • Insulin ○ Long-acting insulin ○ Intermediate-acting insulin ○ Short-acting insulin or fast/rapid-acting insulin ○ Premix insulin ○ Combination of insulins ○ Intermediate-acting insulin • SGLT2-is ○ Empagliflozin ○ Canagliflozin • TZDs ○ Pioglitazone • AGIs ○ Acarbose ○ Miglitol • Meglitinides ○ Repaglinide ○ Nateglinide	
	Comparators Any of the included interventions alone or in combination with another intervention of interest	Potentially enable both direct and indirect comparisons between the interventions of interest; and ensure the broadest possible network of evidence
	Study design • Active or placebo-controlled RCTs • With duration > 4 weeks • with any blinding status	RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the quantity of evidence, studies with double blind, single blind, and open label design were included
	Outcomes Studies reporting at least one of the following	In line with the NICE scope

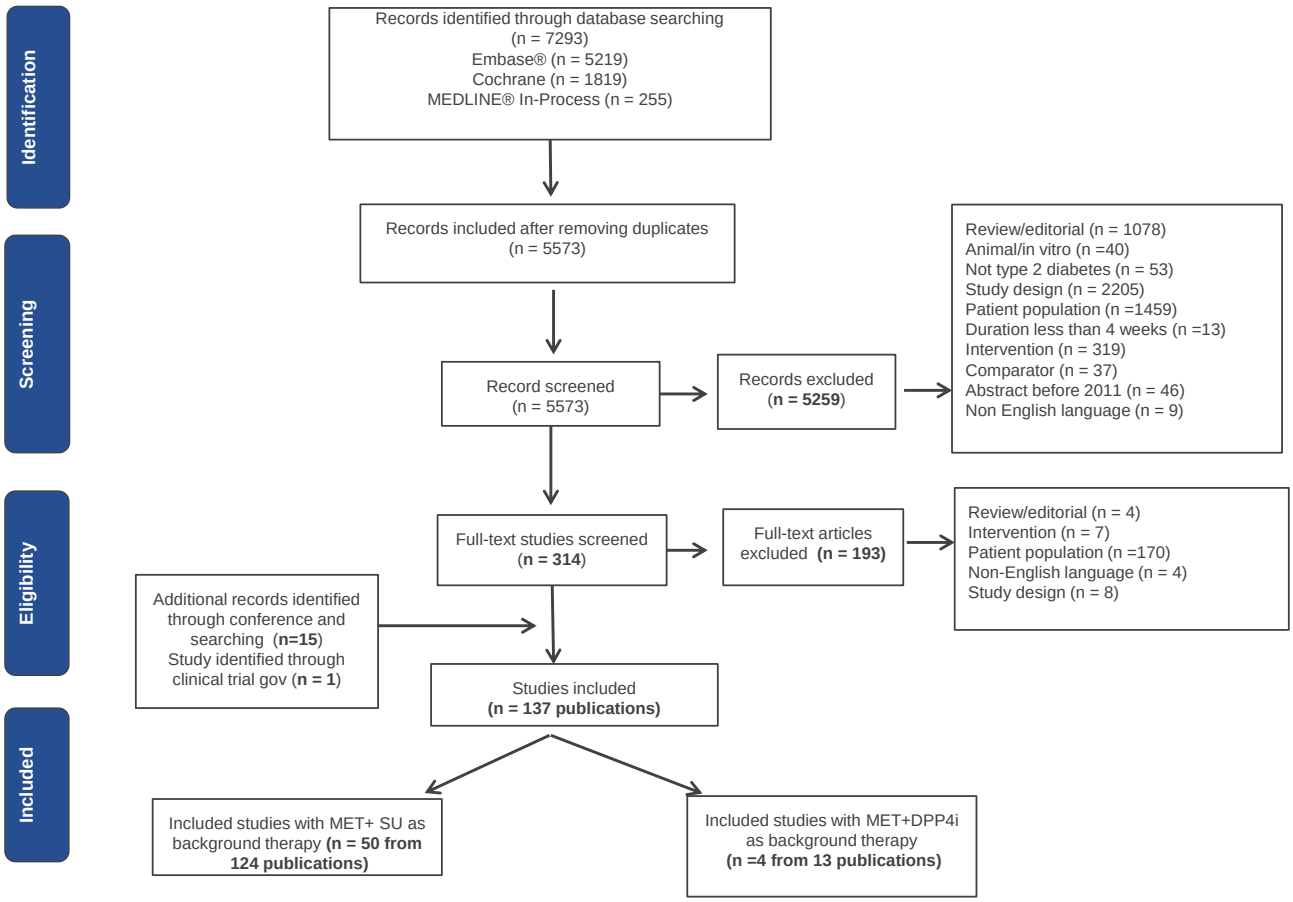
	outcomes of interest: • HbA1c • Body weight • SBP • Hypoglycaemia • Severe hypoglycaemia	
	Language • Only studies with the full-text published in English language were included	The restriction would not limit results substantially due to data availability in English language
	Publication timeframe for literature searches were from database inception to present Clinicaltrials.gov was search for 2015 only	There was no restriction on timeframe
Exclusion criteria	Excluded population • Studies focusing on children or adolescents only (studies enrolling a mixed patient population of children and adults will be excluded if subgroup data for adult patients are not reported) • Studies on type 2 diabetes mellitus patients but focused on other diseases (e.g. chronic kidney disease, etc.) are not of interest • Studies includingT1DM and type 2 diabetes mellitus patient population without sub-population results • All patients having renal or hepatic impairment will be excluded • Studies with >15% of patients using a therapy regimen other than combination therapy with MET and a DPP4-i at baseline • Studies with >15% of patients using a therapy regimen other than combination therapy with MET and a SU at baseline	This study population was not relevant to the decision problem
	Excluded interventions/comparators • Studies not assessing any of the included interventions • Studies assessing combination of included and non-included intervention • Studies where interventions are administered for the treatment of AEs • Studies comparing different doses of the same intervention (i.e. dose-ranging studies), two formulations of the same intervention, and intervention with two different routes of administration	These interventions are not relevant to the decision problem
	Excluded comparators • Studies assessing comparators other than the included comparators • Studies assessing combination of included and non-included comparators	These comparators are not relevant to the decision problem Studies assessing included intervention with the combination of included + non-included intervention will not contribute to the analysis due to lack of a common comparator
	Study design • Non-randomised controlled trials • Prospective/retrospective cohort studies • Single-arm studies • Case studies and case reports • Case-control studies	The design of such studies was not relevant to the decision problem

	• Cross-sectional studies • Review, letters to the editors, and editorials	

MET: metformin; NICE: National Institute for Health and Care Excellence; PPG: postprandial plasma glucose

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 3. A total of 7,293 citations were identified from the database searches, which was reduced to 5,573 (below) after de-duplication.

Figure 3: PRISMA flow diagram of the systematic review process



As shown in the PRISMA flow diagram, 54 studies (reported in 137 publications) met the inclusion/exclusion criteria of the systematic review. Fifty studies provided data explicitly for patients with triple including MET and SU as background therapy and four studies included in the systematic review evaluated triple therapy of type 2 diabetes mellitus including MET and DPP4-i as background therapy.

Included studies with MET + SU as background therapy

Only one of the 50 studies provided data for dapagliflozin in combination with MET and SU in the treatment of patients with type 2 diabetes mellitus who are inadequately controlled when treated with dual therapy with MET and SU (Matthaei 2015c). Forty nine studies provided data for the comparators. A full list of studies identified by the systematic review and relevant to the decision problem is given in Table 8. The list of studies (10 studies) that were included in the systematic review and were relevant to the decision problem but were excluded from the network meta-analysis including the reason for exclusion are also identified in Table 9.

Table 8: List of included studies meeting the inclusion/exclusion criteria of the systematic review and included in the network meta-analysis

Primary reference	Country	Number randomised	Treatment duration (weeks)	Intervention	Secondary reference
Met + SU triple therapy studies (all studies mentioned below were included in the expanded networks)					
Met + SU studies included in restricted network (studies which included DPP4-i and SGLT2-i)					
Hermansen et al., 2007 (Hermansen 2007)	Multinational	229	24	Sitagliptin + Met + SU Placebo + Met + SU	
Haering 2015 (Haering 2015a)	Multinational	669	76	Empagliflozin (25 mg) + Met + SU Empagliflozin (10 mg) + Met + SU Placebo + Met + SU	(Haering 2013c; Haering 2013b; Lewin 2015; Haering 2014; Haering 2013a; Haering 2015b)
Hong et al., 2015 (Hong 2015)	South Korea	344	24	Vildagliptin Met + SU Met + SU (Dose increase)	
Ji et al., 2015 (Ji 2015)	Multinational	678	18	Canagliflozin (300 mg OD) + Met + SU Canagliflozin (100 mg OD) + Met + SU Placebo + Met + SU	
Lukashevich 2014 (Lukashevich 2014)	Multinational	318	24	Vildalgliptin + Met + Glimepiride Placebo + Met + Glimepiride	(Lukashevich 2012; Lukashevich 2013b; Lukashevich 2013a)
Liu et al., 2013 (Liu 2013)	Taiwan	120	24	Pioglitazone + Met + SU Sitagliptin + Met + SU	
Matthaei et al., 2015 (Matthaei 2015c)	Multinational	219	52	Dapagliflozin + Met + SU Placebo + Met + SU	(Grandy 2015; Matthaei 2014a; Matthaei 2013b; Matthaei 2014b; Grandy 2014; Matthaei 2015a; Bowering 2015; Matthaei 2015b; Sternhufvud 2014)

Primary reference	Country	Number randomised	Treatment duration (weeks)	Intervention	Secondary reference
Moses et al., 2014 (Moses 2014)	Multinational	257	24	Placebo + Met + SU Saxagliptin + Met + SU	(Moses 2012; Moses 2013c; Given 2013; Moses 2013b; Moses 2013a)
NCT01590771	China	223	24	Sitagliptin + Met + SU Placebo + Met + SU	
Nogueira et al., 2014 (Nogueira 2014)	Brazil	35	24	Sitagliptin + Met + Glyburide NPH insulin + Met + Glyburide	(Nogueira 2012; Nogueira 2011; Santos 2012)
Owens et al., 2011 (Owens 2011)	Multinational	1058	24	Linagliptin + Met + SU Placebo + Met + SU	(Zeng 2013; Owens 2010)
Round et al., 2013 (Round 2013a)	Asia-Pacific	427	24	Sitagliptin + Met + SU Placebo + Met + SU	(Round 2013b)
Schernthaner et al., 2013 (Schernthaner 2013b)	Multinational	756	52	Canagliflozin + Met + SU Sitagliptin + Met + SU	(Schernthaner 2013a; Polidori 2014; Schernthaner 2012; Bailey 2014; Stull 2013; Schernthaner 2015)
Wilding et al., 2013 (Wilding 2013)	Multinational	469	52	Canagliflozin (300 mg OD) + Met + SU Canagliflozin (100 mg OD) + Met + SU Placebo + Met + SU	(Diels 2015; Vercruysse 2013; Wilding 2015a; Wilding 2012b; Wilding 2012a)
Met + SU studies included in expanded network but not included in basecase NMA					
Aljabri et al., 2004 (Aljabri 2004)	Canada	62	16	Pioglitazone + Met + SU NPH insulin + Met + SU	
Bergenstal et al., 2009 (Bergenstal 2009)	US	372	24	Exenatide + Met + SU BIAsp30 (BID) + Met + SU BIAsp30 (QD) + Met + SU	
Charpentier and Halimi, 2009 (Charpentier 2009)	France	299	28	Pioglitazone + Met + SU Placebo + Met + SU	
Davies et al., 2013 (Davies 2013)	Multinational	222	26	Exenatide + Met + SU Insulin detemir + Met + SU	
Derosa et al., 2009 (Derosa 2009)	Italy	103	15	Acarbose + Met + SU Repaglinide + Met + SU	

Primary reference	Country	Number randomised	Treatment duration (weeks)	Intervention	Secondary reference
Derosa et al., 2010 (Derosa 2010)	Multinational	350	24	Pioglitazone + Met + SU Acarbose + Met+SU	
Diamant et al., 2014 (Diamant 2014)	USA (and Puerto Rico), the European Union, Russia, Australia, Korea, Taiwan, and Mexico	467	156	Exenatide + Met + SU Insulin Glargine + Met + SU	(Diamant 2011; Han 2013; Diamant 2010; Trautmann 2014)
Heine et al., 2005 (Heine 2005)	Multinational	551	26	Exenatide + Met + SU Insulin glargine + Met + SU	(Lofthouse 2006; Matyjaszek-Matuszek 2013; Boye 2006)
Home et al., 2015 (Home 2015b)	Multinational	685	156	Albiglutide + Met + Glimepiride Pioglitazone + Met + Glimepiride Placebo+ Met + Glimepiride	(Stewart 2013; Shamanna 2014; Home 2014a; Home 2014b; Home 2013)
Hartemann-Heurtier et al., 2009	France	28	24	Pioglitazone + Met + SU NPH insulin + Met + SU	(Hartemann-Heurtier 2009)
Holman et al., 2007 (Holman 2007)	Europe	708	156	Prandial Insulin aspart + Met + SU Basal Insulin detemir + Met + SU Biphasic Insulin Aspart + Met + SU	(Hartweg 2009; Farmer 2011; Holman 2009; Farmer 2009; Dinneen 2008; Johnson 2010)
Giorgino et al., 2015 (Giorgino 2015)	Multinational	810	78	Dulaglutide (1.5 mg) + Met + Glimepiride Dulaglutide (0.75 mg) + Met + Glimepiride Insulin glargine + Met + Glimepiride	(Giorgino 2014d; Reaney 2014b; Reaney 2014a; Giorgino 2014c; Giorgino 2014b; Giorgino 2014a)
Kendall et al., 2005 (Kendall 2005)	US	734	30	Exenatide (5 µg BID) + Met + SU Exenatide (10 µg BID) + Met + SU Placebo + Met + SU	
Lu et al., 2013 (Lu 2013)	Taiwan	51	16	Exenatide + Met + SU Placebo + Met + SU	
Lam et al., 1998 (Lam 1998)	China	90	24	Acarbose + Met + Glibenclamide or gliclazide Placebo + Met + glibenclamide or Gliclazide	

Primary reference	Country	Number randomised	Treatment duration (weeks)	Intervention	Secondary reference
Nauck et al., 2007 (Nauck 2007)	Multinational	505	52	Exenatide + Met + SU Biphasic insulin aspart 30/70 + Met + SU	
Nomoto et al., 2015 (Nomoto 2015)	Japan	31	14	Liraglutide+Met+SU Insulin Glargine+Met+SU	
Pan et al., 2014 (Pan 2014)	Multinational	391	24	Lixisenatide + Met + SU Placebo + Met + SU	
Russell-Jones et al., 2009 (Russell-Jones 2009)	Multinational	581	26	Liraglutide + Met + Glimepiride Insulin glargine + Met + Glimepiride Placebo + Met + Glimepiride	(Buse 2015; Russell-Jones D 2009)
Rosenstock et al., 2014 (Rosenstock 2014)	Multinational	859	24	Lixisenatide + Met + SU Placebo + Met + SU	(Ratner 2011; Onishi 2015)
Standl et al., 2001 (Standl 2001)	Multinational	154	24	Miglitol + Met + Glibenclamide Placebo + Met + Glibenclamide	
Strojek et al., 2009 (Strojek 2009b)	Multinational	480	26	Insulin glargine + Met + SU BIAsp30 + Met + SU	(Kalra 2010; Strojek 2009a)
Seino et al., 2014 (Seino 2014)	Multinational	120	6	Lixisenatide QD+Met+SU Lixisenatide BID+Met+SU Placebo+Met+SU	
Wu et al., 2011 (Wu 2011)	China	23	16	Exenatide + Met + SU Placebo + Met + SU	(Wu 2010)
Yang et al., 2013 (Yang 2013)	China and Japan	521	24	BiAsp 30 + Met + Glimepiride Insulin glargine + Met + Glimepiride	(Yang 2012)
Yiangou et al., 2013* (Yiangou K 2013)	Cyprus	54	36	Sitagliptin + Met + Glimepiride Insulin glargine + Met + Glimepiride	
Met + DPP4i triple therapy studies					
Violante et al., 2012 (Violante 2012)	Multinational	255	20	Exenatide + Met + Placebo Exenatide + Sitagliptin + Met	(Oliveira 2012)
Mathieu et al., 2015	Multinational	320	52	Dapagliflozin + Saxagliptin + Met	(Mathieu 2015b; Mathieu 2015a;

Primary reference	Country	Number randomised	Treatment duration (weeks)	Intervention	Secondary reference
(Mathieu 2015d)				Placebo + Saxagliptin + Met	Mathieu 2015c); (Mathieu 2015f; Mathieu 2015e)
Jabbour et al., 2014 (Jabbour 2014)	Multinational	451	48	Dapagliflozin + Sitagliptin + Met Placebo + Sitagliptin + Met	(Jabbour 2012a; Jabbour 2012b)
Derosa et al., 2015 (Derosa 2015)	Italy	53	4..33	Acarbose + Met + Vildagliptin Placebo + Met + Vildagliptin	(Derosa 2014)

NPH, neutral protamine hagedorn; OD: once daily; QD: quaque die (once a day); US: United States; USA: United States of America
*Study includes met + SU + DPP4 but SE cannot be imputed (this study was included in sensitivity analysis)

A full list of all studies excluded from the systematic review is given in Appendix 5.

A number of different networks were carried out with results presented for each network in Section 4.10. Given the heterogeneity in the evidence base in terms of the patient populations, study design and study duration, the base case NMA focuses only on studies that evaluate comparators directly relevant to UK clinical practice: DPP4-is and other SGLT2-is. This is in line with the approach followed by Boehringer Ingelheim in the STA evaluation of empagliflozin in the same patient population. The base case analysis utilises data from study endpoints regardless of study duration to include as much data as possible in the NMA; and as SGLT2-i efficacy has been demonstrated to be consistent over at least two years.

Included studies with MET + DPP4-i as background therapy

Of the four studies on a background of MET and DPP4-i, two studies assessed dapagliflozin; one study assessed exenatide; and one study assessed acarbose. However, at this time due to lack of evidence for the comparators of this appraisal's scope, an indirect comparison was only possible to compare dapagliflozin with acarbose, which is not a treatment relevant to the decision problem of this appraisal (see Section 1.1 for further detail). It is not currently possible to carry out an NMA or indirect comparison compared to any of the comparators in the final scope due to the lack of evidence for the other comparators in combination with MET + DPP4 meaning that a robust, evidence-supported estimate of cost-effectiveness for the use of dapagliflozin + MET + DPP4 is not possible. Therefore, this submission focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET + SU. Should additional evidence become available in the future, NICE could consider an assessment of dapagliflozin on a background of MET + DPP4-i.

Table 9: Studies included in the SLR but excluded from the NMA

Primary study name	Treatment arm	Reason	Secondary reference
Al-Shaikh et al., 2006 (Al-Shaikh 2006)	Human premixed insulin (30% regular, 70% NPH insulin) Insulin Glargine + Met + SU	Triple therapy vs monotherapy (No Met + SU as common comparator)	
Bell et al., 2011 (Bell 2011)	Glimepiride+Metformin SR+pioglitazone Insulin 70/30 mix+metformin SR	No Met + SU as common comparator	

Primary study name	Treatment arm	Reason	Secondary reference
Chen et al., 2015 (Chen 2015a)	Vidagliptin + MET+SU Saxagliptin + MET+SU	Same class comparison (DPP4)	(Chen 2015b)
Esposito et al., 2008 (Esposito 2008)	NPL Insulin + Metformin + Sulfonylurea Insulin glargine + Metformin + Sulfonylurea	Same comparison	
Goudswaard et al., 2004 (Goudswaard 2004)	NPH insulin + MET + SU Human premixed insulin (30% regular, 70% NPH insulin)	Triple therapy vs mono therapy (No Met + SU as common comparator)	
Home et al., 2015 (Home 2015a)	Insulin glargine + Met + glimepiride NPH insulin + Met + glimepiride	Same comparison	
Janka et al., 2005 (Janka 2005)	Insulin glargine + Met + Glimepiride Human premixed insulin (30% regular, 70% NPH insulin)	Triple therapy vs mono therapy (No Met + SU as common comparator)	(Janka 2007)
Onishi et al., 2013 (Onishi 2013)	Insulin degludec + Met + SU Insulin glargine + Met + SU	Same comparison	
Park et al., 2014 (Park 2014)	Insulin glargine + Met Insulin glargine + Glimepiride Insulin glargine + Glimepiride + Met	No Met + SU as common comparator	
Lopez-Alvarenga et al., 1999 (Lopez-Alvarenga 1999)	Acarbose + Met + SU Insulin NPH + Met + SU Placebo + Met + SU	Cross-over study with no data available before cross-over	

NPH, neutral protamine hagedorn; NPL, neutral protamine lispro; SLR: systematic literature review; SR sustained release

4.2 *List of relevant randomised controlled trials*

Clinical evidence base to support the selective submission of the product

AstraZeneca would like NICE to consider dapagliflozin for use in a triple therapy regimen in combination with MET and SU for adults with type 2 diabetes mellitus poorly controlled on MET plus SU: we have therefore presented evidence from the key placebo-controlled phase III trial in type 2 diabetes mellitus patients inadequately controlled on MET plus SU (Study 5) (Matthaei 2015c; AstraZeneca 2013a). At this time due to lack of data for the comparators in this appraisal's scope, it is not possible to carry out an NMA or indirect comparison compared to any of the comparators in the final scope in combination with MET + DPP4-i meaning that an estimate of cost-effectiveness for the use of dapagliflozin + MET + DPP4 is not possible. Therefore, this submission focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET + SU.

Comparison to injectables (insulin and GLP-1s) is not presented in this submission. While it is an option after dual therapy recommended in clinical guidelines (SIGN 2010; NICE 2015), it is not usually considered to be the first option due to expense and the need to inject. IMS data shows that 62% of patients who were previously prescribed MET+SU and are currently prescribed a triple therapy regimen are prescribed a DPP4-i + MET + SU (Patient Data, IMS Information Solutions UK Ltd, December 2015).The DPP4-is are therefore the key comparator for this submission.

The primary data for this appraisal are from Study 5, a placebo controlled Phase III RCT of dapagliflozin with MET plus SU. An overview of this study is presented in Table 10. Study 5 is a 24-week randomised, double-blind, parallel-group Phase III study, with an on-going 28 week blinded extension period, to evaluate the efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus inadequately controlled with the combination of MET plus SU (Table 10) (Matthaei 2013a). In the following sections we report the design, methodology and results of this study. Study 5 contains the core data used in the economic analysis.

As there is no head to head data vs DPP4-is, a NMA has been performed to compare dapagliflozin RCT evidence for triple therapy (add-on to MET plus SU) with DPP4-i RCT evidence in triple therapy (add-on to MET plus SU) (see Section 4.10).

The two other SGLT2-is available in the UK (canagliflozin and empagliflozin) are also comparators in this submission. The NMA provides estimates of comparative effectiveness for dapagliflozin versus these treatments yet found no statistically significant differences.

Supportive evidence

In addition, we present supportive evidence from a sub-analysis of clinical studies (Studies 18 (NCT01031680) and 19 (NCT01042977)) evaluating the efficacy of dapagliflozin as part of a triple combination therapy in Appendix 20.

The two studies assessing dapagliflozin use in combination with MET + DPP4-i are summarised in Appendix 6.

4.3 *Summary of methodology of the relevant randomised controlled trials*

Table 10: Comparative summary of trial methodology

Trial number (acronym)	**Study 5**
Study Description	This was a 24-week, international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, Phase IIIb study with a 28-week blinded extension period evaluating the efficacy and safety of dapagliflozin 10 mg daily in subjects with Type 2 diabetes who were inadequately controlled on MET and SU
Location	46 centres in North America (Canada) and Europe (Czech Republic, Germany, Poland, Slovak Republic, and Spain) enrolled subjects, and 45 centres randomised subjects
Trial design	Phase III randomised double-blind, parallel-group, placebo-controlled trial
Eligibility criteria for participants	Key inclusion criteria: Type 2 diabetes Age ≥ 18 years HbA1c ≥ 7.0–≤ 10.5% (at randomisation) Stable dose combination therapy of MET ≥ 1,500 mg/d and maximum tolerated dose (MTD) of SU (which must be at least half the maximum dose (MD) for ≥ 8 weeks prior to enrolment) MET could not be down-titrated; SU could be down-titrated only once to mitigate hypoglycaemic events; no up-titration of MET or SU was allowed Key exclusion criteria: Diagnosis of type 1 diabetes mellitus, diabetes insipidus or a history of diabetic ketoacidosis Symptoms of poorly controlled diabetes (including marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to enrolment)

	FPG >270 mg/dL (>15 mmol/L) Body mass index (BMI) ≥45.0 kg/m^2 Thyroid-stimulating hormone (TSH) values outside normal range at Visit 1 History of bariatric surgery. History of liposuction was allowed Clinically significant renal, hepatic, haematological, and oncological disorders or those with an immunocompromised status Recent cardiovascular event (within 2 months) or New York Heart Association (NYHA) class III or intravenous (IV) congestive heart failure Systolic blood pressure (SBP) 170 mm Hg or more or diastolic blood pressure (DBP) 110 mm Hg or more Use of any anti-hyperglycemic medications other than MET or SU during the 10 weeks prior to enrolment
Settings and locations where the data were collected	The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Form (eCRF) as specified in the study protocol and in accordance with the instructions provided The patients will record results of self-monitored FPG and information about hypoglycaemic events in paper diaries
Trial drugs	Dapagliflozin (10 mg) OD Placebo OD In combination with MET (≥ 1,500 mg/day) and SU (at MTD but at least 50% of MD)
Primary outcomes (including scoring methods and timings of assessments)	To compare the change from baseline in HbA1c to week 24 between dapagliflozin 10 mg in combination with MET and SU and placebo in combination with MET and SU
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	<u>Secondary outcomes</u> To compare the change from baseline in FPG to week 24 between dapagliflozin and placebo To compare the change from baseline in total body weight to week 24 between dapagliflozin and placebo To compare the proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24 between dapagliflozin and placebo To compare the change from baseline in seated SBP to week 8 between dapagliflozin and placebo <u>Other Outcomes:</u> Change from baseline to week 24 in fasting lipids (total cholesterol (TC), LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, and triglycerides) and C-peptide Proportion of patients who discontinued for lack of efficacy or were rescued for failing to maintain FPG prespecified rescue criteria <u>Safety Outcome:</u> To evaluate the safety and tolerability of dapagliflozin by assessment of AEs, including CV events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycemic events and physical examination findings
Pre-planned subgroups	Subgroup analyses for AEs were performed for age (< 65 and ≥ 65 years), gender, female age, and race. Efficacy subgroups were: Baseline HbA1c < 8% Baseline HbA1c ≥ 8% and < 9% Baseline HbA1c ≥ 8% Baseline HbA1c ≥ 9% Baseline BMI ≥27 kg/m^2 Baseline BMI ≥30 kg/m^2

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Statistical analyses were performed for the 24-week double-blind period (Table 11). The primary objective of this study was to compare dapagliflozin to placebo in terms of the primary efficacy endpoint of change in HbA1c from baseline to week 24.

Four key secondary variables were specified: (1) Change in fasting plasma glucose (FPG) from baseline to week 24, (2) change in total body weight from baseline to week 24 (3) proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0% at week 24, and (4) change in seated SBP from baseline to week 8.

A hierarchical closed testing procedure was used to control the Type I error rate across the primary and key secondary objectives. If the primary endpoint was statistically significant, key secondary variables were tested in the order presented above. Treatment comparisons were individually tested at a two-sided significance level of 0.050. For all other variables, nominal p-values were reported without significance testing.

The efficacy endpoints were evaluated in the full analysis set, which included all randomised subjects who received at least 1 dose of study medication during the 24-week double-blind ST treatment period who had a non-missing baseline value and at least 1 post-baseline value for at least 1 efficacy variable to be analysed at week 24. The intention to treat (ITT) principle was preserved despite the exclusion of subjects who took no study medication, as the decision of whether or not to begin treatment during the randomised treatment period could not be influenced by knowledge of the assigned treatment. Where appropriate, missing data were replaced using the last observation carried forward (LOCF) approach.

The primary efficacy variable, change in HbA1c from baseline to week 24, was analysed by a longitudinal repeated measures analysis using 'direct likelihood', with fixed categorical effects of treatment, week, treatment-by-week interaction, as well as the continuous fixed covariates of baseline and baseline-by-week interaction. Data for scheduled timepoints up to week 24 prior to rescue were included in the longitudinal repeated measures analysis. The model provided least-squares, mean estimates, standard errors (SEs), 2-sided 95% CIs for mean change at week 24 within and between treatments. The treatment group comparison between dapagliflozin 10 mg and placebo at week 24 was performed at the 2-sided 0.05 confidence level. Other continuous variables (including the key secondary endpoints) were analysed using an analysis of covariance (ANCOVA) model including terms for treatment group and baseline covariate, using LOCF to impute missing week 24 values.

The proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24, was analysed using the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu when there are at least 5 responders on average by treatment group. For proportion of responders, estimates, confidence intervals (CIs), and tests were obtained using this methodology with adjustment for baseline HbA1c.

- Efficacy was evaluated in the full analysis set (FAS), with ITT
- The primary endpoint was evaluated using longitudinal repeated measures (LRM) analysis
- The secondary endpoints were evaluated using LOCF analysis
- Safety was evaluated in the safety analysis set

Table 11: Summary of statistical analyses in the RCTs

Hypothesis objective	After 24 weeks of treatment, a greater mean reduction from baseline in hemoglobin A1c (HbA1c) achieved with dapagliflozin 10 mg compared with placebo in subjects with Type 2 diabetes who had inadequate glycemic control on a combination of MET and SU was expected
Statistical analysis	Analysis of efficacy Objectives for the long term (LT) extension period were assessing the safety, tolerability, and long-term efficacy including maintenance of the efficacy of dapagliflozin in combination with MET and SU when administered for the entire duration of the ST + LT period. No statistical hypotheses were defined for the ST + LT period as all analyses were considered exploratory All variables to be analysed after the 24 weeks of double-blind treatment were to be re-examined at the week 52 timepoint. In general, the data from this period were to be summarised descriptively using point estimates and 95% confidence intervals (CIs) Longitudinal repeated measures analysis (52 week study report) For changes from baseline, a longitudinal repeated measures analysis using 'direct likelihood' was performed. The SAS procedure PROC MIXED was to be used. The preferred model had to include the fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Model results were only reported for a timepoint if at least 10 subjects had both baseline and Week t measurements in both treatment groups. Otherwise, just mean, standard deviation (SD), and mean change from baseline (SD) were displayed for Week t in the table LOCF (24 week study report) The LOCF approach means that, for all changes (or percent changes) from baseline to a specific timepoint post-baseline, analyses were based on measurements available at that timepoint or the last post-baseline measurement prior to the timepoint if no measurement was available at that timepoint. Unless otherwise specified, if a subject initiated rescue medication, the last value taken on or before the first rescue dose was used for analysis Analysis of proportions The methodology of Zhang, Tsiatis, and Davidian (Zhang et al 2008) and Tsiatis, Davidian, Zhang, and Lu (Tsiatis et al 2007) was used when there were at least 5 responders on average by treatment group. For the proportion of responders (e.g., meeting HbA1c criteria), estimates, CIs, and tests were obtained using this methodology with adjustment for baseline value (e.g., HbA1c value at baseline). For each treatment group, the probability of response was first modeled using a logistic regression model with baseline value (e.g., HbA1c value at baseline) as covariate. Treatment group estimates of response rate were then obtained by integrating each group's modeled probability of response over the observed distribution of covariates (combined across groups). The difference in response rate between the dapagliflozin treatment group and the placebo group was displayed along with the 95% CI When there were less than 5 responders on average by treatment group, the unadjusted proportions and difference between the treatment groups, exact 95% CI were provided Analysis of safety The safety evaluations included analyses of AEs, laboratory values, electrocardiogram (ECG), vital signs (pulse and BP), hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR) and physical examination findings. The analysis of safety was based on the safety analysis set. Safety data gained during the 24-week double-blind treatment period, the 28-week site- and subject-blinded extension period, as well as during the 3-week safety follow-up period were evaluated. Safety data were summarised descriptively and presented by treatment group. The primary safety analyses included all data regardless of rescue. For data such as hypoglycemia, sensitivity analyses were performed on data collected prior to rescue

Analysis sets	Description of analysis sets The evaluation of efficacy was performed for the full analysis set as outlined below. The primary analysis was based on the full analysis set. The analysis of safety was based on the safety analysis set. A detailed description of analysis sets is given below. The decision to include or exclude subjects from each analysis set was based on relevant protocol deviations and was performed in a blind data review prior to unblinding Safety analysis set The safety analysis set included all randomised subjects who received at least 1 dose of study medication and who provided any safety records. The safety analysis set consisted of all subjects who received at least 1 dose of double-blind study medication during the ST double-blind treatment period. The safety analysis set included any subject who accidentally received double-blind study medication but was not randomised in the study. This subject was presented according to the treatment received. As determined prior to unblinding of the study, all subjects in the safety analysis set were analysed according to the treatment group to which they were randomised. Where appropriate, missing data were replaced using the last observation carried forw ard (LOCF) approach Full analysis set The full analysis set included all randomised subjects (as randomised) who received at least 1 dose of study medication during the 24-week double-blind ST treatment period who have a non-missing baseline value and at least 1 post-baseline value for at least 1 efficacy variable during the ST double-blind treatment period. The intention-to-treat principle was preserved despite the exclusion of subjects who took no study medication, as the decision of whether or not to begin treatment during the randomised treatment period could not be influenced by knowledge of the assigned treatment Short-term Completers Analysis Set The ST Completers Analysis Set consisted of all subjects in the full analysis set who did not receive rescue medication during the ST double-blind treatment period, completed the ST double-blind treatment, and entered the LT extension period. It is a subset of the full analysis set. Whenever using the ST completers analysis set, subjects were presented in the treatment group to which they were randomised at the start of the ST double-blind treatment period
Sample size, power calculation	Sample size and power calculations were based on statistical testing of the primary endpoint, which was the change in HbA1c from baseline to week 24 (end of ST double-blind treatment period). Sample size and power calculations have been described in the study-specific SAP for ST double-blind treatment period and in the 24-week ST clinical study report (CSR)
Data management, patient withdrawals	A subject that decided to discontinue investigational product was always asked about the reason(s) and the presence of any AEs. If possible, the subject underwent procedures of Visit 11 (End of Treatment Visit) as soon as possible after last intake of investigational product and had a Follow-up Visit (Visit 12) 3 weeks after last intake of investigational product. AEs were followed up. Patient's diaries and all investigational products had to be returned by the subject Stop of investigational product led to withdrawal from the study after completion of the Follow-up Visit (Visit 12) Subjects with an increased CK >10 × upper limit of normal (ULN) had their investigational product temporarily stopped and underwent a repeated CK test preferably within 24 hours, but not exceeding 72 hours. If repeated CK was confirmed >10 × ULN, the subject had to permanently discontinue study medication (in which case an AE was reported). Otherwise, investigational product could be resumed unless otherwise contraindicated Subjects with increased liver function tests had repeat liver function tests within 3 days. If repeat liver function tests still were increased, the subject had to immediately permanently discontinue study medication (in which case an AE had to be reported). If repeat liver function tests still were increased but did not meet pre-defined criteria, the subject had to continue study medications unless otherwise contraindicated After discontinuation of investigational product, alternative anti-hyperglycemic treatment was initiated according to the Investigator's judgment and according to local medical practice

4.5 *Participant flow in the relevant randomised controlled trials*

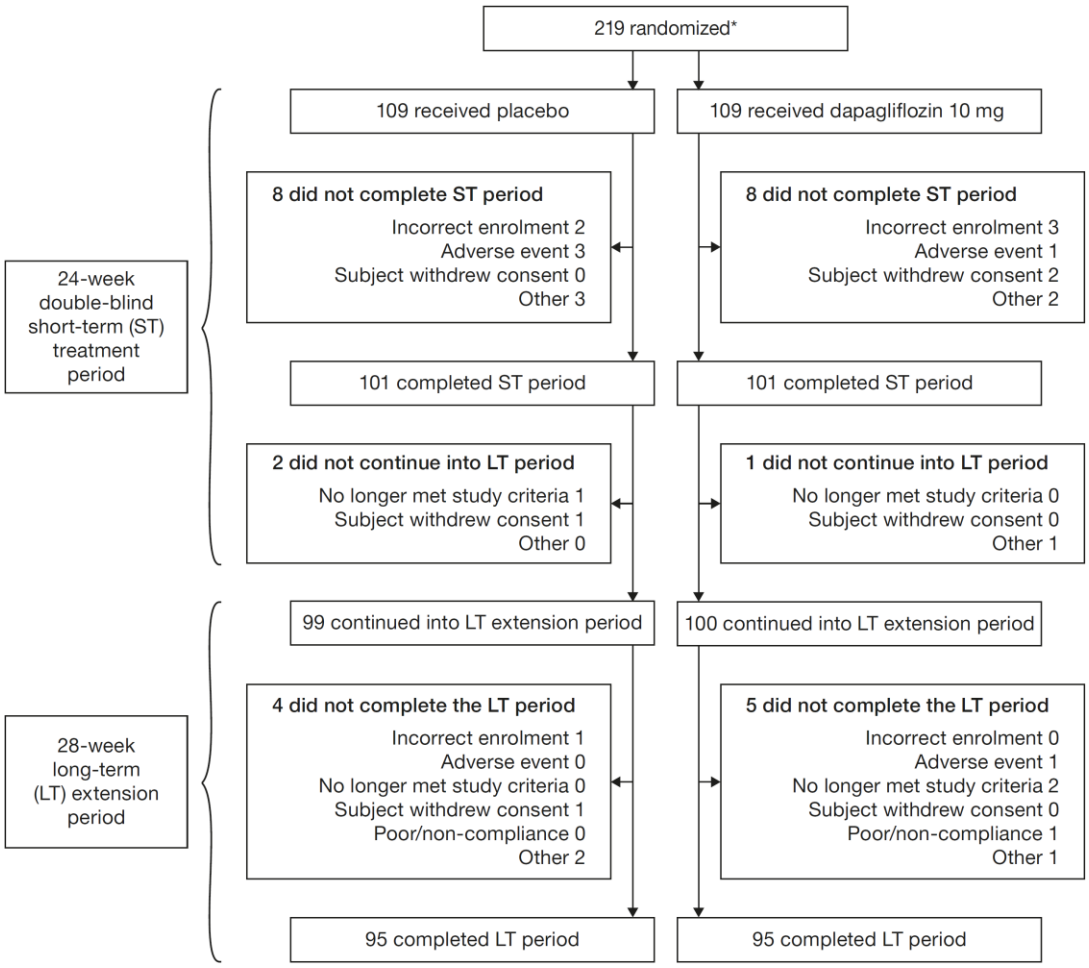
A Consolidated Standards of Reporting Trials (CONSORT) flow chart showing the numbers of patients who were eligible to enter the RCT and who were randomised and allocated to each treatment is presented in Figure 4:.

In total, 311 subjects were enrolled and 268 subjects entered the lead-in period. In total, 219 subjects were randomised.

The most common reasons for not being randomised were incorrect enrolment (i.e. the subject did not meet all inclusion and exclusion criteria) (77 subjects) and withdrawal of consent (12 subjects). One subject died prior to randomisation.

Approximately 93% of the subjects (202 subjects) completed the 24-week ST period. The most common reasons for not completing the 24-week ST period were: incorrect enrolment (5 subjects); occurrence of an AE (4 subjects); and other (5 subjects). In most cases of "other" the subject decided to stop treatment, while in 2 cases, the subject moved abroad. Overall, 99 patients receiving placebo and 100 receiving dapagliflozin continued on to the 28-week long-term extension period and 95 in each group completed it.

Figure 4: Patient participation profile for 52-week follow-up



*One patient died during the placebo lead-in phase.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics (Table 12). They were also balanced with respect to key diabetes baseline characteristics, although there was some difference in gender mix between treatment arms. The exposure to MET and SU was similar in the dapagliflozin and placebo group. Doses of SU were similar in both groups, as were the individual types of SU prescribed.

Table 12: Patient demographics and baseline characteristics – full analysis set (Matthaei 2015b)

Baseline characteristics	Dapagliflozin 10 mg + MET + SU (n=108)	Placebo + MET + SU (n=108)
Age (mean (SD) years)	61.1 (9.7)	60.9 (9.2)
Gender (n (%) female)	62 (57.4)	48 (44.4)
Ethnicity, White (n; (%))	104 (96.3)	102 (94.4)
Duration of diabetes (mean (SD) years)	9.28 (6.49)	9.62 (6.16)
HbA1c (mean (SD) %)	8.1 (0.9)	8.2 (0.9)
Weight (mean (SD) kg)	88.6 (17.6)	90.1 (16.2)
BMI (mean (SD) kg/m2)	31.9 (4.8)	32.0 (4.6)
Fasting plasma glucose (mean (SD) mg/dL)	167.4 (43.3)	180.2 (43.1)
SBP (mean (SD) mmHg)	134.5 (12.6)	136.4 (14.2)
DBP (mean (SD) mmHg)	80.4 (9.2)	81.6 (7.9)
Prior history of CVD (n (%))	91 (84.3)	95 (88.0)
Total daily MET dose at randomisation (median) mg†	2,177.9 (2,000)	2,159.4 (2,000)
Total daily SU dose at randomisation (mean mg/n)† **gliclazide (n=92)** **glimepiride (n=98)** **glibenclamide (n=28)**	 116.5/41 4.2/52 14.3/16	 114.7/51 4.2/46 12.8 /12
Concomitant medications, n (%)		
Thiazide diuretics	30 (27.5)	29 (26.6)
Antihypertensives	89 (81.7)	95 (87.2)
ARB and/or ACEi	75 (68.8)	83 (76.1)

† Data from CSR (AstraZeneca 2013a)
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; MET: metformin; SBP: systolic blood pressure; SD: standard deviation; SU: sulfonylurea

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 13: Quality assessment results for parallel group RCTs

Trial number (acronym)	***Matthaei 2015***
Was randomisation carried out appropriately?	Yes, Randomisation was carried out through interactive voice response system
Was the concealment of treatment allocation adequate?	Yes; The concealment of treatment allocation was adequate
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes; Patient characteristics were similar in both the arms

Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes; the study was double blinded and matched placebo was used.
Were there any unexpected imbalances in drop-outs between groups?	Yes; The withdrawals, completers, and the specific reasons for withdrawal were reported
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes; the authors reported all outcomes they intended to measure according to the NCT01392677.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes; Per protocol population was used for efficacy analysis and ITT population was used for safety analysis
How closely do the RCT(s) reflects routine clinical practice*	Patients included in the study are thought to reflect patients seen in UK clinical practice. Doses of dapagliflozin are reflective of UK clinical practice. The outcomes evaluated in the study are relevant to clinical practice and of benefit to patients.

*If the trials do not reflect clinical practice please provide further details

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

Short-term (ST) treatment period

Dapagliflozin in combination with MET and SU showed significant and clinically relevant benefits in HbA1c and weight, as well as FPG and SBP, compared with placebo. The primary and all key secondary endpoints were met, as shown in Table 14, and described in more detail below.

Table 14: Summary of the primary and key secondary outcome variables of the ST period - full analysis set (Matthaei 2015b)

		Dapagliflozin 10 mg + MET + SU N=108	Placebo + MET + SU N=108
HbA1c (%)			
Week 24 (Longitudinal analysis)	Adjusted mean change from baseline (95% CI) Difference vs. placebo (95% CI)†	-0.86 (-1.00, -0.72) -0.69 (-0.89, -0.49)	-0.17 (-0.31, -0.02)
	p-value for difference vs. placebo	<0.0001 *	
Total body weight (kg)			
Week 24 (LOCF)	Adjusted mean change from baseline (95% CI) Difference vs. placebo (95% CI)†	-2.65 (-3.16, -2.14) -2.07 (-2.79, -1.35)	-0.58 (-1.09, -0.07)
	p-value for difference vs. placebo	<0.0001 *	
FPG (mg/dL)			
Week 24 (LOCF)	Adjusted mean change from baseline (95% CI) Difference vs. placebo (95% CI)†	-34.23 (-40.98, -27.48) -33.45 (-43.08, -23.82)	-0.78 (-7.56, 6.01)
	p-value for difference vs. placebo	<0.0001 *	
Subjects with HbA1c <7%			
Week 24 (LOCF)	Percent adjusted (95% CI†) Difference vs. placebo (95% CI)†	31.8% (23.3, 40.2) 20.7% (10.7, 30.6)	11.1% (5.4, 16.8)
	p-value for difference vs. placebo	<0.0001 *	
Seated SBP (mmHg)			
Week 8 (LOCF)	Adjusted mean change from baseline (95% CI†) Difference vs. placebo (95% CI)†	-4.04 (-6.36, -1.72) -3.76 (-7.05, -0.48)	-0.27 (-2.60, 2.05)
	p-value for difference vs. placebo	0.0250 *	

† Data from CSR. (AstraZeneca 2013a) FPG, fasting plasma glucose; CI, confidence interval; HbA1c, haemoglobin A1c; N, number of subjects in the full analysis set; LOCF, last observation carried forward; SBP, systolic blood pressure; MET, metformin; SU, sulfonylurea. * significant p-value

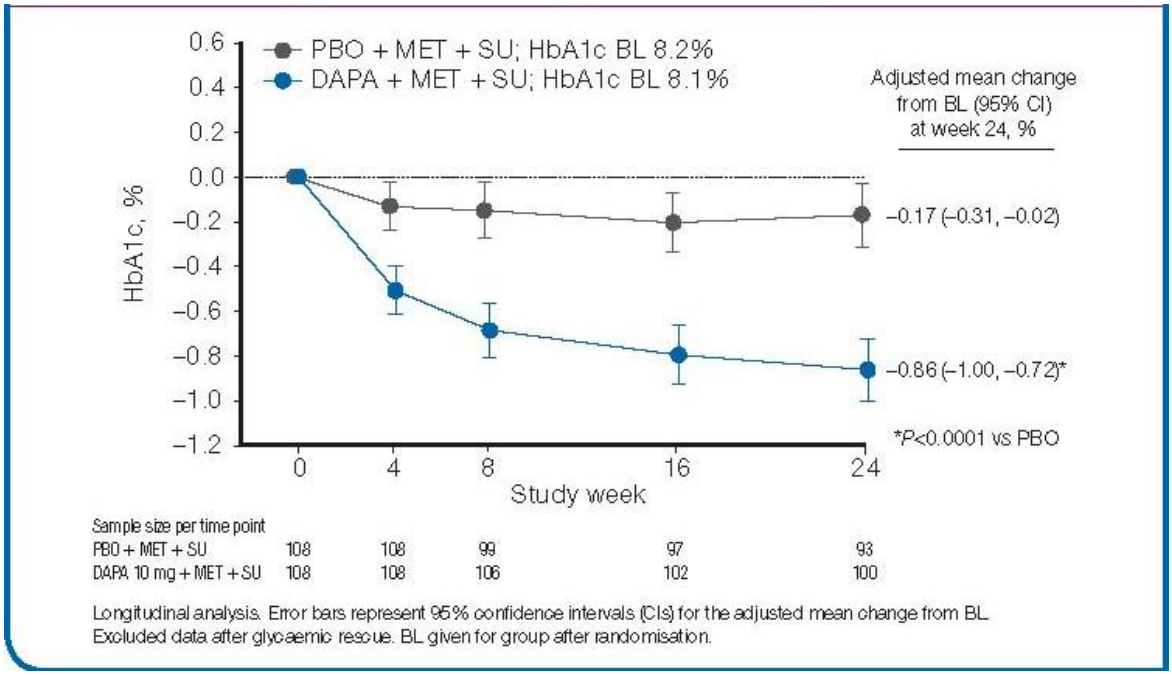
Change from baseline in HbA1c at week 24 (Matthaei 2015b)

Dapagliflozin, compared to placebo, was superior in improving glycaemic control based on the reduction in HbA1c from baseline to week 24.

Subjects in the dapagliflozin group showed an adjusted decrease from baseline in HbA1c of -0.86% at week 24. The placebo-adjusted mean decrease in HbA1c from baseline to week 24 was -0.69% in the dapagliflozin group. In the placebo group, no meaningful change in adjusted mean HbA1c (-0.17 %) was observed. The mean decrease in HbA1c from baseline to week 24 was statistically significantly larger in the dapagliflozin group compared to placebo.

Subjects in the dapagliflozin groups showed a steep, continuous mean decrease in HbA1c from baseline to week 8 that was followed by a small, shallow decrease until week 24. Subjects in the placebo group did not show a meaningful mean change in HbA1c between baseline and week 8 and from weeks 8 to 24 (see Figure 5).

Figure 5: HbA1c (percent) adjusted mean change from baseline over time for the 24-week short-term double-blind treatment period, excluding data after rescue (full analysis set) (Matthaei 2015b)

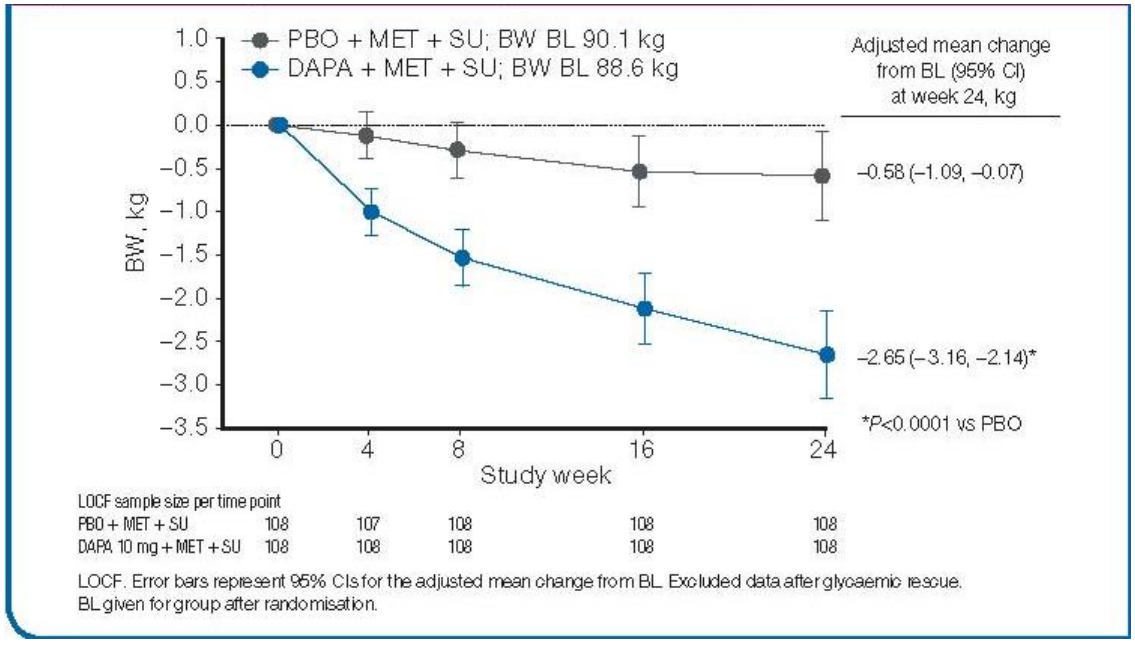


Changes in total body weight at week 24 (Matthaei 2015b; AstraZeneca 2013a)

Obesity is a challenge in the progression and management of type 2 diabetes mellitus. Change is body weight is a particularly important secondary endpoint, representing a key clinical benefit of dapagliflozin. Dapagliflozin, works by removing glucose through the kidneys (Chao 2010), and as a consequence of the excretion of glucose/calories in the urine, dapagliflozin can lead to weight loss.

Dapagliflozin showed a significant difference in body weight change from baseline to week 24 vs. placebo of -2.07 kg (95% CI: -2.79, -1.35) (p value for difference <0.0001) (Figure 6).

Figure 6: Total body weight (kg) adjusted mean change from baseline over time (LOCF) for the 24-week double-blind treatment period, including data after rescue (full analysis set) (Matthaei 2015b)

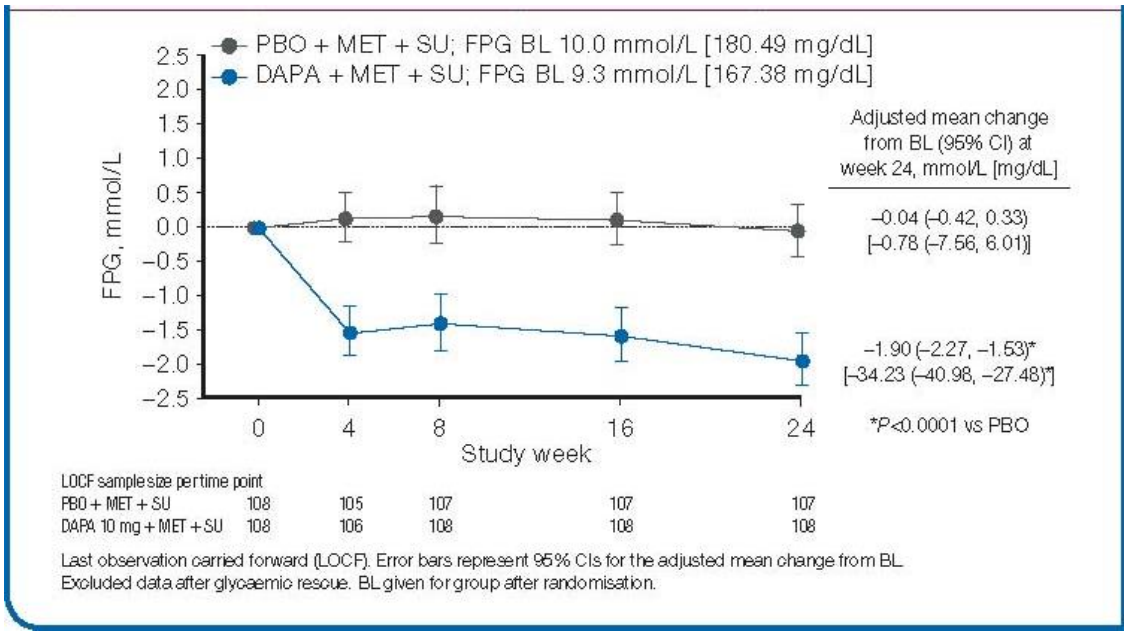


Results of other secondary outcomes

Changes in FPG at week 24 (Matthaei 2015b; AstraZeneca 2013a)

As shown in Figure 7, dapagliflozin was associated with a significant difference in FPG change from baseline to week 24 (LOCF) vs. placebo of -33.45 mg/dL (95% CI: -43.08,-23.82) (p value for difference <0.0001).

Figure 7: FPG (mmol/L) adjusted mean change from baseline over time (LOCF) for the 24-week double-blind treatment period, excluding data after rescue (full analysis set). (Matthaei 2015b)



Proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0%, at week 24 (Matthaei 2015b; AstraZeneca 2013a)

Dapagliflozin compared with placebo led to a higher proportion of subjects with HbA1c <7% at week 24 (LOCF) (31.8% vs. 11.1%, respectively) (Matthaei 2015b). Subjects in the dapagliflozin group showed a placebo-adjusted difference in the proportion of subjects with HbA1c <7% at week 24 (LOCF) of 20.7% (95% CI: 10.7, 30.6). The difference in the proportion of subjects with HbA1c <7% at week 24 (LOCF) was statistically significant (p<0.0001) (Matthaei 2015b).

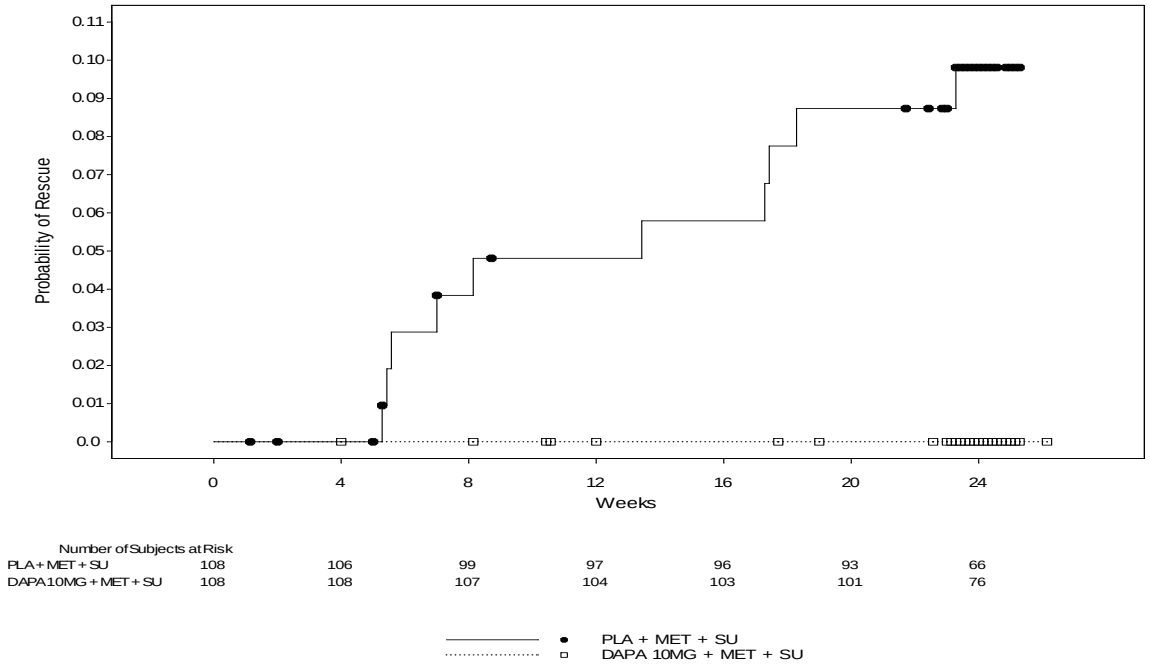
Changes in BP at week 8 (Matthaei 2015b; AstraZeneca 2013a)

The secondary outcome of BP was measured at 8 weeks, and during this period (i.e. 0-8 weeks) no change in background anti-hypertensives was allowed in the study in order to accurately evaluate the effect of dapagliflozin on BP. At 8 weeks dapagliflozin was associated with a modest but clinically and statistically significant fall in placebo-corrected SBP (Matthaei 2015b), which was maintained in the subsequent period to 24 weeks.

Additional secondary endpoint - discontinuation or rescue due to inadequate glycaemic control (Matthaei 2015b; AstraZeneca 2013a)

No subject in the dapagliflozin group, and 10 subjects in the placebo group (9.3%) were rescued due to inadequate maintenance of glycaemic control at 24 weeks (LOCF) (Matthaei 2015b) (Figure 8).

Figure 8: Kaplan-Meier plot of time to discontinuation or rescue due to inadequate glycaemic control (full analysis set) (AstraZeneca 2013a)(AstraZeneca 2013a)



Symbols represent censored observations.
Week is not the scheduled visit week but the actual number of days
from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.

Program Path: /gbs/prod/clin/programs/mb/102/116/stcsr01/rpt/graphs
Program Name: _d-graphs.sas 06MAR2013:06:23:51

Quality of life

Over 24 weeks patients treated with dapagliflozin had greater improvement in weight change-related health related quality of life (HRQoL), similar obesity-specific HRQoL, and greater treatment satisfaction, compared with patients who received placebo. As measured using the five-dimension EuroQol questionnaire (EQ-5D), patients receiving dapagliflozin with MET plus SU, maintained high HRQoL scores over the 24 week trial period (0.84 score at baseline and 0.83 at 24 weeks). For placebo plus MET and SU patients the baseline score was 0.85 at baseline and 0.83 at 24 weeks.

Long-term (LT) extension period

Efficacy outcomes at 52 weeks: Summary

At week 52, HbA1c and fasting plasma glucose improved with dapagliflozin vs placebo, with a 0.8% reduction in HbA1c compared to 0.1% with placebo, consistent with the results at 24 weeks (-0.86% vs. -0.17%) (Table 15). Over 52 weeks more patients achieved glycaemic ADA goal (HbA1c < 7.0%) with dapagliflozin (27.3%) vs placebo (11.3%), and maintained their weight loss (-2.9kg with dapagliflozin compared to -2.65kg at 24 weeks). The reduction in SBP from dapagliflozin treatment compared to week 24 results have attenuated by week 52.

Table 15: Summary of the key outcome variables at 52 weeks (Matthaei 2015c)

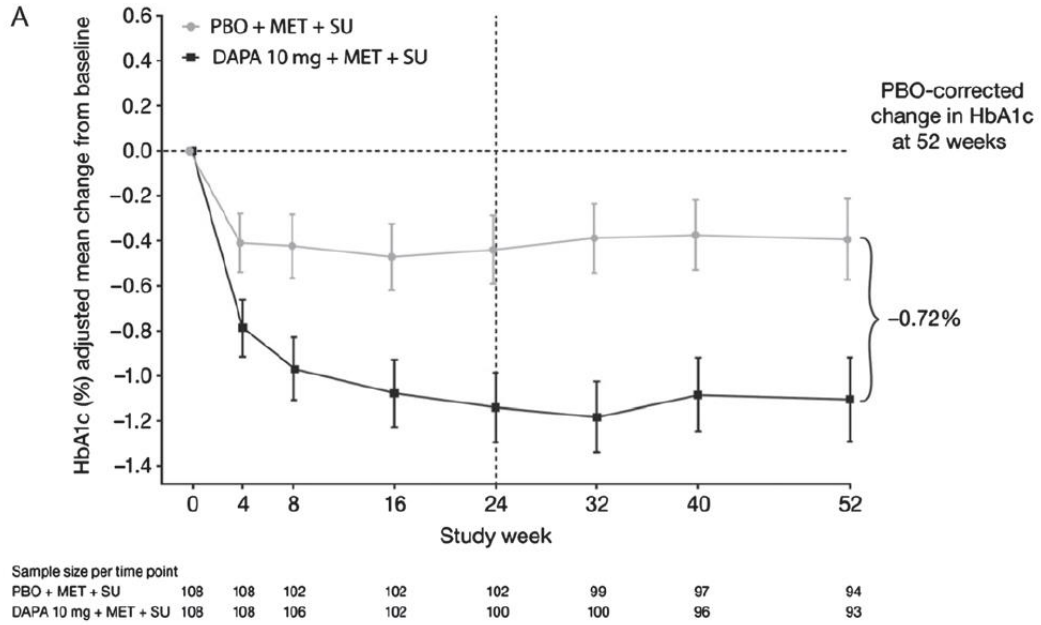
		Dapagliflozin 10mg + MET + SU N=108	**Placebo + MET + SU N=108**
HbA1c (%)			
Week 52 (Longitudinal analysis)	Mean (SD)	7.2 (0.8)	7.6 (0.9)
	Adjusted mean change from baseline (95% CI)	-0.8 (-1.0, -0.6)	-0.1 (-0.3, 0.1)
Total body weight (kg)			
Week 52 (Longitudinal analysis)	Mean (SD)	85.0 (16.9)	88.0 (14.1)
	Adjusted mean change from baseline (95% CI)	-2.9 (-3.6, -2.2)	-1.0 (-1.8, -0.1)
FPG (mg/dL)			
Week 52 (Longitudinal analysis)	Mean (SD)	7.8 (1.9)	9.6 (2.1)
	Adjusted mean change from baseline (95% CI)	−1.5 (−1.9, −1.1)	0.6 (0.1, 1.1)
Seated SBP (mmHg)			
Week 52 (Longitudinal analysis)	Mean (SD)	134 (16.0)	138.0 (12.4)
	Adjusted mean change from baseline (95% CI)	-1.0 (-3.6, 1.6)	1.1 (-2.2, 4.5)

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; N, number of subjects in the full analysis set; MET, metformin; SBP, systolic blood pressure; SD: standard deviation; SU, sulfonylurea.

Change in HbA1c over 52 weeks

The improvement in HbA1c with dapagliflozin compared with placebo over 24 weeks was sustained through to 52 weeks. Patients who received dapagliflozin showed a steep and continuous decrease in HbA1c from baseline to week 8 that was followed by a shallow decrease until week 24 and stable levels through to week 52 (Figure 9).

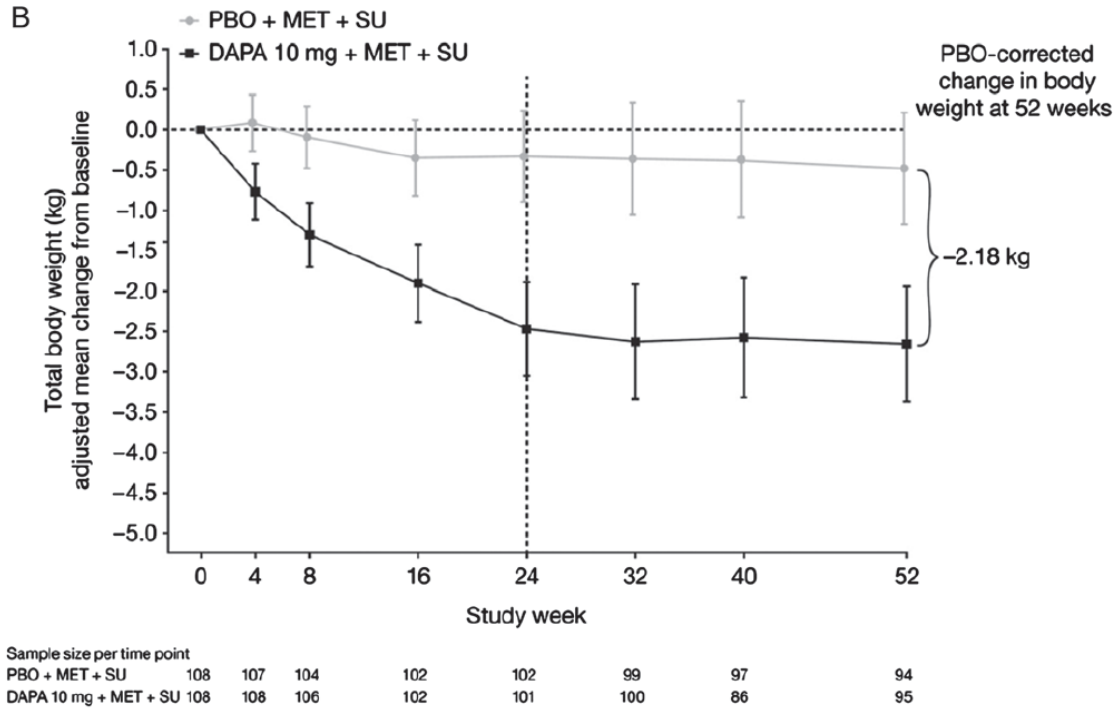
Figure 9: Change in HbA1c levels over 52 weeks



Change in total body weight over 52 weeks

Furthermore, a reduction in body weight from baseline observed at week 24 was maintained through to week 52 (Figure 10).

Figure 10: change in body weight over 52 weeks



Change in BP over 52 weeks (Matthaei 2015c)

Seated SBP in the dapagliflozin and placebo groups had declined from baseline by week 24 (−5.4 vs −1.3 mmHg, respectively) and then increased over the following 28 weeks in both groups (change from baseline at 52 weeks, −1.0 and 1.1 mmHg, respectively).

It should be noted that the results for BP at week 52 are at odds with those observed in the dapagliflozin development programme and two dedicated studies designed to assess the safety and efficacy of dapagliflozin in patients with Type 2 Diabetes with inadequately controlled hypertension treated with antihypertensive medication (as described below). They are also at odds with the 24 week results.

The BP results observed in this specific study at 52 weeks may have been seen for the following reasons:

1. Changes in BP medications and doses occurred to a greater extent in the placebo arm predominantly in the long term extension of study 5, likely masking the BP reducing effects of dapagliflozin. This is supported by the increase in SBP seen at the post-treatment follow-up by 3mmHg in the dapagliflozin arm; whereas those who had been on placebo had a decrease of 1.7mmHg at follow-up (Table 11.3.8.1.1.2 from 52 week clinical study report study D1693C00005)
2. BP is less rigorously assessed than in a dedicated BP study
3. BP was an exploratory efficacy variable and no adjustments were made for Type 1 error so interpretation should be done with caution for this study

<u>BP in the dapagliflozin development programme</u>

While the development programme was not designed to formally evaluate BP as an efficacy endpoint, changes in systolic and diastolic blood pressure (DBP) were analysed as prespecified exploratory efficacy endpoints in the overall population and/or in subjects with baseline elevated BP in all Phase III studies except MB102029. Background antihypertensive medications were not controlled. The exploratory analyses demonstrated numerically larger reductions in the dapagliflozin treatment groups versus placebo, with the largest mean reductions seen in subjects with baseline SBP >140 mmHg.

<u>Dedicated studies</u>

Two dedicated randomised controlled trials assessed dapagliflozin in type 2 diabetes patients with inadequate glycaemic control; and inadequately controlled hypertension despite receiving antihypertensives. The co-primary endpoints were the changes from baseline at Week 12 in seated SBP and HbA1c. Study MB102073 included 613 patients, whilst study MB102077 included 449 patients.

Both studies showed dapagliflozin treatment at a dose of 10 mg OD over 12 weeks was effective in lowering SBP and improving glycaemic parameters in this specific patient population. The main findings of the studies are summarised below:

- Statistically and clinically significant mean decreases for the hierarchically-ordered co-primary endpoints of change from baseline to Week 12 in seated SBP and HbA1c with dapagliflozin 10 mg treatment
- A statistically and clinically significant mean decrease was observed for dapagliflozin 10 mg relative to placebo at Week 12 (LOCF) with respect to the secondary endpoint of 24-hour ambulatory SBP

- Numeric mean decreases favouring dapagliflozin 10 mg were observed for the remaining secondary endpoints of change from baseline at Week 12 in seated DBP, 24-hour mean ambulatory DBP, and serum uric acid
- The exploratory analyses also showed favourable results for dapagliflozin 10 mg relative to placebo at Week 12 with reductions from baseline in FPG, body weight, and ambulatory mean daytime, night-time, and trough SBP and DBP, and higher proportions of dapagliflozin-treated subjects achieving goal BP (< 130/80 mmHg) and improved BP control (< 140/90 mmHg)

Time to discontinuation because of rescue or inadequate glycaemic control

No patient was discontinued from study treatment because of inadequate glycaemic control at any time in the 52-week treatment period. No patients receiving dapagliflozin and 10 (9.3%) patients receiving placebo required rescue medication for lack of glycaemic control by week 24. The adjusted difference in the proportion of patients rescued increased to −32.6% at week 52, primarily because of an increase in the number of those rescued in the placebo group (44.4%) versus the dapagliflozin group (9.3%) (Matthaei 2015c).

Patient reported outcomes (PROs) at 52 weeks (Grandy 2016)

The EQ-5D questionnaire, SHIELD Weight Questionnaire-9 (WQ-9), Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were used to evaluate health status and HRQoL at baseline and week 52. Patients treated with dapagliflozin in combination with MET + SU were compared to patient with placebo, in combination with MET + SU, using a repeated-measures mixed model.

The EQ-5D index score and the EQ-5D visual analogue scale score were high at baseline (0.85 and means score of 73-75, respectively). An increase in EQ-5D VAS was observed for both treatment groups and only a slight change in the mean index score was observed for both treatment groups. These changes were not statistically significant.

The IWQOL-Lite and DTSQ scores improved in the dapagliflozin and placebo groups from baseline to week 52; however, there was no significant difference between groups ($p>0.20$). A numerically greater proportion of the dapagliflozin group reported improvement in all nine SHIELD WQ-9 items compared with placebo, and the difference was statistically significant for physical health ($p=0.017$). Over 52 weeks of therapy, patients maintained their health status and HRQoL when dapagliflozin was added to the treatment.

4.8 *Subgroup analysis*

Reductions in HbA1c were observed with dapagliflozin across all baseline HbA1c categories. Patients with higher HbA1c at baseline had greater reductions in HbA1c at weeks 24 and 52 with dapagliflozin. No effect of baseline body mass index (BMI) was noted on the reduction from baseline in HbA1c with dapagliflozin.

Table 16: HbA1c subgroup analyses excluding data after rescue (full analysis set)

HbA1c subgroup analyses excluding data after rescue (full analysis set)		
Subgroup	**Placebo-corrected adjusted mean reduction in HbA1c at week 24 [mean (95%CI)]**	**Placebo-corrected adjusted mean reduction in HbA1c at week 52 [mean (95%CI)]**
Baseline HbA1c <8%	-0.44% (-0.69, -0.19)	-0.48% (-0.86, -0.10)
Baseline HbA1c ≥8% and <9%	-0.84% (-1.13, -0.54)	-1.17% (-1.54, -0.80)
Baseline HbA1c ≥8%	-0.87% (-1.17, -0.58)	-1.12% (-1.48, -0.75)
Baseline HbA1c ≥9%	-0.96% (-1.69, -0.23)	NA[1]
Baseline BMI ≥27 kg/m2	-0.69% (-0.91, -0.47)	-0.72% (-1.02, -0.42)
Baseline BMI ≥30 kg/m2	-0.74% (-1.00, -0.48)	-0.76% (-1.14, -0.38)

[1] Less than 10 subjects in any group, no adjustment calculable.

4.9 *Meta-analysis*

A meta-analysis of dapagliflozin studies was not possible as only one study included dapagliflozin on a background of MET + SU. A meta-analysis requires two or more studies that contain the intervention of interest. However, a meta-analysis to assess the heterogeneity of studies (assessing other drugs on a background of MET + SU) for inclusion in the network meta-analysis was undertaken. The results of this analysis are presented in Appendix 13.

4.10 *Indirect and mixed treatment comparisons*

Search strategy

The systematic review detailed in Section 4.1 was used to identify trials to include in the indirect treatment comparison for both the treatment under consideration (dapagliflozin) and relevant comparator treatments. The search strategy used to identify relevant studies is given in Appendix 2.

Study selection

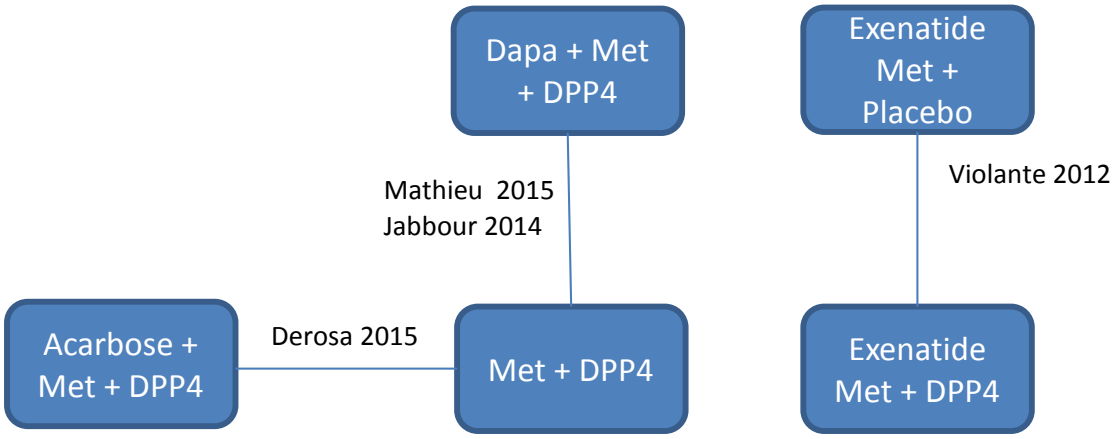
The scope of dapagliflozin for this submission is for use as triple therapy in combination with MET and SU or MET and DPP4-i for adults with type 2 diabetes mellitus poorly controlled on MET plus SU. As there is no head to head data for dapagliflozin versus all relevant comparators, a NMA has been performed to assess the relative efficacy and safety of dapagliflozin in combination with MET and SU with all relevant comparators. Only RCT evidence was included in the NMA.

The clinical systematic review identified 54 studies that met the inclusion criteria of the review. A full list of inclusion/exclusion criteria is given in Table 7. Three studies included dapagliflozin, one in combination with MET + SU (Matthaei 2015c) and two in combination with MET + DPP4-i (Jabbour 2014; Mathieu 2015d). Fifty studies included MET plus SU triple therapy and four studies included MET plus DPP4-i triple therapy.

Of the studies that included MET plus DPP4-i triple therapy, two studies included dapagliflozin (as described above), one study included acarbose (Derosa 2015) and one study included exenatide (Violante 2012). The network diagram of these studies is shown in

Figure 11. The only comparison possible was dapagliflozin versus acarbose, a comparator not relevant to the NICE decision problem. Therefore there is no available evidence at this time to support the comparison of dapagliflozin in combination with MET plus DPP4-i with comparators indicated in the NICE decision problem. These four studies are not discussed further in the main body of this submission, but are described in Appendix 6 with data extraction presented for completeness. The positioning of dapagliflozin in this submission is for use as triple therapy in combination with MET and SU for adults with type 2 diabetes mellitus poorly controlled on MET plus SU.

Figure 11: MET plus DPP4-i network diagram



Of the remaining 50 studies, four studies included MET and SU in combination with other SGLT2-i, canagliflozin (Wilding 2013; Schernthaner 2013b; Ji 2015) or empagliflozin (Haering 2015a), eleven studies included insulin, six included pioglitazone, nine included a DPP4-i and one study included meglitinide (repaglinide). A further 17 studies included comparators not relevant to the decision problem (four included an alpha-glucosidase inhibitor (acarbose or migilitol) and 13 included GLP-1. These were included as part of the systematic review to ensure all studies relevant to the decision problem were identified and that the network meta-analysis was comprehensive. It should be noted that the number of studies does not sum to 50 as one study may include more than one comparator.

4.10.1 Provide a rationale for the exclusion of any eligible study not included in the ITC or MTC.

Ten studies identified in systematic literature review (SLR) did not provide sufficient data to be included in the network meta-analysis. These studies are shown in Table 9.

It should be noted that the systematic review methodology utilised a broad inclusion criteria for comparators. The use of pioglitazone in UK clinical practice is rare. Insulin is only available in an injectable formulation and used later in the treatment path and therefore not a relevant comparator.

IMS data shows that 62% of patients who were previously prescribed MET+ SU and are currently prescribed a triple therapy regimen are prescribed a DPP4-i + MET + SU (Patient Data, IMS Information Solutions UK Ltd, December 2015). The DPP4-is are therefore the key comparator for this submission. Since the launch of dapagliflozin, two other SGLT2-is, canagliflozin and empagliflozin have launched in the UK; and are also comparators in this submission.

There are RCT data for dapagliflozin in combination with MET + DPP4-i demonstrating clinical benefit compared to placebo (see Appendix 6). However, based on the results of the systematic review carried out for this submission, it is not possible to carry out an NMA or indirect comparison compared to any of the comparators in the final scope meaning that a robust, evidence-based estimate of cost-effectiveness for the use of dapagliflozin + MET + DPP4-i is not possible.

Therefore, this submission focuses on the evidence demonstrating the clinical and cost effectiveness of dapagliflozin used in combination with MET + SU.

Furthermore, given the heterogeneity in the evidence base in terms of the patient populations, study design and study duration, the base case NMA focuses only on studies that evaluate comparators directly relevant to UK clinical practice: DPP4-is and other SGLT2-is. This is in line with the approach followed by Boehringer Ingelheim in the STA evaluation of empagliflozin in the same patient population. The base case analysis utilises data from study endpoints regardless of study duration to include as much data as possible in the NMA; and as SGLT2-i efficacy has been demonstrated to be consistent over at least two years.

Studies contributing to the base case analyses are shown in Table 17.

Table 17: Summary of RCTs included in the base case NMA

Author, Year	Country	Number randomised	Treatment duration (weeks)	Intervention
Haering 2015	Multinational	669	76	Empagliflozin (25 mg) + MET + SU Empagliflozin (10 mg) + MET + SU Placebo + MET + SU
Hermansen et al., 2007	Multinational	229	24	Sitagliptin + MET + SU Placebo + MET + SU
Hong et al., 2015	South Korea	344	24	Vildagliptin + MET + SU MET + SU (Dose increase)
Ji et al.,	Multinational	678	18	Canagliflozin (300 mg OD) + MET + SU

2015				Canagliflozin (100 mg OD) + MET + SU Placebo + MET + SU
Lukashevich 2014	Multinational	318	24	Vildalgliptin + MET + Glimepiride Placebo + MET + Glimepiride
Liu et al., 2013	Taiwan	120	24	Pioglitazone + MET + SU Sitagliptin + MET + SU
Matthaei et al., 2015	Multinational	219	52	Dapagliflozin + MET + SU Placebo + MET + SU
Moses et al., 2014	Multinational	257	24	Placebo + MET + SU Saxagliptin + MET + SU
NCT01590771	China	223	24	Sitagliptin + MET + SU Placebo + MET + SU
Nogueira et al., 2014	Brazil	35	24	Sitagliptin + MET + Glyburide NPH insulin + MET + Glyburide
Owens et al., 2011	Multinational	1058	24	Linagliptin + MET + SU Placebo + MET + SU
Round et al., 2013	Asia-Pacific	427	24	Sitagliptin + MET + SU Placebo + MET + SU
Schernthaner et al., 2013	Multinational	756	52	Canagliflozin + MET + SU Sitagliptin + MET + SU
Wilding et al., 2013	Multinational	469	52	Canagliflozin (300 mg OD) + MET + SU Canagliflozin (100 mg OD) + MET + SU Placebo + MET + SU

NPH, neutral protamine hagedorn

Methods and outcomes of included studies

4.10.2 Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected

HbA1c reduction

HbA1c is the standard measure of glycaemic control and is indicative of the short term (ST) glucose levels. Reductions in HbA1c have been shown to be associated with a lower rate of diabetic complications and CV events (Stratton 2000). Indeed, a 1% reduction in HbA1c at 10 years was associated with a:

- 21% decrease in diabetes related death
- 14% decrease in all-cause mortality
- 14% decrease in fatal and non-fatal MI
- 12% decrease in fatal and non-fatal stroke
- 37% decrease in microvascular endpoints (e.g. fatal or non-fatal renal failure)
- 43% decrease in amputation or death from peripheral vascular disease

Rates of hypoglycaemia

Severe hypoglycaemia has important clinical consequences, especially in the elderly. Up to 25% of hospital admissions associated with diabetes were due to severe hypoglycaemia (Greco 2004). Severe hypoglycaemia is also associated with increased mortality, for example SU-induced hypoglycaemia has an estimated mortality rate of 9% (Campbell 1985). Although mild symptomatic hypoglycaemia episodes are not reported to have serious clinical effects they can still have detrimental consequences such as fear of hypoglycaemia, which may in turn inhibit concordance with therapy (Amiel 2008).

Hypoglycaemia has been shown to have significant detrimental impact on quality of life measures, such as HRQoL, health related utility (HRU) as measured by EQ-5D (Lundkvist 2005). In a recent cross-sectional survey of 9 European countries, including the UK, it was found that even 2 or more non-severe episodes of hypoglycaemia had a significant detrimental effect on quality of life (as measured by ADDQoL, DTSQ and the Hypoglycaemia Fear Survey [HFS]-II) (Bradley 2010).

Weight loss

Patients with diabetes have a tendency to be overweight so achieving any loss in weight is beneficial to both the management of their disease and their quality of life. It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in BP, cholesterol, and triglycerides achievable with just a 5-10% reduction in initial body weight (Goldstein 1992).

Thus any therapies that alleviate weight gain and minimise potential progression to more expensive therapies (e.g. GLP-1 analogues, weight-loss clinic, bariatric surgery) can only benefit the patient.

Blood pressure (BP)

BP control is a cornerstone of CV risk management. A 10/5 mmHg (SBP/DBP) drop in BP in patients with type 2 diabetes mellitus achieved a significant reduction in risk of 32% for death related to diabetes, 44% for stroke, 37% for microvascular disease and 56% in heart failure (UKPDS 38 1998). Even an isolated SBP reduction of 12 mmHg was found to reduce the risk of stroke by 36%, MI or CV death by 17% (SHEP 1991).

Overview of included studies in the base case NMA

Baseline characteristics of the patient population in the studies that were included in the SLR and NMA are given in Table 18 and Table 19 and study inclusion/exclusion criteria are given in Table 20. All studies included patients whose diabetes was inadequately controlled on MET and SU. Baseline characteristics across the studies were similar and comparable to patients included in the dapagliflozin RCT. A number of studies included in the base case NMA were a source of heterogeneity in the analysis. Two studies were identified that lead to an increase in the heterogeneity of the analysis. The study by Ji et al (Ji 2015) was an 18 week study that evaluated the efficacy of canagliflozin as a triple therapy treatment regimen (MET + SU) as a sub-group patient population. The study by Hong et al (Hong 2015) included increasing SU dose.

Table 18: Baseline characteristics of studies included in the base case NMA

Author, Year	Average age (years)	% Male	Average duration of DM (years)	Average HbA1c (%)
Haering 2015	57.1	51	37% with >5-10 year and 40% with >10 years	8.1
Hermansen et al., 2007	57.2	52.4	10.0	8.3

Hong et al., 2015	61.7	64.1	Median: 9.0	8.5
Ji et al., 2015	57.3	49.2	7.9	8
Lukashevich 2014	55.1	47.8	7.3	8.8
Liu et al., 2013	59.1	37.5	7.8	8.41
Matthaei et al., 2015	61	49.1	9.45	8.15
Moses et al., 2014	57	59.9	NR	8.3
NCT01590771*	57.0 ± 9.4	50.0	NR	8.6 ± 1.0
Nogueira et al., 2014	56.8	42.9	10.9	8.05
Owens et al., 2011	58.1	47.2	73.3% > 5 years	8.15
Round et al., 2013	54.9	45.7	7.8	8.4
Schernthaner et al., 2013	56.7 ± 9.5	55.9	9.6 ± 6.2	8.1 ± 0.9
Wilding et al., 2013	56.8	51	9.6	8.1

DM, diabetes mellutis; NR, not reported

Table 19: Baseline mean, SU as per inclusion criteria, and duration of stable therapy of studies included in the base case NMA

First Author	Year	Mean dose (mg/day) of combination therapy, at baseline/screening			Allowable SU and dose as per study criteria	Duration of stable combination therapy prior to study entry (months)
		MET	SU			
		(mg/day)	Agent	Dose		
				(mg/day)		
Haering	2015	≥1,500 mg/day or MTD or MD according to local label	NR	NR	Greater than or equal to half the MRD, or the MTD, or the MD according to local label	≥3 (≥12 weeks)
Hermansen	2007	NR	Glimepiride	NR	Any OAD, or no agent at all	≥2.3
Hong	2015	1,100-1,200	Glimepiride	NR	Glimperide and Gliclazide for 12 weeks. In one of the group dose of SU was increased by 25% at random and further 25% at week 12 follow up if HbA1c was not within target level (<7%)	3
			Gliclazide	4 mg		
			Gliclazide	60 mg		
Ji	2015	MET, ≥1,500 mg/day	NR	SU, at least half-maximal labelled dose	NR	3 (4-week AHA adjustment period followed by an 8-week AHA dose-stable period)
Lukashevich	2014	≥1,500 mg	glimepiride	≥4 mg	glimepiride up to 4 mg	3
Matthaei	2015	≥1,500 mg/day and MTD	Gliclazide	half MD	half MD	≥2 (8 weeks)
			Glimepiride			
			Glyburide			
Moses	2014	≥1,500	NR	Greater than equal to 50% of	Any SU - ≥ half maximal	≥1.85

				the MRD	recommended dose	
Nogueira	2014	2.4 ± 0.3 x 2.3 ± 0.6	Glyburide	17.6 ± 3,1 x 18.1 ± 4.1	Glyburide	NR
NCT01590771	2015	≥1,500	gliclazide glimepiride	NR	Gliclazide or glimepiride according to the China drug label	≥2
Owens	2011	Daily dose of ≥ 1,500 mg MET (or the MTD, if lower)	NR	MTD of SU	Any oral glucose-lowering drug	≥2 (≥10 weeks)
Round	2013	MET ≥1,500 mg/day	Glimiperide, Gliclazide	Glimiperide ≥2 mg, Gliclazide (≥50% of maximum registered dose)	Glimiperide ≥2 mg, Gliclazide (≥50% of maximum registered dose)	2.3
Schernthaner	2013	≥2,000 mg/day or ≥1,500 mg/day if unable to tolerate a higher dose	Glipizide	minimum daily dose required at randomisation: 20 mg	SU - Half-maximal labeled dose or more	NR
Seino	2014	1.6-2.0 g/day mean dose	Glibenclamide, Glibomet, Gliclazide, Glimeperide, Glipizide, Tolbutamide	NR	NR	3

Wilding	2013	≥2,000 mg/day or ≥1,500 mg/day if unable to tolerate a higher dose	Glipizide	minimum daily dose required at randomisation: 20 mg	Any SU- maximally or near-maximally effective dos	NR
			Glyburide/glibenclamide	minimum daily dose required at randomisation: 10 mg		
			Glimepiride	minimum daily dose required at randomisation: 4 mg		
			Gliclazide	minimum daily dose required at randomisation: 160 mg daily		
			Gliclazide modified release	minimum daily dose required at randomisation: 60 mg daily		
			Glipizide extended release	minimum daily dose required at randomisation: 10 mg		

BID: bis in die (twice daily); NR: not reported; MD: maximum dose; MRD:maximum recommended dose; MTD: maximum tolerated dose; OAD: oral antidiabetic agent; SU: sulfonylurea

Table 20: Study inclusion/exclusion criteria

Author, Year	Inclusion Criteria	Exclusion Criteria
Haering et al., 2015	Eligible patients were aged ≥18 years; BMI ≤45 kg/m^2) with inadequately controlled type 2 diabetes (HbA1c ≥ 7 to ≤10%) despite a diet and exercise program and a stable regimen (unchanged for ≥12 weeks prior to randomisation) of MET immediate release plus a SU. Patients with HbA1c >10% were eligible to participate in an open label treatment arm	Exclusion criteria included uncontrolled hyperglycemia (glucose level >13.3 mmol/L) after an overnight fast, confirmed by a second measurement), acute coronary syndrome, stroke or transient ischemic attack within 3 months prior to consent, indication of liver disease, impaired kidney function (estimated glomerular filtration rate [eGFR] ,30 mL/min/1.73 m^2) during screening or run-in, contraindications to MET or SU according to the local label, gastrointestinal surgeries that induce chronic malabsorption, history of cancer (except basal cell carcinoma) or treatment for cancer within 5 years, bloody scrasias or any disorders causing hemolysis or unstable erythrocytes, treatment with antiobesity drugs 3 months prior to consent, use of any treatment at screening that leads to unstable body weight, treatment with systemic steroids at time of consent, change in dosage of thyroid hormones within 6 weeks of consent, alcohol or drug abuse within 3 months of consent, and investigational drug intake within 30 days of the trial

Hermansen et al., 2007	Men and women, ≥18 and ≤75 years of age, with Type 2 diabetes were recruited for this study. Only the following patients were eligible to be screened: (i) already taking glimepiride alone (at any dose) or in combination with MET (at any dose), (ii) taking another OAD in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any OADs over the prior 8 weeks	History of type 1 diabetes; were treated with insulin within 8 weeks of the screening visit; had renal dysfunction (creatinine clearance <45 ml/min or <60 ml/min if on MET); or had a history of hypersensitivity, intolerance or a contraindication to the use of glimepiride, SU agents, MET or pioglitazone (which was included in this study as rescue therapy)
Ji et al., 2015	Men and women ≥18 and ≤80 years of age with Type 2 diabetes who had inadequate glycaemic control [glycated haemoglobin (HbA1c) ≥7.0 and ≤10.5%] on MET alone or MET + SU, with both agents at maximum or near-maximum effective doses	Patients with a history of diabetic ketoacidosis or Type 1 diabetes; had a repeated fasting plasma glucose (FPG) ≥15mmol/l (≥270mg/dl) during the pretreatment phase; had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2; had MI or unstable angina (UA), had undergone a revascularization procedure or experienced a cerebrovascular event ≤3months before screening; had uncontrolled hypertension; or were taking any AHA other than MET or SU ≤12weeks before screening
Liu et al., 2013	Males and females with type 2 diabetes (>20 years of age) who were taking stable doses of MET (≥1,500 mg/d) and an SU (≥half maximal dose, modified release gliclazide 60 to 120 mg daily or glimepiride 4 to 8 mg daily) for at least 10 weeks prior to the screening visit and had inadequate glycemic control (glycosylated hemoglobin [HbA1c] ≥7.0 and <11.0%) were recruited for the study	Patients were excluded if they had type 1 diabetes, insulin use within 12 weeks of the screening visit, any contraindications for the use of pioglitazone or sitagliptin, impaired renal function (serum creatinine >1.4 mg/dL), alanine aminotransferase (ALT) or aspartate aminotransferase levels (AST) >2.5 times the ULN, current or planned pregnancy, or lactation
Lukashevich et al., 2014	Age 18–80 years; body mass index (BMI) ≥22 to ≥45 kg/m^2, inadequately controlled on a stable dose of OADs for at least 12 weeks prior to the screening visit. Acceptable background therapy prior to enrollment included MET ≥1,500 mg as monotherapy [haemoglobin A1c (HbA1c) ≥8.5 and ≤11%] or dual combination of MET ≥1,500 mg with SU, TZD or glinide (HbA1c ≥7.5 and ≤11%)	Patients were excluded if they had fasting plasma glucose (FPG) ≥15.0 mmol/l; significant hepatic, renal or cardiovascular medical conditions; significant laboratory abnormalities; and pregnant or lactating females
Matthaei et al., 2015	Type 2 diabetes; age ≥ 18 years; HbA1c ≥ 7.0 – ≤ 10.5% (at randomisation); stable dose combination therapy of MET ≥ 1,500 mg/d and MTD of SU (which must be at least half the MD for ≥ 8 weeks prior to enrolment). MET could not be down titrated; SU could be down-titrated only once to mitigate hypoglycaemic events; no up-titration of MET or SU was allowed	Patients were excluded if: diagnosis of type 1 diabetes; body mass index ≥45.0 kg/m^2; serum creatinine ≥133 µmol/l (1.5 mg/dl) for men or ≥124 µmol/l (1.4 mg/dl) for women; unstable or rapidly progressing renal disease; recent cardiovascular events; congestive heart failure class IV; systolic blood pressure ≥160 mmHg; and diastolic blood pressure ≥100 mmHg at randomisation

Moses et al., 2014	Patients were ≥18 years old with type 2 diabetes, body mass index≤ 40 kg/m^2 and inadequate glycaemic control [HbA1c, 7.0–10.0% (53–86 mmol/mol)] on combination therapy with a stable MTD of MET plus a SU) daily for ≥8 weeks before screening. Women of childbearing potential were required to be using an adequate method of contraception and have a negative urine pregnancy test at visit 2 and each visit thereafter	The primary exclusion criteria were symptoms of poorly controlled diabetes; estimated creatinine clearance (CrCl) <1.0 ml/s or creatinine kinase ≥ 10 times ULN at visit 2; congestive heart failure; active liver disease and/or significant abnormal liver function; history of haemoglobinopathies; history of alcohol abuse or drug abuse ≤ 12 months before screening; use of insulin, DPP4-is, GLP-1 analogues or oral antidiabetic agents other than MET and SUs currently or within 3 months of screening; treatment with systemic glucocorticoids other than replacement therapy; treatment with cytochrome P450 3A4 inducers or potent 3A4 or 3A5 inhibitors; and pregnancy or breast-feeding
NCT01590771	18 Years to 79 Years Has Type 2 diabetes is currently on a stable regimen of gliclazide or glimepiride, either alone or in combination with MET for ≥ 10 weeks has a Visit 1/Screening HbA1c between 7.5% and 11.0% is a male, or a female who is highly unlikely to conceive during the study and for 14 days after the last dose of study medication	Patients who • had a history of type 1 diabetes mellitus or a history of ketoacidosis • has been treated with any antihyperglycemic therapies other than a SU (alone or with MET) within the prior 12 weeks or has ever been treated with a dipeptidyl peptidase-4 inhibitor or a glucagon-like peptide-1 mimetic or analogue has a history of intolerance or hypersensitivity, or has any contraindication to sitagliptin, gliclazide/glimepiride, or MET is on a weight loss program and not in the maintenance phase, or has started a weight loss medication or has undergone bariatric surgery within 12 months has undergone a surgical procedure within 4 weeks or has planned major surgery during the study has a medical history of active liver disease has had new or worsening signs or symptoms of coronary heart disease within the past 3 months, or has acute coronary syndrome, coronary artery intervention, or stroke or transient ischemic neurological disorder has a diagnosis of congestive heart failure with New York Heart Association Class III - IV cardiac status has a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 90 mmHg has human immunodeficiency virus (HIV) has severe peripheral vascular disease is currently being treated for hyperthyroidism or is on thyroid hormone therapy and has not been on a stable dose for at least 6 weeks • has a history of malignancy ≤ 5 years before the study, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer has a clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia) is pregnant or breast feeding, or is expecting to conceive or donate eggs during the study, including 14 days after the last dose of study medication is a user of recreational or illicit drugs or has had a recent history of drug abuse
Nogueira et al., 2014	Outpatients with Type 2 Diabetes aged 57 ± 7 years (mean ± SD) inadequately controlled with MET plus glyburide	Exclusion criteria: patients with severe heart failure, respiratory failure, uncontrolled hypertension, coronary heart disease, arrhythmias, hepatic and renal dysfunctions, endocrine and gastrointestinal disorders, malignancy, alcohol abuse, use of insulin, beta blockers or calcium channel antagonists and type 1 diabetes mellitus

Owens et al., 2011	Men and women with Type 2 diabetes aged ≥18 and ≤ 80 years, with a BMI ≤ 40 kg/m^2 and HbA1c ≥ 53 mmol/mol (≥ 7.0%) and ≤ 86 mmol/mol (≤ 10.0%) despite receiving a total daily dose of ≥ 1,500 mg MET (or the MTD, if lower) and the MTD of SU. The dose and regimen of MET and the SU must have been unchanged for ≥ 10 weeks before enrolment	MI, stroke or transient ischaemic attack within 6 months before enrolment; impaired hepatic function; renal failure or renal impairment; current acute or chronic metabolic acidosis; hereditary galactose intolerance; or being unable or unwilling to avoid nursing or pregnancy. Patients treated with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months of enrolment were also excluded
Round et al., 2013	Male or female patients with age 18 to 78 years. Patients with Type 2 diabetes and HbA1c ≥ 7.5% and ≤10.5 at screening visit were included. Patients were receiving stable dose of either glimepiride or gliclazide and MET (≥1,500 mg/day) for at least 10 weeks	Patients withT1DM; history of ketoacidosis, previous treatment with DPP4 or a GLP-1 mimetic; requirement of insulin therapy within 12 weeks prior to signing informed consent, significant active cardiovascular disorder, renal and liver impairement
Schernthaner et al., 2013	Eligible subjects were men and women with18 years of age or older with type 2 diabetes using stable MET and SU therapy. Subjects at screening already using the combination of MET and SU with both agents at maximally or near-maximally effective doses (MET ≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate a higher dose]; SU at half-maximal labeled dose or more), who had A1C ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol), and who met all other enrollment criteria directly entered the 2-week single-blind placebo run-in period before randomisation	Exclusion criteria included the following: repeated fasting plasma glucose (FPG) or fasting self-monitored blood glucose measurements ≥16.7 mmol/L (300mg/dL), or both, during the pretreatment phase; history of type 1 diabetes, cardiovascular disease, or uncontrolled hypertension; treatment with either a PPARg agonist, ongoing insulin therapy, another SGLT2-i, or any other AHA (other than MET and a SU) Within 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based on restriction of MET use in the MET local label); or serum creatinine ≥124 mmol/L (men) and ≥115 mmol/L (women)
Wilding et al., 2013	Eligible patients were men and women aged 18– 80 years with Type 2 diabetes who had inadequate glycaemic control (HBA1c ≥7% to ≤10.5%) on MET plus SU, with both agents at maximally or near-maximally effective doses	Patients with a history of diabetic ketoacidosis or T1DM, repeated fasting plasma glucose (FPG)≥15.0 mmol/l during the pretreatment phase, history of ≥1 severe hypoglycaemia episode within 6 months before screening, estimated glomerular filtration rate (eGFR) < 55 ml/min/1.73 m^2 (or < 60 ml/min/1.73 m^2 based upon restriction of MET use in the local label) or serum creatinine ≥124 µmol/l for men and ≥115 µmol/l for women, uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg), or taking any antihyperglycaemic agent other than MET plus SU within 12 weeks prior to screening

OAD: oral antidiabetic; T1DM: Type 1 diabetes mellutis

Risk of bias

A detailed critical appraisal of all studies included in the SLR is given in Table 21. All studies selected for the NMA met the minimum internal validity criteria so were considered sufficiently robust for inclusion. Some studies were considered high risk of bias due to the an open-label study design; and a sensitivity analysis was run to exclude such studies from the NMA, however most studies were at a low risk of bias when considering its statistical analyses. Most studies used a ITT analysis for efficacy. Overall, the quality of the studies was high.

Table 21: Quality assessment of included randomised clinical trials based on NICE checklist

Author year	JADAD Score	Concealment Grade	Randomisation	Allocation Concealment	Baseline characteristics	Blinding	Withdrawals	Study Reporting	Statistical Analysis
Haering et al., 2015	4	A	Low risk; the method of randomisation and allocation concealment was done by IVRS	Low risk; The concealment of treatment allocation was adequate	Low risk; There was no significant difference in the baseline characteristics reported between the treatment arms	Not Clear; This was a double-blinded trial but the exact details of the blinding methodology were Unclear	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01159600)	Low risk; The safety and efficacy analysis was done using mITT population
Hermansen et al., 2007	4	A	Low risk; Randomisation was carried out through interactive voice response system	Low risk; The concealment of treatment allocation was adequate	Low risk; There was no significant difference in the baseline characteristics reported between the treatment arms	Not Clear; This was a double-blinded trial but the exact details of the blinding methodology were Unclear	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; The safety and efficacy analysis was done using mITT population
Hong et al., 2015	3	B	Low risk; Randomisation was carried out using table of random number generated by statistician	Not clear; The method of concealment of treatment allocation was not reported	Low risk; Baseline demographics and clinical characteristics were similar between the two groups; no significant difference was obtained	High risk; This was an open label study; however there was discrepancy in findings with clinical trial gov where study was mentioned as double-blinded	Low risk; The number and the reason of withdrawal are adequately reported	Low risk; Author has measured all the outcomes that have been reported in clinical trial registry (NCT01099137)	Not clear; Per protocol analysis was used for efficacy; while safety was assessed using ITT analysis
Ji et al., 2015	4	A	Low risk; The randomisation was carried out	Low risk; The concealment of treatment	Low risk; There was no significant difference in the baseline	Not clear; Although this was a double-blind,	Low risk; The withdrawals, completers,	Low risk; Author has measured all the outcomes	Low risk; The safety analysis was done using

			appropriately using computer-generated randomisation schedule	allocation was adequate	characteristics reported between the treatment arms	however the details of blinding were not reported. However, HbA1c and FPG values were masked to study centres after randomisation to maintain the treatment blind unless FPG met prespecified glycaemic withdrawal criteria	and the specific reasons for withdrawal were reported	that have been reported in published protocol and in clinical trial registry (NCT01381900)	mITT population and efficacy analysis was done using varied population
Liu et al., 2013	3	A	Low risk; Randomisation was carried out through central interactive voice response system	Low risk; The concealment of treatment allocation was adequate through central interactive voice response system	Low risk; There were no statistically significant differences between the treatment groups with respect to baseline demographics, clinical characteristics, or laboratory measurements with the exception of TC and TG levels, which were higher in patients randomly assigned to pioglitazone	High risk; This was an open label study	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; the authors reported the same set of outcomes as mentioned in NCT01195090	Low risk; mITT analysis was used for efficacy and ITT analysis was used for safety analysis
Lukashevich et al., 2014	3	B	Not clear; Randomisation and allocation concealment details were not provided	Not clear; The method of concealment of treatment allocation was not reported	Low risk; Baseline characteristics were similar between the treatment groups	Not clear; The study is double-blind but the method of blinding is not clear	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; authors reported the same set of outcomes as mentioned in NCT01233622	Low risk; mITT principle has been implemented for efficacy and safety analysis
Matthaei et al., 2015	5	A	Low risk; Randomisation was carried out	Low risk; The concealment of treatment	Low risk; Patient characteristics were similar in both the arms	Low risk; the study was double blinded and matched	Low risk; The withdrawals, completers,	Low risk; the authors reported all outcomes	Low risk; Per protocol population was

			through interactive voice response system	allocation was adequate		placebo was used	and the specific reasons for withdrawal were reported	they intended to measure according to the NCT01392677	used for efficacy analysis and ITT population was used for safety analysis
Moses et al., 2014	4	A	Low risk; The randomisation was carried out appropriately by using an interactive voice response system	Low risk; The concealment of treatment allocation was adequate using IVRS	Low risk; Baseline characteristics were similar between the treatment groups	Not clear; Although this was a double-blind, however the details of blinding were not reported	Low risk; The details of withdrawals and completers were reported	Low risk; The authors reported the same set of outcomes as mentioned in NCT01128153 or D1680L00006	Low risk; Safety was performed using ITT analysis
NCT01590771	4	B	Not clear; This was a randomised study but the method of randomisation was not reported	Not clear; The method of concealment of treatment allocation was not reported	Low risk; There was no significant difference in the baseline characteristics reported between the treatment arms	Low risk; This was a double-blind study: Subjects, investigators, and local sponsor personnel remained blinded	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry NCT01590771	Low risk; The safety and efficacy analysis was done using ITT-LOCF population
Nogueira et al., 2014	1	B	Not clear; This was a randomised study but the method of randomisation was not reported	Not clear; The method of concealment of treatment allocation was not reported	Low risk; There were no significant differences between the two groups	Not clear; the details of blinding were not reported	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear, As there is no evidence to ensure that the reported outcome same as protocol	Not clear, There is no enough information available for statistics analysis
Owens et al., 2011	3	B	Not clear; This was a randomised trial but the method of randomisation was not reported	Not clear; The method of concealment of treatment allocation was not reported	Low risk; There was no significant difference in the baseline characteristics reported between the two treatment arms	Not Clear; This was a double-blinded trial but the exact details of the blinding methodology were Unclear	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	High risk; Author has not measured all the outcomes that have been listed in clinical trial registry (NCT00602472)	Low risk; The safety and efficacy analysis was done using mITT population

Round et al., 2013	3	B	Not clear, This was a randomised study but method of randomisation was unclear	Not clear; The method of concealment of treatment allocation was not clear	Low risk; Baseline demographics were similar between the treatment arms	Not clear; This was a double-blinded trial but the exact details of the blinding methodology were not reported	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Not clear; Per protocol analysis was used for efficacy; while safety was assessed using mITT analysis
Schernthaner et al., 2013	5	A	Low risk; The randomisation was carried out appropriately using Interactive Voice Response System/ Interactive Web Response System	Low risk; The concealment of treatment allocation was adequate	Low risk; There was no significant difference in the baseline characteristics between the two treatment arms	Low risk; This was a double-blind study: Subjects, investigators, and local sponsor personnel remained blinded	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01137812)	Not clear; Per protocol analysis was used for efficacy; while safety was assessed using mITT analysis
Wilding et al., 2013	5	A	Low risk; The randomisation was carried out appropriately using Interactive Voice Response System/ Interactive Web Response System	Low risk; The concealment of treatment allocation was adequate	Low risk; There was no significant difference in the baseline characteristics reported between the treatment arms	Low risk; This was a double-blind study: Subjects, investigators, and local sponsor personnel remained blinded throughout the extension period	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01106625)	Low risk; The safety analysis was done using mITT population and efficacy analysis was done using varied population

ITT: Intention to Treat; mITT: modified Intention to treat; IVRS: Interactive Voice Response System; NICE: National Institute for Clinical Excellence; TC: total cholesterol; TG: triglyceride

Methods of analysis and presentation of results

NMA Methodology

An NMA can be performed using a fixed effect approach or a random effects approach. Review of the study populations, heterogeneity in methods used for measuring outcomes, and sample size of included trials suggested that the a priori choice of model is a random effects model, based on the assumption that there is not one true effect. The deviance information criterion (DIC) was used to compare the fit of the random effects and fixed effect models. The recommended methodology for comparing fit among a series of competing models is that a model whose DIC is at least three points lower than that of another model is deemed to have a better fit (Spiegelhalter 2002). Also taken into consideration in selecting the preferred model was the mean total residual deviance (compared against the number of fitted data points).

The NMA used Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS. Code for the NMA was based on that recommended by the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit (NICE 2013). Vague priors were used on all unknown parameters. All chains were run for a substantial number of iterations after burn-in to obtain satisfactory convergence of the posterior distributions. Specifically, three MCMC chains were simulated, starting from different initial values of select unknown parameters. Each chain contained (at least) 20,000 burn-in iterations followed by (at least) 100,000 update iterations. Convergence was assessed by visualizing the histories of the chains, of relevant parameters, against the iteration number; overlapping histories provided an indication of convergence and also the BGR statistics. The accuracy of the posterior estimates was assessed by calculating the Monte Carlo error; less than about 5% of the sample standard deviation for each parameter of interest was deemed acceptable (i.e. U(0,5). The WinBUGS code used is presented in Appendix 9.

Heterogeneity and inconsistency

Sources of clinical heterogeneity were summarised, and inconsistency between the direct and indirect evidence were evaluated by calculating inconsistency factor using R software V 3.0.3.

Statistical heterogeneity was estimated for pairwise comparisons based on I2 statistics, tau square and Cochran's Q statistic. The I2 statistic quantifies the question, "What proportion of the observed variance reflects real differences in effect size?", with I2 below 30% indicating low heterogeneity, and >60-70% indicating considerable heterogeneity, whilst the tau squared statistic is the value of the between-studies variance; values closer to zero are indicative of less heterogeneity. The Cochran's Q statistic tests the null hypothesis that all studies share a common effect size, and given its low power, it is typically rejected when $p < 0.1$.

Analysis

The mean change in HbA1c, weight and SBP were analysed using the mean difference scale, and the proportion of subjects with any hypoglycaemia was analysed based on an odds ratio (OR). The NMA was conducted at three different time points: study endpoint, 24 weeks, 52 weeks.

Sensitivity analysis

- Excluding poor quality studies (defined as trials that were not double-blinded)
- Excluding cross-over studies was planned yet no cross-over studies were included in the base case network; and therefore this analysis was not relevant

- Excluding studies with sub-group data only
- Excluding studies, which increased heterogeneity
- Adding missing data (after imputing SE values)

Model Selection for the Base Case Analysis

For the outcomes of HbA1c and weight (Kg), the random effects model was selected as the preferred analytical model over the fixed effect model based on a comparison of DIC values. In addition, the uncertainty around the between studies variance (SD) was low for both these outcomes compared with an un-informative prior of U(0,10), which supported a priori selection of the random effects model as the preferred model (Table 22 and Table 23).

Table 22: Model fit statistics for HbA1c

	Fixed effect	Random effect
Deviance information criterion	-32.74	-32.77
Mean total residual deviance *	36.18	31.94
Between-studies standard deviation #	NA	0.1 (0.005, 0.26)

NA, not applicable

*compared with 31 data points, # compared with a vague prior of U(0,10)

Table 23: Model fit statistics for weight (Kg)

	Fixed effect	Random effect
Deviance information criterion	40.654	37.74
Mean total residual deviance *	30.17	23.86
Between-studies standard deviation #	NA	0.56 (0.08, 1.55)

NA, not applicable

*compared with 24 data points, # compared with a vague prior of U(0,10)

For the outcomes of SBP (mmHg) the random and fixed effects models had similar model fit characteristics based on DIC criteria. In addition, the random effects model was selected over fixed effects model for its wider acceptance and based on the reasonable uncertainity in between studies standard deviation estimates in the random effects model (Table 24).

Table 24: Model fit statistics for systolic blood pressure (mmHg)

	Fixed Effect	Random Effects
Deviance information criterion	69.98	71.60
Mean total residual deviance *	15.04	15.80
Between-studies standard deviation #	NA	2.68 (0.10, 8.73)

NA, not applicable

*compared with 17 data points, # compared with a vague prior of U(0,10)

For hypoglycaemia, the random effects model has a better fit than the fixed effects model based on a comparison of DIC values. However, there was considerable uncertainty in

estimating the between-studies standard deviation, leading to wide credible intervals (CrIs) for the random effects model (Table 25). Hence, given the inability to estimate the between studies SD with precision with an un-informative prior distribution as wide as U(0,10) in the random effects model, the fixed effects model is considered the preferred model.

Table 25: Model fit statistics for hypoglycaemia Fixed Effect

	Fixed Effect	Random Effects U(0,2)	Random Effects U(0,5)	Random Effects U(0,10)
Deviance information criterion	197.76	180.20	180.15	180.19
Mean total residual deviance*	52.57	28.23	28.16	28.23
Between-studies standard deviation#	NA	0.85 (0.35,1.66)	0.88 (0.36, 1.83)	0.87 (0.36, 1.82)

NA, not applicable

*compared with 27 data points, # compared with a vague priors specified in column heading

The results for the random effects analyses for the outcomes of HbA1c and weight (Kg), and SBP and the fixed effect analyses for hypoglycaemia represent the NMA base case and are presented below.

NMA Results

As discussed above the base case NMA included evidence from those studies evaluating the effectiveness of relevant comparators only, i.e. DPP4-i and other SGLT2-is. Furthermore, the analysis included data from study endpoints regardless of study duration and used data as reported in the studies. This increased the evidence base from eight studies (if a 52 weeks timepoint was chosen) to eleven studies in most cases. The use of only 52 week data in the NMA also resulted in higher SD values and greater CrIs when a random effects model was used providing rationale to use the endpoint network as the base case.

All results are presented for dapagliflozin 10 mg dose versus relevant comparators (in line with the dose in the key triple dapagliflozin RCT).

HbA1c: change from baseline

The base case network diagram for the mean change from baseline is show in Figure 12.

Results from the expanded network using 24 week, 52 week and endpoint data, along with the base case (restricted network) analysis is presented in Table 26. Fourteen studies contributed to the base case analysis. The base case uses a random effects model based on DIC and resdev.

From the NMA the main finding was of no statistically or clinically significant difference in mean change in HbA1c between dapagliflozin versus DPP4is (base case: mean difference = -0.06 [95% CrI: -0.43, 0.33]) in combination with metformin + SU for all networks (Table 26). No statically significant difference was also observed between dapagliflozin versus other SGLT2-is over all networks.

In terms of assessing heterogeneity for the comparison of primary interest for this submission of dapagliflozin vs. DPP4 inhibitors, there was only one dapagliflozin study hence between study heterogeneity of treatment effect was not an issue. For the pairwise comparisons of the DPP4i class vs. placebo the I2 statistic was 42.4%, indicating moderate heterogeneity, with a tau squared statistic of 0.008

Figure 12: Network diagram showing HbA1c change from baseline at study endpoint (base case)

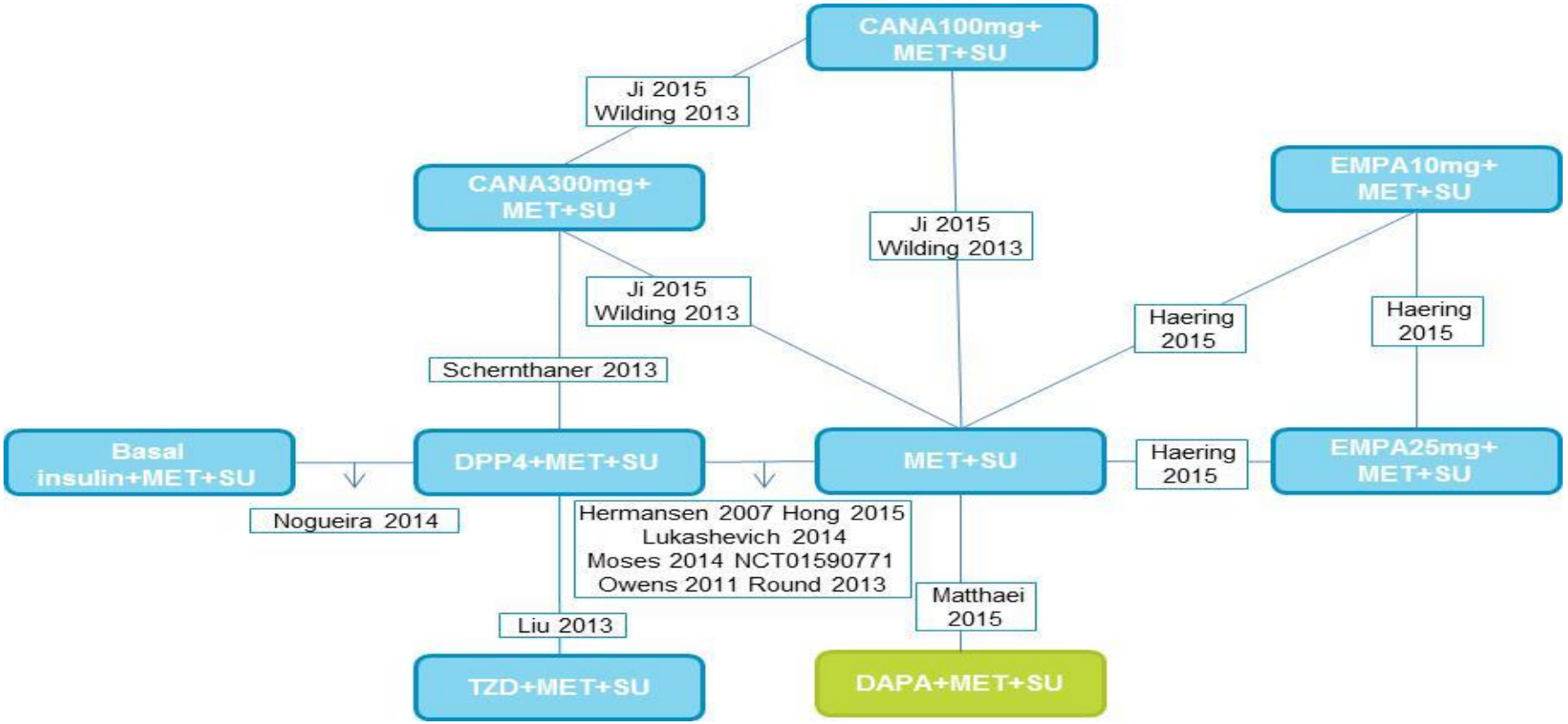


Table 26: HbA1c: change from baseline (base case results shaded in grey)

	24 weeks		52 weeks		Study Endpoint		Base Case	
MET + SU + dapagliflozin vs.	**Fixed effect model**	**Random effect model**	**Fixed effect model**	**Random effect model**	**Fixed effect model**	**Random effect model**	**Fixed effect model**	**Random effect model**
DPP4+MET+SU	-0.04 (-0.26, 0.18)	-0.03 (-0.40, 0.35)	-0.10 (-0.47, 0.27)	-0.10 (-13.15, 12.81)	0.00 (-0.39, 0.38)	0 (-0.63, 0.62)	-0.06 (-0.33, 0.21)	-0.06 (-0.43, 0.33)
CANA300 mg+MET+SU	0.18 (-0.07, 0.42)	0.16 (-0.26, 0.57)	0.27 (-0.07, 0.62)	0.27 (-10.35,10.70)	0.27 (-0.02, 0.56)	0.22 (-0.3, 0.72)	0.27 (-0.02, 0.56)	0.24 (-0.19, 0.64)
CANA100 mg+MET+SU	-0.02 (-0.29, 0.26)	-0.03 (-0.48, 0.41)	0.05 (-0.29, 0.40)	0.06 (-10.72, 10.60)	0.03 (-0.29, 0.35)	0 (-0.54, 0.53)	0.03 (-0.29, 0.35)	0.02 (-0.44, 0.44)
EMPA10 mg+MET+SU	-0.04 (-0.29, 0.21)	-0.04 (-0.52, 0.43)	0.1 (-0.28, 0.49)	0.10 (-10.50,10.8)	0.08 (-0.22, 0.38)	0.16 (-0.34, 0.7)	0 (-0.39, 0.38)	0 (-0.51, 0.52)
EMPA25 mg+MET+SU	-0.09 (-0.34, 0.16)	-0.09 (-0.57, 0.39)	0.0 (-0.38, 0.39)	0.0 (-10.66, 10.76)	0.17 (-0.22, 0.55)	0.25 (-0.37, 0.89)	0 (-0.38, 0.38)	0 (-0.52, 0.52)
MET+SU	**-0.69 (-0.90, -0.48)**	**-0.69 (-1.04, -0.34)**	**-0.7 (-0.96,-0.44)**	-0.69 (-8.17,6.81)	**-0.70 (-0.97, -0.44)**	**-0.7 (-1.14, -0.26)**	**-0.7 (-0.97, -0.44)**	**-0.7 (-1.06, -0.34)**

Statistically significant results are in bold text. Values less than 0 favours intervention (dapagliflozin

Body weight: change from baseline

The base case network diagram for the mean change from baseline is shown in Figure 13. Results from the expanded network using 24 week, 52 week and endpoint data, along with the base case (restricted network) analysis is presented in Table 27. Eleven studies contributed to the base case analysis. The base case analysis uses a random effects model based on DIC and resdev.

Compared to DPP4-is, dapagliflozin in combination with MET plus SU was associated with a statistically significant decrease in body weight vs DPP4-is (Table 27), across all networks using a random effects model (base case = -2.33 [95%CrI -4.17, -0.49]). The same finding of a significant difference in change in body weight from baseline in favour of dapagliflozin vs. the DPP4-is was also found using a fixed effects model across all time points. An analysis at 52 weeks was not possible due to limited data: the Schernthaner 2013 study comparing canagliflozin 300 mg and DPP4-is could not be connected within the network for the 52 week timepoint analysis due to a missing common comparator.

Compared to other SGLT2-is, there were no statistically significant results across all networks.

In terms of assessing heterogeneity for the comparison of primary interest for this submission of dapagliflozin vs. DPP4-is, there was only one dapagliflozin study hence between study heterogeneity of treatment effect was not an issue. For the pairwise comparisons of the DPP4-i class vs. placebo the I2 statistic was 63.5%, with a tau squared statistic of 0.1454. There was no clinical rationale to exclude any studies contributing to the heterogeneity (Appendix 13.1).

Figure 13: Network diagram showing change in body weight from baseline at study endpoint (base case)

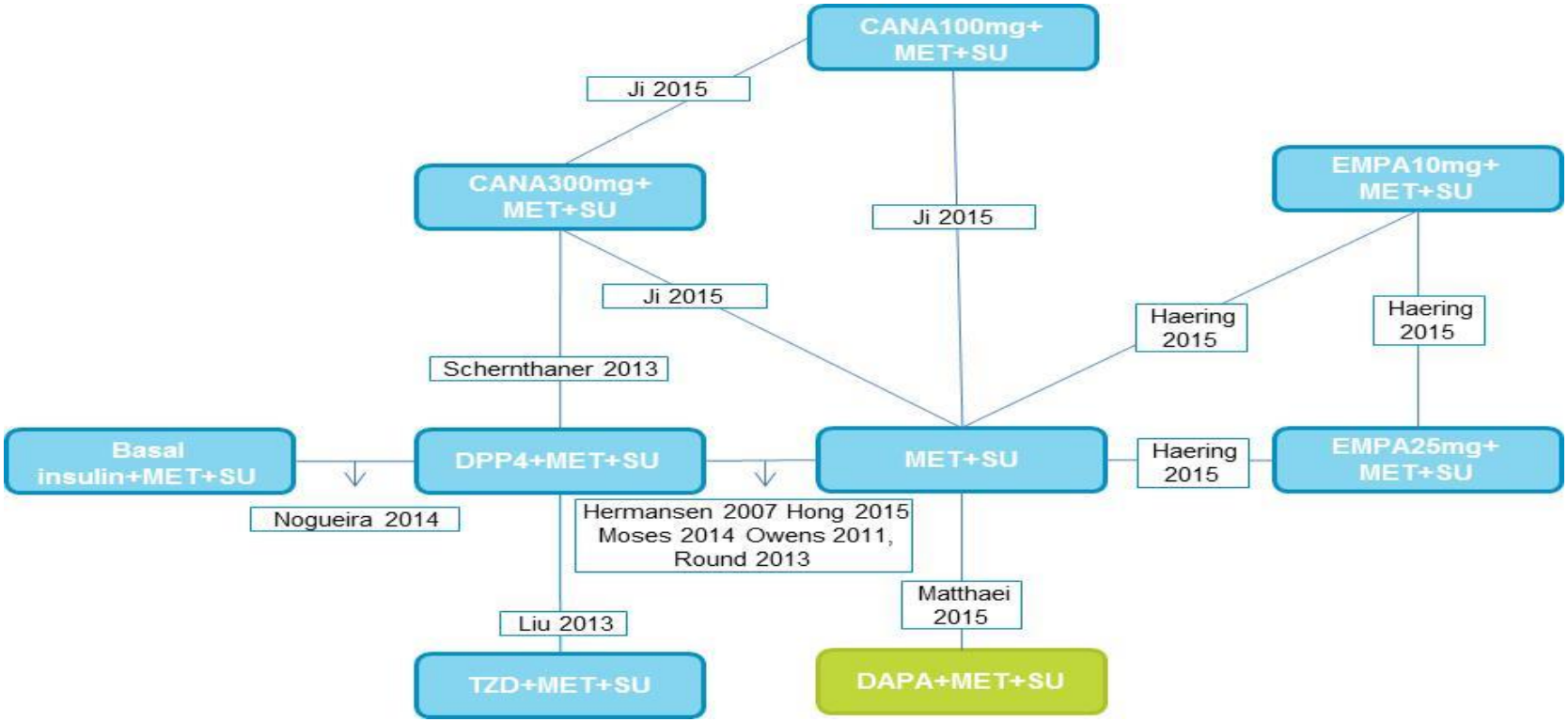


Table 27: Mean change in body weight from baseline (base case results shaded in grey)

	24 weeks		52 weeks		Study Endpoint		Base Case	
MET + SU + dapagliflozin vs.	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model
DPP4+MET+SU	**-2.48 (-3.23 ,-1.73)**	**-2.58 (-3.91,-1.30)**			**-2.28 (-3.38, -1.2)**	**-2.38 (-3.79, -1.06)**	**-2.27 (-3.39, -1.13)**	**-2.33 (-4.17, -0.49)**
CANA300 mg+MET+SU	0.38 (-0.46,1.23)	0.15 (-1.44,1.61)			-0.13 (-1.51, 1.25)	-0.18 (-1.89, 1.44)	-0.13 (-1.54, 1.29)	-0.14 (-2.3, 2.02)
CANA100 mg+MET+SU	-0.24 (-1.47,0.97)	-0.36 (-2.20,1.44)			-0.4 (-1.92, 1.08)	-0.47 (-2.29, 1.33)	-0.41 (-1.93, 1.11)	-0.42 (-2.78, 1.95)
EMPA25 mg+MET+SU	-0.07 (-0.90, 0.76)	-0.07 (-1.68 , 1.55)	0.10 (-1.13, 1.33)	0.11 (-11.30, 11.64)	-0.19 (-1.39, 1)	-0.24 (-1.87, 1.35)	-0.2 (-1.44, 1.04)	-0.2 (-2.46, 2.04)
EMPA10 mg+MET+SU	-0.30 (-1.13, 0.52)	-0.30 (-1.91 ,1.33)	0.10 (-1.13, 1.33)	0.12 (-11.27, 11.73)	-0.08 (-1.29, 1.1)	-0.14 (-1.77, 1.44)	-0.1 (-1.33, 1.13)	-0.1 (-2.33, 2.15)
MET+SU	**-2.07 (-2.78,-1.35)**	**-2. 07 (-3.28,-0.86)**	**-1.90 (-3, -0.81)**	-1.89 (-9.86, 6.39)	**-1.89 (-2.97, -0.84)**	**-1.93 (-3.25, -0.66)**	**-1.9 (-3, -0.79)**	**-1.9 (-3.61, -0.18)**

Statistically significant results are in bold text. Values less than 0 favours intervention (dapagliflozin)

SBP: change from baseline

The base case network diagram for the mean change from baseline is show in Figure 14. Results from the expanded network using 24 week, 52 week and endpoint data, along with the base case (restricted network) analysis is presented in Table 28. Seven studies contributed to the base case analysis. The base case analysis uses a random effects model although DIC and resdev were lower for fixed effects model, the results were quite similar. A random effects model is more appropriate given the heterogeneity in the study design across the studies contributing to the analysis.

No statically significant difference were associated with SBP change from baseline between dapagliflozin versus DPP4-is (Table 28), (base case = -4.96 [-17.82, 8.41]). The same finding of a non-significant difference in SBP change from baseline in favour of dapagliflozin vs. the DPP4-is was also found using a fixed effects model. This was consistent over all networks.

Compared to other SGLT2s, there were no statistically significant results for dapagliflozin across the networks (Table 28).

In terms of assessing heterogeneity for the comparison of primary interest for this submission of dapagliflozin vs. DPP4-is, there was only one dapagliflozin study hence between study heterogeneity of treatment effect was not an issue.

Figure 14: Network diagram showing change in systolic blood pressure from baseline at study endpoint (base case)

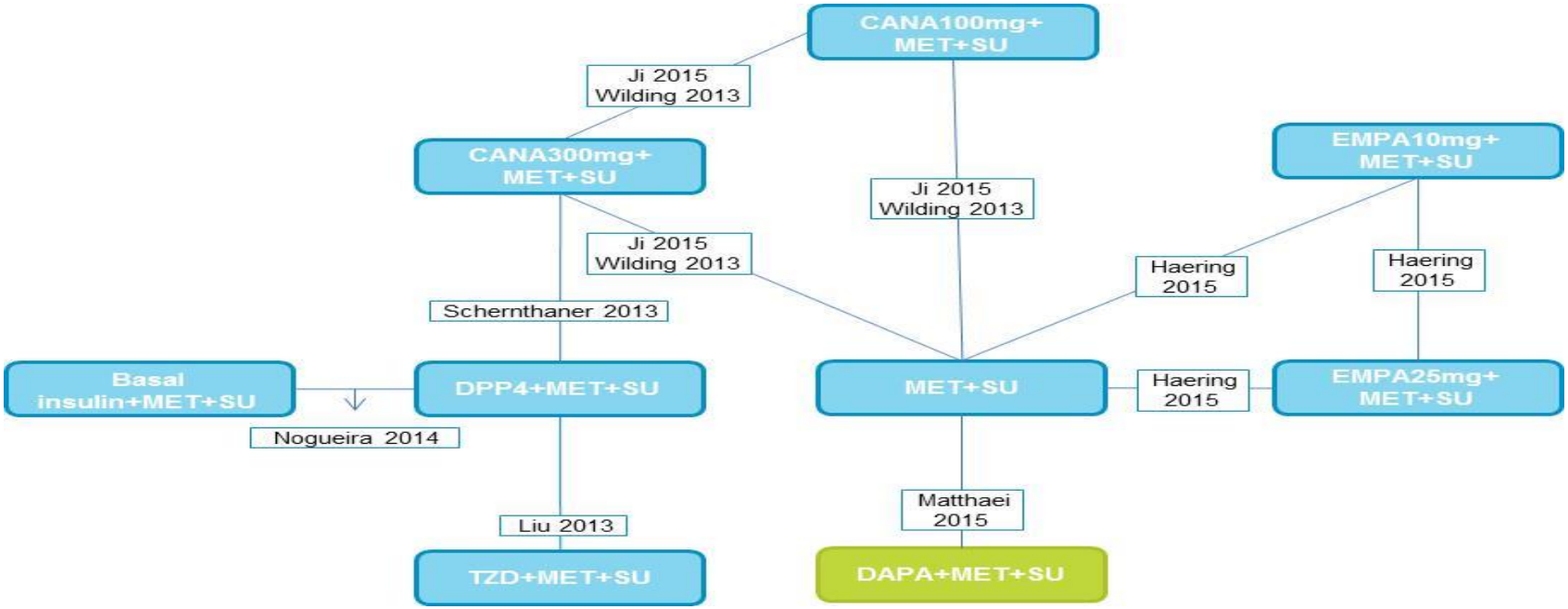


Table 28: mean change in systolic blood pressure from baseline (base case results shaded in grey)

	24 weeks		52 (± 6) weeks		Study endpoint		Base Case	
MET + SU + dapagliflozin vs.	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model
DPP4+MET+SU	-0.71 (-14.34, 13.06)	-1.42 (-19.96, 17.31)	-5.08 (-10.48, 0.37)	-5.08 (-26.92,16.82)	-4.50 (-9.62, 0.66)	-4.05 (-12.06, 4.94)	-5.02 (-10.3, 0.27)	-4.96 (-17.82, 8.41)
CANA300 mg+MET+SU	-2.12 (-6.13, 1.88)	-1.95 (-11.93, 8.88)	0.91 (-4.12, 5.99)	0.91 (-17.03, 18.85)	1.31 (-3.53, 6.16)	1.43 (-5.94, 9.13)	0.97 (-3.95, 5.92)	1.05 (-9.27, 11.65)
CANA100 mg+MET+SU	-1.60 (-5.62, 2.40)	-1.50 (-11.54, 9.35)	1.71 (-3.30, 6.78)	1.70 (-16.30, 19.55)	1.83 (-3.05, 6.74)	1.84 (-5.76, 9.54)	1.67 (-3.26, 6.55)	1.67 (-8.78, 12.07)
EMPA25 mg+MET+SU	-1.89 (-5.55, 1.74)	-1.89 (-13.26, 10.03)	0.43 (-4.19,5.07)	0.37 (-17.46,18.16)	0.01 (-4.6,4.68)	-0.04 (-8.16,8.12)	0.02 (-4.6, 4.65)	0.06 (-11.36, 11.78)
EMPA10 mg+MET+SU	-1.29 (-4.96, 2.34)	-1.29 (-12.73, 10.60)	0.83 (-3.8,5.5)	0.77 (-17.05,18.65)	0.1 (-4.51,4.79)	0.07 (-8.03,8.22)	0.12 (-4.51, 4.76)	0.19 (-11.31, 11.92)
MET+SU	**-3.99 (-7.10, -0.91)**	3.97 (-12.24, 4.54)	-2.08 (-6.28,2.15)	-2.13 (-14.94,10.84)	-2.08 (-6.29, 2.15)	-2.12 (-8.33, 4.19)	-2.07 (-6.29, 2.14)	-2.04 (-10.51, 6.45)

Statistically significant results are in bold text. Values less than 0 favours intervention (dapagliflozin).

Any hypoglycaemic event

The base case network diagram for the mean change from baseline is show in Figure 15.

Results from the expanded network using 24 week, 52 week and endpoint data, along with the base case (restricted network) analysis is presented in Table 29. Twelve studies contributed to the base case analysis. The base case analysis uses a fixed effects model. The random effects model did not converge. No statically significant differences were associated with risk of any hypoglycaemic event between dapagliflozin versus DPP4-is, (base case: = 1.14 [0.48, 2.92]). The same finding of a non-significant difference in any hypoglycaemic event for dapagliflozin vs. the DPP4-is was also found using a random effects model. This was consistent over all timepoints.

In terms of assessing heterogeneity for the comparison of primary interest for this submission of dapagliflozin vs. DPP4-is, there was only one dapagliflozin study hence between study heterogeneity of treatment effect was not an issue. For the pairwise comparisons of the DPP4-i class vs. placebo the I^2 statistic was 79.8%, with a tau squared statistic of 0.579. Sensitivity analysis was conducted by removing the study contributing to high I^2 statistic (Appendix 13.1)

No analysis was possible for severe hypoglycemia due to a significant number of studies reporting zero events in both treatment arms.

Figure 15: Network diagram showing risk of any hypoglycaemic event from baseline at study endpoint (base case)

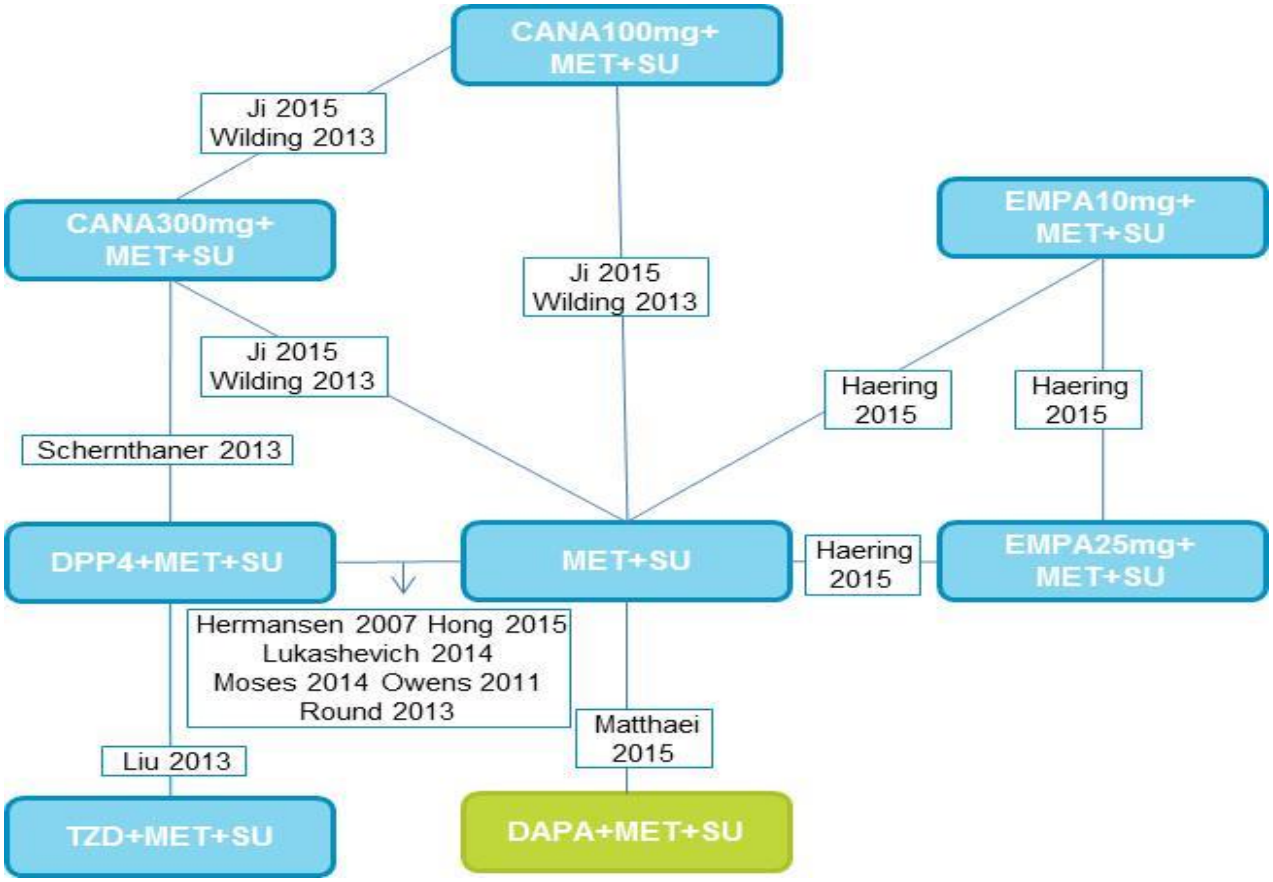


Table 29: Risk of any hypoglycaemic event (base case results shaded in grey)

	24 weeks		52 weeks		Study Endpoint		Base Case	
MET + SU + dapagliflozin vs.	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model	Fixed effect model	Random effect model
DPP4 + MET + SU	2.33 (0.76, 9.09)	1.96 (0.32, 12.56)	0.87 (0.31, 2.56)	0.89 (0.01, 86.63)	1.12 (0.46, 2.86)	0.98 (0.21, 4.40)	1.14 (0.48, 2.92)	0.95 (0.1, 8.04)
CANA300 mg + MET + SU	2.47 (0.73, 10.28)	2.38 (0.33, 18.72)	0.79 (0.29, 2.22)	0.8 (0.02, 35.13)	0.95 (0.38, 2.46)	0.85 (0.17, 4.31)	0.96 (0.39, 2.5)	0.84 (0.08, 8.56)
CANA100 mg + MET + SU	2.28 (0.68, 9.45)	2.21 (0.31, 17.21)	0.89 (0.33, 2.51)	0.9 (0.02, 38.69)	0.96 (0.37, 2.56)	0.88 (0.16, 4.72)	0.97 (0.38, 2.59)	0.86 (0.07, 9.78)
EMPA25 mg + MET + SU	3.04 (0.87, 12.99)	3.06 (0.35, 29.35)	NA	NA	1.68 (0.63, 4.68)	1.69 (0.26, 11.22)	1.68 (0.63, 4.67)	1.68 (0.1, 27.98)
EMPA10 mg + MET + SU	2.44 (0.70, 10.31)	2.45 (0.28, 23.37)	NA	NA	1.46 (0.55, 4.04)	1.47 (0.22, 9.78)	1.46 (0.55, 4.01)	1.45 (0.09, 24.2)
MET + SU	**4.13 (1.39,15.81)**	4.17 (0.79,25)	2.09 (0.9,5.16)	2.11 (0.14,31.41)	2.09 (0.89,5.17)	2.11 (0.51,8.95)	2.09 (0.9, 5.19)	2.08 (0.28, 16.39)

Statistically significant results are in bold text. Values less than 1 favour intervention (dapagliflozin).

Sensitivity Analyses Results

The results of the sensitivity analyses were consistent with those from the base case analysis with the following exceptions:

- *Removing poor quality studies:*
  - A statistically significant result for change in total body weight for dapagliflozin versus MET + SU (placebo) was not shown in the RE model -1.89 (-3.91, 0.11) (the best fitting model), although remained statistically significant in the FE model: -1.9 (-2.99, -0.8)
- *Removing sub-group studies:*
  - A statistically significant result for change in HbA1c favouring canagliflozin 300mg versus dapagliflozin was shown in the FE model only; the RE model being the best fitting model
  - A statistically significant result for change in total body weight for dapagliflozin versus DPP4-is was not shown in the RE model -2.16 (-4.71, 0.41) (the best fitting model), although remained statistically significant in the FE model
  - A statistically significant result for change in total body weight for dapagliflozin versus MET + SU (placebo) was not shown in the RE model -1.89 (-4.23, 0.45) (the best fitting model), although remained statistically significant in the FE model
- *Removing studies increasing heterogeneity*:
  - A statistically significant result for change in HbA1c favouring canagliflozin 300mg versus dapagliflozin was shown in the FE model only; the RE model being the best fitting model

Strengths and limitations

Strengths:

The key strength of this analysis is the ability to generate estimates of relative efficacy and safety of dapagliflozin in combination with MET plus SU by combining direct and indirect evidence through a Bayesian NMA. The analysis was conducted according to a protocol specified in advance, using transparent, reproducible methods to identify evidence, perform data abstraction, and conduct the analysis. For each outcome the selection of a random or fixed effects model as the preferred analysis were based on DIC criteria and between studies standard deviation estimates, although results based on both models has been presented for transparency.

Key outcomes in the NMA were change in baseline in HbA1c, the main outcome for assessing the relative efficacy of Type 2 diabetes drugs, and change from baseline in weight (kg) for which dapagliflozin as an SGLT2-i produces favourable outcomes relative to DPP4-is. For these outcomes there was a large evidence base available to inform the networks (12486 and 10172 patients for each of the HbA1c and weight networks respectively in the total study endpoint network; and 5270 and 4150 patients for these networks in the restricted study network).

The findings from the triple therapy NMA were as expected and consistent with those found in previous NMAs informing prior NICE appraisals of SGLT2-is demonstrating no significant differences between the SGLT2-is in efficacy and safety.

Limitations:

The majority of the studies in the NMA were of 24 weeks duration; and there was variation in endpoint data of longer duration being 52 weeks for canagliflozin and dapagliflozin studies; and 76 weeks for the empagliflozin data. Whilst this is a potential limitation there is a large body of evidence from other RCTs extension studies in the dual therapy setting showing the durable maintenance of HbA1c and weight reduction for dapagliflozin over a longer time horizon. Further, there is no clinical rationale to expect a different treatment effect for the SGLT2-is at these different timepoints; we therefore took the decision to pool the data together in the base case as well as present data for a 24 week and a 52 week network separately. The results of the networks are similar at each timepoint with the exception of BP for which the dapagliflozin trial results varied over time, as described in Section 4; and hypoglycaemia for which a greater placebo effect was observed at 52 weeks versus 24 weeks in the dapagliflozin trial (Table 33 in Section 4.13).

A limitation for the SBP outcome was the relatively fewer studies that are available for this network, although it still numbered over 2496 patients.

The evidence base was also limited for the hypoglycaemia outcome due mainly to differences in how hypoglycaemia is defined across studies. Hypoglycaemia was not adequately defined by the majority of trials, and where reported, definitions differed according to the blood glucose threshold applied, and whether or not the episode needed to be confirmed, was symptomatic, or asymptomatic. Major episodes, defined as episodes requiring third party intervention, were infrequently reported. Also, it was not always possible to distinguish between severe (i.e. requiring hospitalisation) and less severe hypoglycaemic events, and it is likely that only the former will impact significantly on patient outcomes.

Heterogeneity identified could not always be addressed in sensitivity analyses where there was no clinical rationale to remove certain studies increasing the heterogeneity.

Other issues:
There are a number of general issues associated with NMAs in the field of Type 2 diabetes that we considered:

- In the main analysis we took the decision to group drug therapies into drug classes rather than treating each agent on its own (with the exception of the SGLT2-is). For DPP4-is (the comparator of direct interest in this submission), there is published evidence that they are non-inferior to each other, hence justifying this approach
- The assumption underlying network meta-analyses is that of exchangeability: that trials in the network are sufficiently similar in design, outcomes definition, and enrolled patient population that the true relative effect size to be estimated using the design of a trial comparing A vs B would be the same as the effect size estimated using the design of a trial comparing B vs C. However, included RCTs varied in terms of included patient population, baseline clinical values, trial design, and dosing and titration of agents. Although these aspects may affect absolute outcomes, they were not considered to modify the relative effect. Baseline HbA1c was the only covariate assumed to modify the relative effect of agents, and this factor was explored using meta-regression and did not result in meaningful changes in the estimates
- Aggregate, study-level summaries provided estimates for inclusion in the analysis, and are subject to ecological bias. The alternative would be to use individual patient-level data; however these data was not available for the comparators. Nevertheless, summary-level data are the most readily available data; and represent a large number of RCTs in varied settings

Summary

The NMA demonstrates the following key findings:

- No statistically significant differences between dapagliflozin and the DPP4-is in change from baseline in HbA1c and SBP; and the incidence of 'any hypoglycaemic event'
- A significantly greater reduction in total body weight with dapagliflozin compared with DPP4-is
- In line with previous findings across all the analyses it appears that dapagliflozin has a similar efficacy and safety to the other SGLT2-is
- No significant differences between dapagliflozin and the other SGLT2-is based on a comparison versus each individual dose (canagliflozin 300 mg; canagliflozin 100 mg; empagliflozin 10 mg; empagliflozin 25 mg) in the key outcomes of HbA1c; SBP; change in total body weight; and any hypoglycaemic event
- It should be noted that within the NMA individual treatment doses have been compared. In clinical practice however, 100 mg is the starting dose for all patients on canagliflozin and this is increased to 300 mg as required. The canaglilfozin trials are not reflective of this dose increase with patients initiated on the 300 mg dose at study start

4.11 *Non-randomised and non-controlled evidence*

Results presented here are from a retrospective observational study which was conducted using UK patient records. The Clinical Practice Research Datalink database contains patient records from 684 primary care practices throughout the UK and was used to identify patients with patients with type 2 diabetes mellitus diagnosis. The inclusion criteria also identified a patient cohort who was given a first prescription for dapagliflozin between November 2012 and September 2014, who were registered ≥6 months prior to that prescription and remained registered for ≥3 months after dapagliflozin initiation. Changes in HbA1c and weight were reported for patients with a measure pre-initiation and at least one measure during dapagliflozin treatment (up to 12 months follow-up). There were 2401 patient records with ≥1 prescription for dapagliflozin, of which 1732 fulfilled the inclusion criteria of the study. Patient records were analysed according to background therapy with 480 patients being prescribed dapagliflozin as part of a triple therapy treatment regimen. The baseline characteristics are reflective of patents seen in UK clinical practice and are consistent with patients included in clinical study programme for dapagliflozin (Table 30). However, it should be noted that the baseline glycaemic control was slightly worse and had a greater mean body weight than in the clinical trials. The results of this real world study shows, that the most common usages were dual therapy with MET (25%), triple therapy (28%) and add-on to insulin (19%).

Table 30: Baseline characteristics per treatment group

	All (n=1732)	Dual therapy with MET (n=435)	Triple therapy (n=480)	Add-on to Insulin (n=332)
Age (years); mean (SD)	57.5 (10.5)	55.6 (10.0)	59.1 (10.4)	57.6 (10.7)
Male (%)	57.9	55.2	61.3	55.7
*HbA1c (%) mean (SD)	9.48 (1.64)	9.15 (1.61)	9.36 (1.50)	9.90 (1.60)
*HbA1c (mmol/mol) mean (SD)	80.1 (17.9)	76.5 (17.6)	78.8 (16.3)	84.7 (17.5)
*Weight (kg) mean (SD)	103.1 (23.0)	106.0 (23.0)	99.8 (21.4)	103.9 (21.7)
Years since Type 2 diabetes diagnosis, mean (SD)	9.5 (6.0)	6.7 (4.4)	8.8 (4.9)	13.0 (6.7)

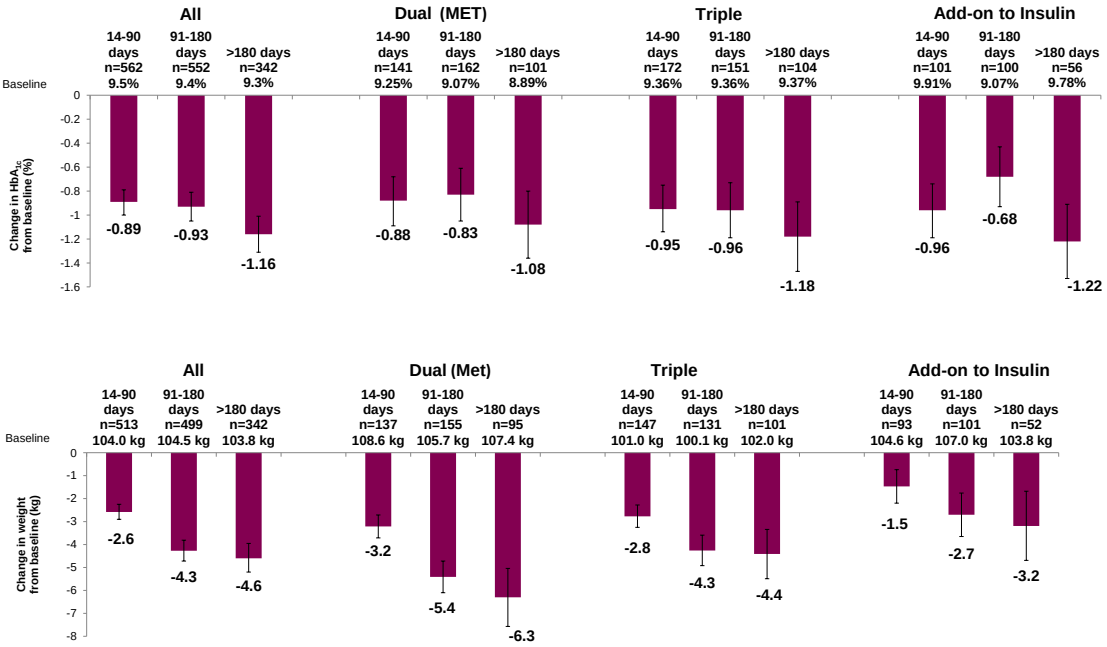
SD: standard deviation; *Number of patients for whom a reading was recorded ranged from 92 – 99%

Similar to results seen in the clinical study, the addition of dapagliflozin resulted in an overall reduction in HbA1c levels (0.89-1.16% [9.7-12.6 mmol/mol]) with a 1.18% reduction in HbA1c levels observed in the triple therapy cohort (Figure 16:). A greater reduction was observed in patients with higher baseline HbA1c as compared to lower baseline (Wilding 2015b).

A decrease in body weight was also observed within 14-90 days of treatment and maintained for up to 180 days (Figure 16:). Reduction in body weight was between 2.6 and 4.6kg over a 180 day period.

It should be noted that 69.1% of patients on dual, triple, and add-on to insulin treatment regimens (with follow-up >180 days after starting dapagliflozin [n=194]), had a decrease in both HbA1c and weight.

Figure 16: Change from baseline in HbA1c and body weight following dapagliflozin initiation



Observational Real World Evidence studies allow the assessment of treatment use and outcomes in the wider population. The results of this observational study show that the overall reductions in HbA1c (0.89-1.16%) and weight (2.6-4.6 kg) observed in UK clinical practice are consistent with results from the dapagliflozin clinical trial programme. Furthermore, dapagliflozin is already being used in a triple regimen in the UK demonstrating a clinical need in UK clinical practice for this regimen.

4.12 *Adverse reactions*

- In Study 5 treatment with dapagliflozin used as add on treatment to MET and SU was well tolerated over 24 and 52 weeks. While the proportion of AEs was similar in both groups, the proportion of patients with serious adverse events (SAEs) was higher in the placebo group at 24 and 52 weeks
- More subjects in the dapagliflozin arm reported hypoglycaemic episodes. However, the rate of recurrent hypoglycaemic episodes was higher in the placebo group. None of these were considered serious, and none led to discontinuation
- The data from Study 5 correspond with the findings of other Phase III studies of dapagliflozin in combination with OADs
- Non-statistically significant imbalances in the number of cases of breast, bladder and prostate cancer have been observed for dapagliflozin vs. control across the whole clinical trial programme. However, causality has not been established
- A meta-analysis of 21 Phase IIb/III clinical trials involving nearly 9,000 patients (over 4 years) confirms no increased CV risk and suggests the potential for a beneficial CV effect with dapagliflozin, which is consistent with the multifactorial benefits on CV risk factors associated with SGLT2-is

A key safety endpoint across the dapagliflozin clinical trial programme was the rate of hypoglycaemia. In addition, genital infections (GIs) and urinary tract infections (UTIs) were

considered events of special interest in the dapagliflozin development programme given that, due to its mechanism of action, dapagliflozin causes glucosuria, and that these infections are known to be more common in diabetic patients than in the general population. We report the results for these AEs within the presentation of the overall safety results from the dapagliflozin as an add-on to MET plus SU.

Dapagliflozin add-on to MET plus SU - Study 5
AEs and SAEs

The safety analysis set from study 5 was used in all summaries of safety data i.e all randomised subjects who received at least 1 dose of study medication and who provided any safety records.

The overall proportions of subjects with AEs and discontinuations due to an AE were similar in both treatment groups while the proportion of subjects with SAEs was higher in the placebo group. There were no deaths during the 24-week ST treatment period (Table 31).

Table 31: Summary of adverse events over the 24 week period - including data after rescue - safety analysis set (Matthaei 2015b)

Adverse events (AEs)	Dapagliflozin 10 mg + MET + SU N = 109 [n (%)]	Placebo + MET + SU N = 109 [n (%)]
At least one AE	53 (48.6)	56 (51.4)
Death	0	0
At least one SAE	1 (0.9)	6 (5.5)
AE leading to discontinuation*	2 (1.8)	3 (2.8)
SAE leading to discontinuation*+§	1 (0.9)	1 (0.9)
AEs with frequency ≥ 3% in any group (by preferred term)		
Bronchitis	5 (4.6)	1 (0.9)
UTI	5 (4.6)	7 (6.4)
Hypertension	1 (0.9)	4 (3.7)
Special interest categories		
At least one event of hypoglycaemia	14 (12.8)	4 (3.7)
Hypoglycaemia leading to discontinuation*	0	0
At least one event of GI	6 (5.5)	0
At least one event of UTI	7 (6.4)	7 (6.4)
Renal impairment/failure¶	2 (1.8)	0

AE: adverse event; GI: genital infection; n: number of subjects; SAE: serious adverse event; MET: metformin; SU: sulfonylurea; UTI: urinary tract infection.
* of study medication. + dapagliflozin group: COPD; placebo group: renal cell carcinoma. ¶ All events of renal impairment/failure were decreased renal creatinine clearance. § Data from CSR (AstraZeneca 2013a)

Hypoglycaemia

While more subjects in the dapagliflozin arm (12.8%) reported hypoglycaemic events than in the placebo group (3.7%), the number of episodes of hypoglycaemia per patient was lower in the dapagliflozin group (1.7) compared to the placebo group (3.8) (AstraZeneca 2013a).This suggests the dapagliflozin arm was less likely to experience recurrent hypoglycaemic episodes.

No major episodes and no discontinuations due to hypoglycaemic events were reported. In clinical practice, as per the SPC recommendations (SPC Forxiga 2013) , this would be mitigated by a reduction in the SU dose at initiation of dapagliflozin.

Urinary Tract Infections

The number of UTIs was low in both groups (6.4% dapagliflozin, 6.4% placebo) (Matthaei 2015b). UTIs were mainly reported by women. No UTIs were considered serious, and no subject was discontinued from study medication as a result. Three subjects in the dapagliflozin group experienced two events from UTI, all others were single events. One event, treated in the dapagliflozin group, required additional treatment due to inadequate response to the original course of antibiotics.

Genital infections

GIs were more common in the dapagliflozin group (5.5%) than in the placebo group (0%) (Matthaei 2015b) and were almost exclusively reported by women. All were of mild or moderate intensity. No subject experienced an event assessed as serious and no subject was discontinued as a result of a GI. Most events were treated with a single course of treatment, although two patients required an additional course.

Malignant and unspecified neoplasms

One subject each in the dapagliflozin group (bladder neoplasm) and placebo group (renal cell carcinoma) experienced an AE of malignant and unspecified neoplasms. The subject on dapagliflozin was a 53 year old current smoker with haematuria due to UTI at randomisation and also two months later. This led to further investigation and the diagnosis of a non-serious, unspecified neoplasm of the bladder was made on Day 114, 3.5 months after start of study medication. The subject continued on study medication and voluntarily discontinued from the study five months later. The neoplasm was considered unrelated to study medication. Resection of the tumour six months after start of study medication showed a Grade 1 transitional cell carcinoma.

52-week safety data (Matthaei 2015c)

In dapagliflozin vs placebo groups the frequency of AEs were 69.7% vs 73.4%, SAEs 6.4% vs. 7.3%, and hypoglycaemic events 15.6% vs. 8.3% (Table 32). GIs were reported by 10.1% vs 0.9% of patients with dapagliflozin vs. placebo (women 14.3 vs 2.0%; men 4.3 vs. 0%) and UTIs by 10.1% vs 11.0% (women 12.7% vs. 22.4%; men 6.5% vs. 1.7%). In conclusion, dapagliflozin as add-on to MET plus SU was well tolerated over 52 weeks.

Table 32: Safety and tolerability of dapagliflozin over 24 and 52 weeks.

	Patients with events observed over 24 weeks		**Patients with events observed over 52 weeks**	
	Placebo (N=109)	Dapagliflozin (N=109)	Placebo (N=109)	Dapagliflozin (N=109)
	n (%)	n (%)	n (%)	n (%)
At least one AE	56 (51.4)	53 (48.6)	80 (73.4)	76 (69.7)
At least one SAE	6 (5.5)	1 (0.9)	8 (7.3)	7 (6.4)
Deaths	0	0	0	0
AEs leading to treatment discontinuation	3 (2.8)	2 (1.8)	4 (3.7)	2 (1.8)
Most common AEs (>4% in either group over 52weeks)*				
Nasopharyngitis	3 (2.8)	2 (1.8)	7 (6.4)	11 (10.1)
UTI	7 (6.4)	5 (4.6)	10 (9.2)	8 (7.3)
Bronchitis	1 (0.9)	5 (4.6)	3 (2.8)	9 (8.3)
Hypertension	4 (3.7)	1 (0.9)	7 (6.4)	5 (4.6)
Asymptomatic bacteriuria	2 (1.8)	2 (1.8)	5 (4.6)	4 (3.7)
Back pain	0 (0)	1 (0.9)	1 (0.9)	5 (4.6)
AEs of special interest				
Hypoglycaemia	4 (3.7)	14 (12.8)	9 (8.3)	17 (15.6)
Minor events	4 (3.7)	14 (12.8)	9 (8.3)	17 (15.6)
Major events	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (0.9)	0 (0)	1 (0.9)	0 (0)
GI†	0 (0)	6 (5.5)	1 (0.9)	11 (10.1)
Women	0/49	5/63	1/49	9/63
Men	0/60	1/46	0/60	2/46
UTI†	7 (6.4)	7 (6.4)	12 (11.0)	11 (10.1)
Women	6/49	4/63	11/49	8/63
Men	1/60	3/46	1/60	3/46
Hypovolaemia†	0 (0)	1 (0.9)	0 (0)	2 (1.8)
Chronic pyelonephritis	0 (0)	1 (0.9)	0 (0)	1 (0.9)
Renal impairment/failure†	0 (0)	2 (1.8)	0 (0)	2 (1.8)
Creatinine renal clearance	0 (0)	2 (1.8)	0 (0)	2 (1.8)
Malignant and unspecified neoplasms†	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)

GI, genital infection;

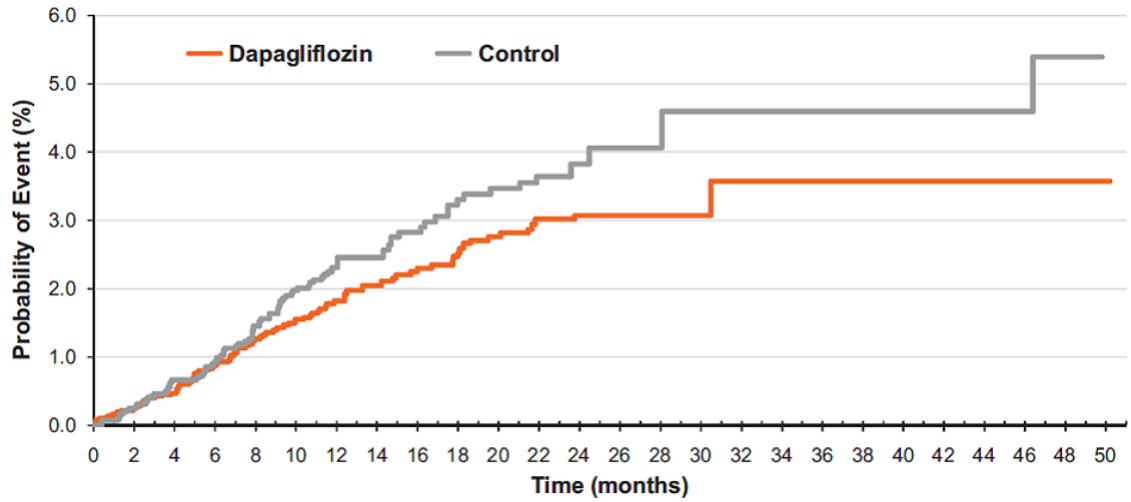
Cardiovascular (CV) safety and malignancy risk

The dapagliflozin CV safety and cancer risk were presented in a previous NICE submission (TA288) (NICE TA288 2013). This is not repeated here - instead we present updated data presented to the Food and Drug Administration (FDA) Endocrinologic & Metabolic Drug Advisory Committee (EMDAC) in December 2013 (EMDAC 2013).

CV safety

In an updated meta-analysis of 21 Phase IIb/III clinical trials involving over 9,000 patients for the FDA, where CV events were prospectively and blindly adjudicated by an independent committee, dapagliflozin was still not associated with an increased risk of CV events for a composite of CV death, MI, stroke and hospitalisation for unstable angina (UA) (EMDAC 2013). The estimated hazard ratio between dapagliflozin and control for the composite primary endpoint of CV death, MI, stroke, and hospitalization for UA, using Cox proportional hazards method, was 0.787 (95% CI: 0.579, 1.070), for the secondary composite endpoint 0.758 (95% CI: 0.581, 0.988) and for the composite endpoint of major adverse cardiovascular events (MACE) was 0.772 (95% CI: 0.543, 1.097) (EMDAC 2013). A Kaplan-Meier curve for the cumulative probability of the primary composite endpoint over time is shown in Figure 17 (EMDAC 2013). The cumulative probability of the primary endpoint shows a separation of the 2 curves starting at approximately 250 days and then continuously increasing during the treatment period. There was no statistically significant deviation from proportional hazards.

Figure 17: Kaplan-Meier Estimate for Primary Endpoint (MACE+UA), All Phase IIb and III Pool (30-MU) (EMDAC 2013)



30-MU: 30-month update; Dapa: dapagliflozin; MACE: major adverse cardiovascular events; UA: unstable angina
The effect of dapagliflozin on CV outcomes will be definitively evaluated post-approval in DECLARE (TIMI-58, Study D1693C00001)

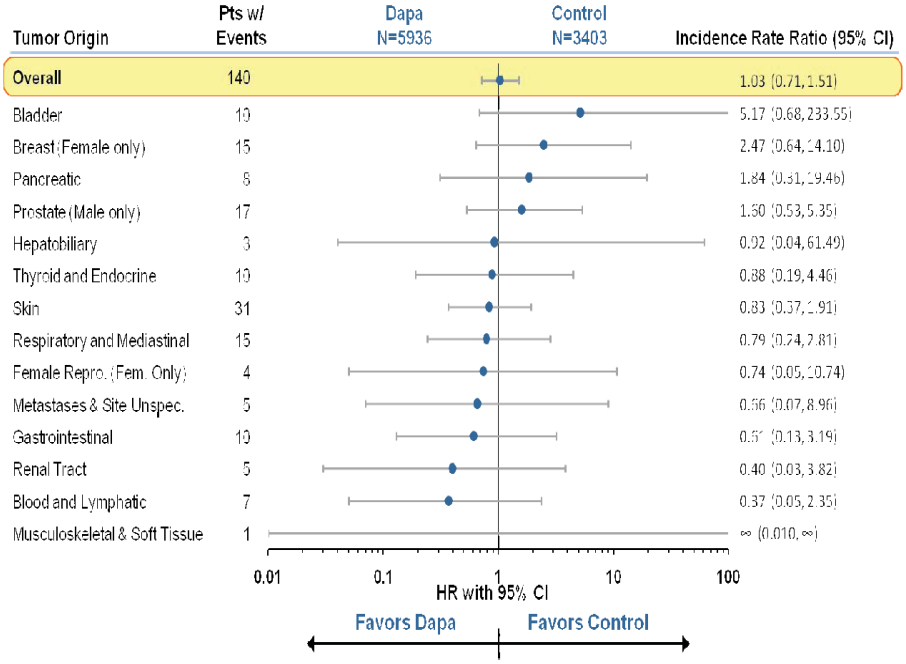
Beneficial or neutral point estimates were reported for all individual CV event types with dapagliflozin versus control, including a beneficial estimate on hospitalization for heart failure (hazard rate [HR] [95% CI]: 0.361 [0.156, 0.838]). Furthermore, no increased risk for MACE was observed with dapagliflozin in patients who experienced a hypoglycemic event prior to MACE compared with those who did not (Sonesson 2016).

Malignancy risk

The comprehensive non-clinical and clinical data updated for the recent FDA submission support the conclusion that dapagliflozin does not present a risk for initiating or promoting cancer (EMDAC 2013). The clinical data show no overall imbalance in malignancies with some tumours being more frequent in control and some being more frequent in dapagliflozin, none of these imbalances being statistically significant (Figure 18).

The preclinical data show that dapagliflozin is not genotoxic, and there is no evidence of tumour initiation by dapagliflozin at high multiples of exposure. Further, dapagliflozin is not a tumour promoter. There were no dapagliflozin-related hyperplastic changes in the nonclinical programme, and dapagliflozin did not trigger the characteristic gene expression signature of a tumour promoter (Reilly 2014).

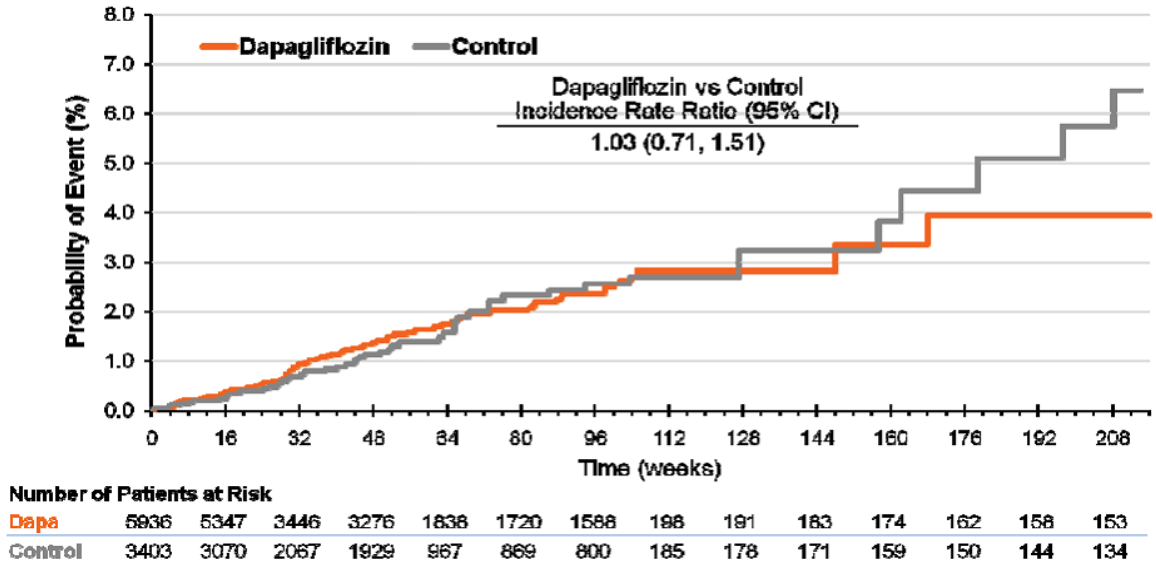
Figure 18: Malignancies by tumour type, all Phase IIb and III pool (30-MU)



30-MU= 30-month update; CI, confidence interval; Dapa, dapagliflozin; Fem, female; HR, hazard ratio; Pts, patients; repro, reproduction; Unspec, unspecified.

The Kaplan-Meier plot of time to malignancy shows matched curves for dapagliflozin and control (Figure 19). There is no upward inflection over time in the dapagliflozin curve, as would be observed with a carcinogen.

Figure 19: Time to first event of malignant and unspecified tumours, all phase IIb and III pool (30-MU) (EMDAC 2013)



30-MU= 30-month update; CI, confidence interval; Dapa, dapagliflozin.

Despite more than 2000 additional patient years of exposure, no additional cases of bladder cancer were identified across the 21 unblinded Phase IIb and III studies in the 30-month update (30-MU). Subsequent to the integrated database lock for the 30-MU, one additional case detected early in the treatment course has been reported in a female patient in Study 5. As described above, this patient was a smoker (50 pack-years), had a hematuria at baseline, and her bladder cancer was diagnosed a mere 3.5 months after treatment initiation. Including this newest case, the incidence rate ratio for dapagliflozin vs control is 6.11 (95% CI: 0.827, 272.02).

All 10 cases of bladder cancer in patients on dapagliflozin were reported within 2 years of starting study treatment (range: 43 to 727 days), and all but one were diagnosed or showed the first clinical sign (hematuria) of bladder cancer within 6 months of starting dapagliflozin therapy. In distinct contrast to the pattern expected for a directly causative agent, the incidence rate remained stable over the first 2 years of drug exposure and then fell, with no additional cases between 2 and 4 years of exposure, albeit with only 428 patient-years exposure during this time period. The time to bladder cancer diagnosis on dapagliflozin divided into 6 month exposure intervals was: 5 patients (< 6 months); 1 patient (6 to <12 months); 2 patients (12 to < 18 months); 2 patients (18 to < 24 months); and 0 patients (> 24 months). Carcinogenicity risk assessment supports the chronic safety of dapagliflozin in the treatment of type 2 diabetes mellitus (Reilly 2014).

4.12.1 Provide details of any studies that report additional adverse reactions to those reported in Section 4.2, including:

No additional studies were identified.

4.12.2 Provide a brief overview of the safety of the technology in relation to the decision problem

Overall, the safety profile of dapagliflozin presented in this submission is consistent with the safety profile seen in other clinical trials evaluating dapagliflozin in type 2 diabetes mellitus.

See Section 4.13.1.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The relevance of the key type 2 diabetes mellitus outcomes included in the key study for dapagliflozin as an add-on to MET plus SU (Study 5) are discussed below.

HbA1c

HbA1c is the primary recommended measure of glycaemic control in clinical guidelines including the SIGN, National Institute for Health and Care Excellence (NICE), the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) (SIGN 2010; NICE 2009; IDF Clinical Guidelines Task Force. 2012; American Diabetes Association 2012). Furthermore, HbA1c levels have been shown to be a good predictor of a patient's long-term risk of microvascular and macrovascular complications (Stratton 2000). Dapagliflozin as an add-on to MET plus SU achieved superior and clinically meaningful HbA1c reduction vs. placebo (Study 5).

Body weight

Weight management is a major component of effective diabetes care (SIGN 2010; NICE 2009; IDF Clinical Guidelines Task Force. 2012; American Diabetes Association 2012). Obesity is the primary modifiable risk factor for type 2 diabetes mellitus, and is also associated with insulin resistance (Gastaldelli 2007) and increased CV risk (de 2007) (Bays 2011). It has been suggested that reductions in weight of 5-10% may be associated with health benefits (Goldstein 1992). Dapagliflozin (as an add-on to MET plus SU) was associated with an absolute 24-week weight reduction of -2.65 kg; and a reduction vs. placebo of -2.07 kg and -1.9 kg at 24 and 52 weeks, respectively in Study 5. The NMA reported in section 4.10 shows statistically significant weight reduction with dapagliflozin compared to DPP4-is as a class. In addition, there is evidence from the wider trial programme that dapagliflozin is associated with sustained weight loss; in a 4 year extension analysis to a 52 week dual therapy RCT of dapagliflozin as an add-on to MET vs SU plus MET the dapagliflozin group showed a change in weight from baseline of −3.65 kg (Study 4) (Del 2013).

Systolic Blood Pressure (SBP)

NICE and SIGN have recommended that hypertension in people with diabetes should be treated aggressively with lifestyle modification and drug therapy (SIGN 2010; NICE 2009). Hypertension is positively related to risk of CVD death, with a progressive increase in risk with rising systolic pressures and each 10 mm Hg reduction in systolic pressure is associated with a 15% (95% CI 12 to 18%) reduction in the risk of CVD death over ten years (Adler 2000) (Turner 1998). In Study 5 (add-on to MET plus SU study) a key secondary outcome

was the change from baseline in SBP to week 8 in the dapagliflozin vs placebo groups. During this period (i.e. 0-8 weeks) no change in background anti-hypertensives was allowed in the study in order to accurately evaluate the effect of dapagliflozin on BP. At 8 weeks dapagliflozin was associated with a modest but clinically and statistically significant fall in placebo-corrected SBP, which was maintained in the subsequent period to 24 weeks. Over a 4-year period SBP was reduced with dapagliflozin (plus MET) in the supportive dual therapy study (Study 4) (Del 2013).

Adverse events (AEs), including hypoglycaemia

The AEs reviewed in the dapagliflozin RCTs bear close relevance to those observed in clinical practice. Hypoglycaemia is of concern for patients with diabetes, and SUs and insulin in particular are associated with an increased risk of hypoglycaemic episodes. The dapagliflozin studies specifically monitored for hypoglycaemia and showed a low incidence, and no major events. In addition to hypoglycaemia, adverse events of special interest included events suggestive of UTIs and GIs. These particular infections were carefully monitored because it was hypothesised that increasing urinary glucose through the SGLT2 mechanism of action may promote microbial growth. Although there was in general a higher incidence of UTIs and GIs in the dapagliflozin trials (which may be a consequence of the proactive monitoring for these AEs in the trials), the incidence was still modest and most of the events were mild/moderate, responded to treatment and none led to treatment discontinuation in Study 5.

4.13.2 Strengths and limitations of the clinical evidence base

Strengths:

Dapagliflozin trial programme

The dapagliflozin trial programme is one of the largest diabetes trial programmes to date, with 29 clinical studies completed or on-going. The entire Phase III programme was conducted globally, with 42% of patients from European countries. In the Phase IIb and III clinical trial programme 4,287 patients were exposed to dapagliflozin and 1,941 to control, covering 4,009 and 1,682 patient-years, respectively.

The Phase III RCTs were large and well designed, with sufficient power to detect differences between treatment arms. Blinding was conducted adequately, and continued in the extension phases. Baseline demographic characteristics were comparable between study arms. All end-points calculated using ITT analyses, which provided robust results for both efficacy and safety.

Dapagliflozin as a triple regimen evidence base

Data are available from a 24 week RCT trial to evaluate the efficacy and safety of dapagliflozin as add-on to MET plus SU, with an additional 28 week follow-up (52 weeks data in total study duration) (AstraZeneca 2014; Matthaei 2015b; Matthaei 2015c). In addition, the evidence for dapagliflozin as triple therapy is supplemented from an analysis of a sub-population of high CV risk patients inadequately controlled with MET plus SU from two clinical trials (Studies 18 and 19) in type 2 diabetes mellitus patients with CVD (and hypertension) (Appendix 20).

Furthermore, the patient population included in Study 5 are comparable to patients in the UK who are inadequately controlled on their dual therapy. Baseline characteristic of patients included in study 5 were comparable to patient demographics of people included in The Health Improvement Network (THIN) database who are experiencing their second intensification, although duration of diabetes was slightly longer in patients included in study

5 compared to the THIN dataset (9.28 years versus 8.5 years for study 5 and THIN respectively) (Table 12).

Supporting the external validity of the dapagliflozin trials, results reported from a retrospective observational study which used UK patient records from patients diagnosed with type 2 diabetes mellitus diagnosis showed that the overall reductions in HbA1c (0.89-1.16%) and weight (2.6-4.6 kg) observed in UK clinical practice are consistent with results from the dapagliflozin clinical trial programme.

Additionally, the benefits of dapagliflozin in triple therapy are consistent with findings from other phase III RCTs for dapagliflozin in combination with MET and as add-on to insulin, and there is longer term follow-up data in these RCTs which shows the benefits are durable over a 4-year period.

Limitations:

The main limitation of the evidence is that the trials were placebo controlled (there are no head-to head trials for dapagliflozin triple therapy vs a DPP4-i).

It should be noted that the SBP results at week 52 from study 5 are at odds with those observed in the dapagliflozin development programme and two dedicated studies designed to assess dapagliflozin in patients with Type 2 Diabetes with inadequately controlled hypertension. They are also at odds with the 24 week results.

The potential reasons for this result are documented in Section 4.

4.14 *Ongoing studies*

There are several ongoing clinical studies of dapagliflozin including a type 2 diabetes population (Table 33). Only one of these studies (D1690C00025) assesses the use of dapagliflozin in a triple regimen (on a background of MET + DPP4-i); and this is a single centre study to evaluate the effect of dapagliflozin on tissue specific insulin sensitivity, so it would not provide information to inform the decision of this appraisal.

Table 33: Ongoing studies from which additional evidence is likely to be available in the next 12 months

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin (Dapa)/Total
Phase III		
Add on to insulin		
MB102-137	Subjects must have type 2 diabetes with inadequate glycemic control, defined as HbA1c = 7.5% and = 11.0% obtained at screening visit. - Subjects must be taking a stable mean dose of = 20 IU injectable insulin daily for at least 8 weeks prior to enrollment	Dapagliflozin with background insulin Placebo with background insulin N = 273 Countries = China, Republic of Korea, Singapore
D1692C00013	Stable (unless adjustment is required based on Fasting Plasma Glucose values) dose insulin* mono-therapy with the mean insulin [up to two types of insulin within authorised indication in Japan] dose of = 0.2 IU/kg/day AND > or = 15 IU/body/day over the past 8 weeks prior to enrolment. - HbA1c > or = 7.2% and < 11% from the blood samples collected at Visit 1 (enrolment) and Visit 3, observed from the central laboratory	Dapagliflozin 5 mg Placebo N = 266 Country = Japan
Other		
D1690L00026	Subjects treated with either stable dose of MET alone > or = to 1500mg/day or stable dose of insulin > or = to 30 units/day and up to 2OAD medications for at least 8 weeks - Hemoglobin A1c (HbA1c) 7.5% to 10.5% at screening – Body mass index (BMI) < or = to 45	Dapagliflozin with MET Placebo with MET

	kg/m^2	Dapagliflozin with insulin Placebo with insulin N = 226 Country = US
D1690C00025	Type 2 Diabetes mellitus defined as HbA1c of ≥ 6.5% and ≤ 10.5%. Stable (≥ 3 months) T2D treatment with MET and/or MET + DPP4-is Body mass index (BMI) ≤ 40 kg/m^2.	Dapagliflozin 10 mg Placebo N = 32 Country = Finland

IU, international unit;

5 Cost effectiveness

Summary

- The cost-utility model described herein has been used to perform a cost-effectiveness analysis, with focus given to the comparison of dapagliflozin to other DPP4-is, both as an add on to MET + SU. Dapagliflozin was predicted to be cost saving (a saving of £112), with a minor QALY gain (0.03), when compared to other DPP4-is. Therefore, dapagliflozin was expected to dominate the DPP4-is in terms of cost-effectiveness.
- Although the cost of therapy of SGLT2-is is exactly the same with no significant differences in efficacy and safety results (as estimated from the previously described NMA), cost effectiveness analyses were also performed for the comparison of dapagliflozin versus empagliflozin (10mg and 25 mg regimens) and canagliflozin (100mg and 300mg regimens). Results of these analyses demonstrate negligible cost and QALY differences with ICER estimates resulting in a mix of dominant, cost-effective and dominated outcomes. However, care should be taken when interpretting these results, due to the tendency of small incremental outcomes to significantly affect ICER estimates.
- Further, canagliflozin and empagliflozin (with MET + SU) received positive NICE recommendations based on similar economic results presented in this submission for dapagliflozin (dominant results versus the DPP4-is)
- Conclusion: We propose all three SGLT2-is should have the same NICE recommendation in triple therapy with dapagliflozin now recommended as a treatment option for treating type 2 diabetes in combination with MET + SU alongside the other already recommended SGLT2-is.

5.1 *Published cost-effectiveness studies*

Identification of studies

A systematic search and review covering economic evaluations of relevance to a UK context for drug interventions for type 2 diabetes mellitus (including dapagliflozin and comparator drugs) was performed. The scope of this appraisal provided the context for the systematic search by specifying the patient populations covered, relevant comparators to dapagliflozin, outcomes of interest, economic outcomes and other considerations.

To avoid running two separate searches, a single comprehensive search strategy was developed to cover the identification of relevant cost-effectiveness studies (this section), as well as health measurement/valuation (i.e. utility) studies (Section 5.7.5).

The search was based on addressing the following objective:

To assess published primary health economic evaluations and utility data for the treatment of patients with Type 2 diabetes inadequately controlled on MET plus SU or MET plus DPP4-is.

The key inclusion criteria for the search covered:

- **P**atient population: Adult patients with inadequately controlled type 2 diabetes mellitus despite treatment with MET + SU or MET + DPP4-i

- **I**ntervention: GLP-1 analogues, DPP4-is, insulin, SGLT2-is, SUs, TZDs, alpha-glucosidase inhibitors, meglitinides
- **C**omparators: Any of the included interventions alone or in combination with another intervention of interest
- **O**utcomes: Cost analysis (currency, direct and/or indirect cost and resource use, budget impact details, results, and assumptions), Cost effectiveness analysis (cost effectiveness and/or cost utility, sub group analysis, sensitivity analysis), Patient-reported outcomes (EQ5-D, SF-36 etc; data specify to utility values will be captured)
- **S**tudy design: Cost-effectiveness analyses, Cost-utility analyses, Cost-benefit analyses, Cost-minimisation analyses, Budget impact models, Cost-consequence studies, Studies reporting utility data
- English language only publications
- Publication timeframe was from 2005

Further details of the single comprehensive search strategy (databases searched -, electronic and non-electronic, search strategies, additional exclusion criteria, data extraction strategy) are provided in Appendix 16.

Description of identified studies

5.1.1 Provide a brief overview of each cost-effectiveness study relevant to decision-making in England. Describe the aims, methods and results for each study. Each study's results should be interpreted with reference to a critical appraisal of its methodology. Provide justification for the exclusion of each study

A total of 40 studies were identified that were either cost-effectiveness analyses, cost-minimisation analyses or a budget impact analyses. The review included a total of 35 studies which were either cost-effectiveness or cost-utility analyses; out of these 35 studies, 13 studies reported cost per QALY outcomes in a UK context, whilst the remaining 22 studies were not discussed as they reported economic outcomes in countries other than the UK (Belgium, Brazil, Canada, China, Colombia Czech Republic, France, Germany Ireland, Norway, Spain Switzerland, Portugal, Poland, Slovakia, USA).

Two published economic evaluations were identified from the search covering the use of dapagliflozin in type 2 diabetes patients. One study was reported as an abstract (Charokopou 2014) and the second was the SMC report (SMC 799 2012). Both of these studies were cost-utility analyses that evaluated the use of dapagliflozin in combination with MET + SU compared to DPP4-is in the Scottish healthcare setting. The model structure and assumptions in these studies are similar as those used in this submission.

In total, 13 economic evaluations that reported cost per QALY outcomes in a UK context for therapies as an add-on to MET + SU (i.e. triple therapy) were identified. Three of these studies evaluate the use of exenatide (a GLP-1 analogue). These studies are not discussed further as exenatide is not considered a relative comparator to the decision problem and has not been evaluated in the economic analysis presented in this submission. A brief overview of the methods and results of the ten triple therapy evaluations relevant to this submission are presented in Table 34.

The key findings from the triple therapy evaluations included in the review were:

- All the studies adopted a lifetime horizon and used the UK Prospective Diabetes Study (UKPDS) risk equations to estimate long term outcomes associated with the incidence of complications
- Two of the studies used the CORE model, and two used the ECHO model that had been previously published; one study used the Cardiff diabetes model and one was a de novo model used in a SMC submission
- Nine of the ten studies appear to be manufacturer-sponsored and seven studies were part of an HTA evaluation

The cost-effectiveness model presented in this submission is the same as the model identified in the SMC submission (No. 799/12) and that published by Charokopou and colleagues, which describes the SMC model.

Table 34: Summary list of published cost-effectiveness studies

Study	Analysis Type	Country	Summary of model	Patient population (average age in years)	QALYs (interventioncomparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(Thompson 2014)	CEA	UK	ECHO-T2DM is a stochastic microsimulation annual cycle model based on Markov health states that reflect the key elements of T2DM and its treatment. It draws cohorts of hypothetical patients from distribution based on initial patient demographics (eg., age, gender, disease characteristics (eg, duration of disease, HbA1c, BMI), and comorbidities). It allows user-defined treatment algorithm of dug intensification, designed to control blood glucose and to treat for hypertension, dyslipidaemia, excessive weight. Patient biomarker values (ie. HbA1c, BMI, SBP, and lipids) are updated annually to reflect drug-specific treatment effects and "drifts" in these biomarkers over time due to the progressive nature of the disease. Risk functions are used to predict event rates over time (eg, MI, stroke, amputation, macular oedema), and are driven by changes in biomarkers (ie, HbA1c, BMI, SBP). Treatment-related AEs and tolerability can lead to discontinuation. It allows the user to assign costs for disease-related complications (initial and annual state), AEs, treatment interventions, quality of life weights to reflect patient preferences for health states. All costs, LYs and QALYs are	NR	Canagliflozin 300 mg+ Met+ SU: 9.4 Sitagliptin 100 mg+ Met+ SU: 9.36	Canagliflozin 300 mg+ Met+ SU: £ 28941 Sitagliptin 100 mg+ Met+ SU: £ 28270	17,813/QALY 27,621/LYG

			aggregated for each patient at the end of the time horizon or death.				
(Shyangdan 2011)	CUA	UK	NR	NR	NR	NR	Liraglutide 1.8 mg+ MET + SU: NR Insulin glargine+ MET + SU: 15,130/QALY
(Aguiar-Ibanez 2014)	CUA	UK	A micro-simulation model was developed based on the United Kingdom Prospective Diabetes Study (UKPDS68) and the Januvia Diabetes Economic (JADE) model.	NR	Empagliflozin 10mg + MET + SU:6.991 Empagliflozin 25mg + MET + SU:6.978 Canagliflozin 100mg + MET + SU:6.98 Canagliflozin 300mg + MET + SU:6.976	Empagliflozin 10mg + MET + SU: 31,409 Empagliflozin 25mg + MET + SU: 31,557 Canagliflozin 100mg + MET + SU: 31,217 Canagliflozin 300mg + MET + SU: 32,087	Empagliflozin 10mg + MET + SU vs Empagliflozin 25mg + MET + SU: Dominant/QALY Empagliflozin 10mg + MET + SU vs Canagliflozin 100mg + MET + SU: 17,445/QALY Empagliflozin 10mg + MET + SU vs Canagliflozin 300mg + MET + SU: Dominant/QALY
(Charokopou 2014)	CUA	UK	The model utilises United Kingdom Prospective Diabetes Study (UKPDS) 68-derived risk equations to estimate long run microand macro-vascular complications, diabetes and non-	NR	Incremental QALY Dapagliflozin + Met + SU vs	Incremental cost Dapagliflozin+ Met + SU vs DPP4-is +	10,995/QALY

			diabetes mortality and time paths for risk factors such as HbA1c and systolic blood pressure.		DPP4-is+ MET + SU: 0.023	MET + SU: £ 253	
(SMC 993 2014)	CUA	Scotland	The model simulated a cohort of patients and estimated the efficacy, safety, discontinuation, costs and utilities associated with each treatment arm. Based on the United Kingdom Prospective Diabetes Study (UKPDS) risk equations, patients progress through the model in 6 month cycles until death or the end of the time horizon and their profiles are updated according to time varying risk factors, adverse events experienced and complications.	NR	Incremental QALY: Empagliflozin 10mg+ MET + SU vs. Sitagliptin+ MET + SU: 0.036 Empagliflozin 25mg+ MET + SU vs. Sitagliptin+ MET + SU: 0.018	Incremental cost: Empagliflozin 10mg+ MET + SU vs. Sitagliptin+ MET + SU: £29 Empagliflozin 25mg+ MET + SU vs. Sitagliptin+ MET + SU: £150	Empagliflozin 10mg+ MET + SU vs. Sitagliptin+ MET + SU: £806 Empagliflozin 25mg+ MET + SU vs. Sitagliptin+ MET + SU: £8306
(SMC 505 2008)	CUA	Scotland	The model was a patient simulation model with a lifetime horizon, and patients could progress to other treatments depending on their response to treatment (i.e. when a threshold level of HbA1c of 8% was reached). The model allowed for risk factors and adverse events such as HbA1c level and weight, and diabetes related complications, to impact on patient cardiovascular and other health outcomes.	NR	NR	NR	Sitagliptin + MET + SU vs. Thiazolidinedione + MET + SU: £1902
(NICE TA336 2015)	CUA	UK	The IMS CORE model was an individual patient-level microsimulation model using IMS CORE. It modelled individual patients' transitions between health states using a fixed cycle length of 1 year over a lifetime horizon.	NR	Empagliflozin 10 mg+MET + SU: 7.571 Empagliflozin 25mg+MET + SU: 7.564 Canagliflozin 100mg+MET + SU: 7.569	Empagliflozin 10mg+ MET + SU: £58778 Empagliflozin 25mg+ MET + SU: £58711 Canagliflozin 100mg+ MET + SU: £58794	Empagliflozin 10 mg+ MET + SU vs. Empagliflozin 25 mg+ MET + SU: £9571 Canagliflozin 100mg+ MET + SU

					Canagliflozin 300mg+MET + SU: 7.616 Sitagliptin 100mg+MET + SU: 7.466	Canagliflozin 300mg+ MET + SU: £59000 Sitagliptin 100mg+ MET + SU: £59390	vs. Empagliflozin 10mg + MET + SU: Dominated Canagliflozin 300mg + MET + SU vs. Empagliflozin 10mg+ MET + SU: £4933 Sitagliptin 100mg+ MET + SU vs. Canagliflozin 300mg+ MET + SU: Dominated
(Copley 2013)	CEA	UK	The model uses risk equations from UKPDS 68 to simulate the macro-vascular complications of IHD, MI, stroke, and congestive heart failure, (CHF) given key biomarker values (e.g. age, BMI, HbA1c, SBP etc). The model has three parallel sets of micro-vascular complications and five types of macro-vascular complications represented as Markov states. There is a health state where the patient is free from complications, and then micro-vascular health states relating to chronic kidney disease (includes 7 stages); neuropathy (includes 5 conditions); and retinopathy (includes 4 conditions). Patients can also experience macro-vascular complications and peripheral vascular disease.	NR	Incremental QALY: Canagliflozin 100mg + MET + SU vs Sitagliptin+ MET + SU: 0.016 Canagliflozin 100mg + MET + SU vs Insulin Aspart + MET + SU: 0.514 Canagliflozin 100mg + MET + SU vs GLP-1-a +	Canagliflozin 100mg vs. DPP4-i: £25,734 vs. £25,776 Canagliflozin 100mg vs. Insulin LA £25,712 vs. £25,577 Canagliflozin 100mg vs. GLP £25,822 vs. £27,119 Canagliflozin 300mg vs. DPP4-i: £26,657 vs. £26,196	Canagliflozin 100mg + MET + SU vs Sitagliptin+ MET + SU: - Dominated Canagliflozin 100mg + MET + SU vs Insulin Aspart + MET + SU: £263 Canagliflozin 100mg + MET + SU vs GLP 1-a + MET + SU: -

					MET + SU: 0.001 Canagliflozin 300mg + MET + SU vs Sitagliptin+ MET + SU: 0.035 Canagliflozin 300mg + MET + SU vs Insulin Aspart + MET + SU: 0.624 Canagliflozin 300mg + MET + SU vs GLP-1-a + MET + SU: 0.004	Canagliflozin 300mg vs. Insulin LA: £26,705 vs. £26,326 Canagliflozin 300mg vs. GLP: £26,468 vs. £27,153	Dominated Canagliflozin 300mg + MET + SU vs Sitagliptin+ MET + SU: £13,287 Canagliflozin 300mg + MET + SU vs Insulin Aspart + MET + SU: £607 Canagliflozin 300mg + MET + SU vs GLP-1-a + MET + SU: - Dominated
(SMC 799 2012)	CUA	Scotland	The model simulated a cohort of patients over a 40 year time horizon. Patients entered the model with a set of baseline characteristics and modifiable risk factors for long run micro-vascular complications including blindness, amputation and nephropathy and macro-vascular complications including ischemic heart disease, myocardial infarction, congestive heart failure and stroke. At the end of the first 6 month cycle, risk equations derived from the United Kingdom Progressive Diabetes Study (UKPDS) were used to determine the occurrence of the fatal and non-fatal complications as well as non-cardiovascular all cause diabetes deaths. The effect of a change in body weight and impact on body mass index (BMI) is also incorporated in the model via the	NR	Incremental QALY Dapagliflozin + MET + SU vs DPP4-is + MET + SU: 0.023	Incremental cost Dapagliflozin+ MET + SU vs DPP4-is+ MET + SU: £ 253	10,995/QALY

			risk of experiencing cardiovascular complications.				
(SMC 963 2014)	CUA	Scotland	Cohorts of patients moved through the model based on a set of characteristics, and would move into health states designed to reflect the natural progression of type 2 diabetes mellitus. The health states included: complication free, chronic kidney disease, neuropathy, retinopathy, and a variety of macro-vascular events (such as stroke, myocardial infarction, and congestive heart failure).	NR	Canagliflozin 100 mg vs. DPP4-is: 0.021 Canagliflozin 100 mg vs. GLP-1 agonists: 0.002 Canagliflozin 100 mg vs. Insulin: 0.195 Canagliflozin 300 mg vs. DPP4-is: 0.019 Canagliflozin 300 mg vs. GLP-1 agonists: 0.004 Canagliflozin 300 mg vs. Insulin: 0.276	Incremental cost: Canagliflozin 100 mg vs. DPP4-is: £ 45 Canagliflozin 100 mg vs. GLP-1 agonists: -£ 721 Canagliflozin 100 mg vs. Insulin: £380 Canagliflozin 300 mg vs. DPP4-is: £ 426 Canagliflozin 300 mg vs. GLP-1 agonists: -£ 256 Canagliflozin 300 mg vs. Insulin: £704	Canagliflozin 100 mg vs. DPP4-is: £2158 Canagliflozin 100 mg vs. GLP-1 agonists: Dominant Canagliflozin 100 mg vs. Insulin: £1951 Canagliflozin 300 mg vs. DPP4-is: £22187 Canagliflozin 300 mg vs. GLP-1 agonists: Dominant Canagliflozin 300 mg vs. Insulin: £2555

5.1.2 *Provide a complete quality assessment for each relevant cost-effectiveness study identified in the appendix*

A quality assessment of the 10 economic evaluations in type 2 diabetes identified from the search are presented in Appendix 17. This shows that the evaluations are generally of a reasonable standard in terms of model structure and methodology. However, there are some limitations across studies in terms of transparency, for example none of the studies presented disaggregated outcomes or separated resource use and unit costs. This may have been related to constraints on manuscript length imposed by the journal.

5.2 *De novo analysis*

Patient population

5.2.1 *State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials. Please provide the rationale for any differences. Explain the implications of this for the relevance of the evidence base to the decision problem*

This submission covers the use of dapagliflozin in combination with MET and SU (triple therapy) in adults aged 18 years and older with type 2 diabetes mellitus for whom MET and SU alone does not provide adequate glycaemic control, as an alternative to current use of DPP4-is and other SGLT2-is in combination with MET plus SU. Previously, submissions to NICE have evaluated the cost-effectiveness of dapagliflozin in dual therapy (in combination with MET), and as an add-on to insulin. The economic evaluation for triple therapy uses the Cardiff economic model as was used for the previous submissions to NICE of dapagliflozin

There is published RCT data in combination with MET + DPP4-i demonstrating the clinical benefit of dapagliflozin compared to placebo. However, based on the results of the systematic review carried out for this submission, it is not possible to carry out an NMA or indirect comparison compared to any of the comparators in the final scope meaning that an estimate of cost-effectiveness for the use of dapagliflozin + MET + DPP4 is not possible. This is primarily due to a lack of evidence for other comparators in combination with MET + DPP4-i.

Type 2 diabetes mellitus is a condition characterised by excess micro- and macro-vascular morbidity and mortality and blood glucose control forms a central feature of risk factor management in patients with type 2 diabetes mellitus. The symptoms of type 2 diabetes mellitus typically become manifest during middle age and are often associated with excess body weight that further worsens patient prognosis. Achieving good glycaemic control, whilst limiting adverse events of treatment such as weight gain and hypoglycaemia, are important aspects of risk factor management in patients with type 2 diabetes mellitus (NICE 2009; Matthaei 2015c).

Dapagliflozin is a competitive inhibitor of SGLT2. SGLT2 is a major transporter for renal glucose reabsorption, so dapagliflozin as an SGLT2-i acts on the kidney to block the

reabsorption of glucose hence providing glycaemic control. The clinical study evidence reported in Section 4 of this submission has demonstrated the efficacy of dapagliflozin in reducing HbA1c in patients with elevated levels, the primary endpoint in many of the Phase III RCTs of dapagliflozin. However, dapagliflozin also represents a significant advance in oral anti-diabetic therapies in the reduction of patient weight and BMI, whereas many of the other oral therapies used in clinical practice are associated with weight gain (e.g. SUs and TZDs), or at best weight neutrality (such as the DPP4-is).

Model structure

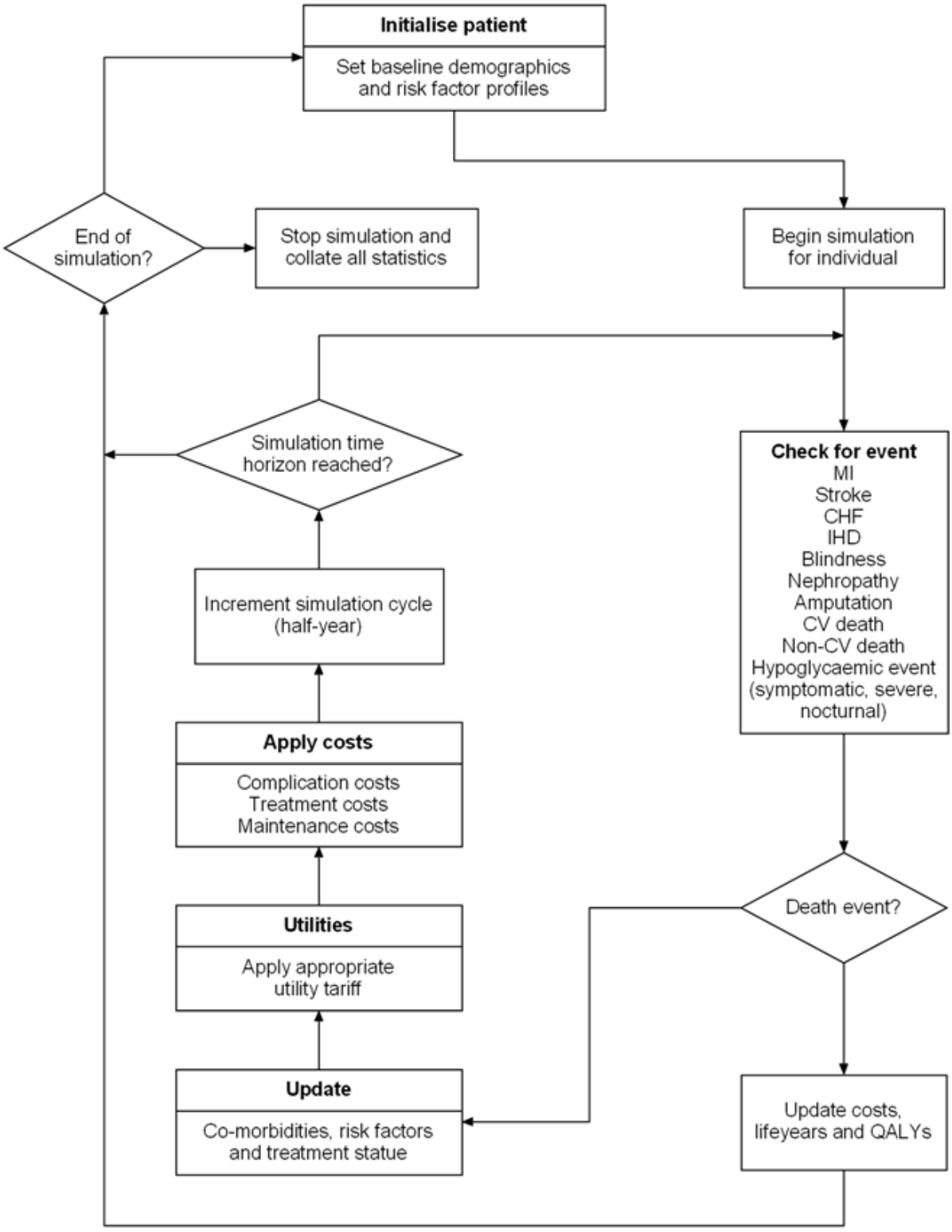
5.2.2 Describe the model structure and provide a diagram of the model submitted, including the following:

- ***Type of de novo analysis***

The Cardiff Diabetes Model is a patient level fixed-time increment, Monte Carlo micro-simulation model. It has been designed to run within a Microsoft Excel front-end that provides data input for dynamic link libraries (dlls) that perform the computational component of the simulations. The simulation engine is written in C++ and compiled into a dll to minimise computation time.

The model is similar to other established diabetes models used in previous NICE submissions and peer-reviewed publications in the UK (e.g. the UKPDS Health Outcomes model (Clarke 2004), the CORE model (Palmer 2004b), and the Januvia Diabetes Economic (JADE) model (Charokopou 2016), in that it utilises UKPDS derived risk equations to estimate long term micro- and macro-vascular complications, diabetes and non-diabetes mortality, and clinical risk factor trajectories. The model has the advantage of reflecting clinical reality to a greater extent than the UKPDS outcomes model as it allows diabetes treatment sequences to be modelled. The original Cardiff model has been subject to systematic validation (McEwan 2015b; McEwan 2015a; McEwan 2010) and was presented along with the other established models at the Mount Hood Challenge Meeting IV, a forum for determining the validity of diabetes models. A schematic of the model is provided in Figure 20.

Figure 20: Schematic of the cost-effectiveness model structure



Abbreviations: CHF, congestive heart failure; CV, cardiovascular; IHD, ischaemic heart disease; MI, myocardial infarction; QALYs ,quality-adjusted life years

- ***Justification of the chosen structure in line with the clinical pathway of care described in Section 3.4***

Type 2 diabetes is a condition characterised by excess micro- and macro-vascular morbidity and mortality and blood glucose control forms a central feature of risk factor management in patients with Type 2 diabetes. Current evidence and guidelines advocate the attainment of sustained near normal glycaemia levels (Nathan 2009). Metformin is widely accepted and established as the treatment of choice for the initiation of pharmacotherapy in Type 2 diabetes; however, secondary failure of oral monotherapy with MET occurs in 60% of patients (Monami 2009), resulting in the need for multiple pharmacotherapy and eventually insulin initiation. In recent years, a variety of anti-diabetes agents (TZDs, DPP4-is, GLP-1 analogues) have been introduced into clinical practice. The current Type 2 diabetes clinical guideline issued by NICE advocates a stepwise failure-driven therapy algorithm for blood-glucose lowering that leads to the sequential addition of therapies (NG28) (NICE 2015). In line with the current NICE guideline insulin is included after triple therapy in our economic analysis (Section 3.4; NG28 (NICE 2015). A cost-utility analysis (CUA) has been performed for the comparison of dapagliflozin 10mg/day with the DPP4-i class, with health benefits measured in terms of QALYs. For completeness, a comparison with other SGLT2-is (empagliflozin and canagliflozin) recommended by NICE for triple therapy has also been conducted to demonstrate equivalent costs and benefits. The perspective adopted was that of the NHS and personal social services (PSS) in England. As is appropriate for a chronic disease and standard in diabetes models a lifetime horizon was adopted consisting of a model time horizon of 40 years. The effect of model time horizon was investigated in sensitivity analysis. A summary of the key structural features of the model are provided in Table 35 below.

The patient cohort enters the model with predefined baseline characteristics and modifiable risk factors. The modifiable risk factors used to inform base case analyses are as follows: HbA1c, total body weight, TC, high density lipoprotein (HDL) cholesterol and SBP. The value of these parameters will change as the model simulation progresses, through the influence of treatment effects and subsequent natural progression, based on the UKPDS risk equations.

The risks associated with patient clinical history are considered in the model by defining the proportion of patients who have previously experienced each of the complications. Clinical history is updated during the simulation when patients incur a specific event, and consequently the risk of subsequent events is modified.

The model predicts the incidence of specific macro and micro-vascular complications utilising the UKPDS risk equations. The analysis herein utilises the UKPDS 68 equations which, due to their extensive use and validation compared to the more contemporary UKPDS 82 equations, are considered the base case. The use of the UKPDS 82 equations are investigated in scenario analyses and provide the capability to model an additional 4 clinical endpoints – second MI, second stroke, second amputation, and ulcer. In total, seven diabetes complications are included in the model alongside non-CV death.

Macro-vascular events predicted in the model are:

- ischaemic heart disease (IHD)
- MI
- congestive heart failure (CHF)
- stroke

Micro-vascular events predicted in the model are:

- amputation
- nephropathy
- blindness

The model also captures the probability of drug related hypoglycaemic events, and other specified AEs.

The model simulates a cohort of patients with type 2 diabetes over the 40-year time horizon. For the purpose of this analysis, a total of 5,000 simulations, each containing 5,000 patients, were undertaken to ensure stability in the simulation results. Patients in the intervention and comparator groups are simulated through the model in 6 month cycles. Treatment effect estimates associated with dapagliflozin and comparators for HbA1c, SBP, weight and lipids are applied upon the initiation of treatment and influence the probability of complication events occuring. At the end of each 6 month cycle, the UKPDS risk equations are utilised to determine the occurrence of fatal and non-fatal complications, with the order in which checks for events are undertaken randomized. In addition, non-CV (all-cause) and direct diabetes mortality is estimated based on risk equations from the UKPDS 68 study (Clarke 2004). If the patient survives beyond the first cycle they transition to the next cycle where they remain at risk of treatment related AEs and long term complications. Once a fatal event occurs, life years and QALYs are updated and the simulation ends for that patient. Only initial complication events are modelled. Although the model has the capacity to include secondary events, due to a lack of data and to reduce complexity, only the absolute risk of the first event is estimated (in line with other diabetes economic evaluations, e.g. (Schwarz 2008).

- ***How the model structure and its health states capture the disease or condition for patients identified in Section 3.3***

An overview of type 2 diabetes and the course of the disease is presented in Section 3.1. Type 2 diabetes is a progressive metabolic disorder characterised by an impaired response to insulin and a progressive deterioration in the capacity to secrete endogenous insulin resulting in chronic hyperglycaemia. As a consequence of elevated levels of glucose in the blood, diabetes-related complications including CVD, renal disease and retinopathy develop at later stages of disease progression. The symptoms of type 2 diabetes typically become manifest during middle age and are often associated with excess body weight that further worsens patient prognosis. Lower blood glucose levels, as reflected by hbA1c measurements, were associated with reduced incidence of diabetes-related complications. Based on the strength of this evidence, achieving good glycaemic control has become a cornerstone of risk factor management in patients with type 2 diabetes.

The model captures the progressive nature of type 2 diabetes by an underlying progressive deterioration in the capacity to secrete endogenous insulin which is reflected in a gradual increase in hbA1c over time. In addition to HbA1c, the model incorporates additional time-dependent risk factors associated with type 2 diabetes that impact upon the risk of occurrence of micro- and macro-vascular events, namely, BMI, TC, HDL-C and SBP. The value of these variables may change as the model simulation progresses, through the application of treatment effects and subsequent natural progression. As a consequence of changing risk factor profiles the risk of events will change during the simulation period, reflecting the changes in these parameters. The model additionally captures the effect of

several non-clinical risk factors upon complication risk, namely, age, duration of diabetes, gender, ethnicity and smoking status.

The economic model is able to accommodate up to two additional therapy lines after the initial modelled treatment, dapagliflozin and the comparator for add-on to MET and SU. The simulation consists of a cohort of patients who receive dapagliflozin (the 'treatment' cohort), and a cohort with the same baseline characteristics who receive comparator treatments (the 'comparator' cohort). Simulated patients in each cohort will receive a particular therapy until their HbA1c increases to a specified threshold which represents inadequate glycaemic control, at which point they cease receiving that therapy and move on to the next therapy line.

Table 35: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum of 40 years)	Type 2 diabetes is a chronic, progressive disease. Treatments have impact on costs and outcomes over a patient's lifetime
Were health effects measured in QALYs; if not, what was used?	Yes	As per NICE Methods Guide
Cycle length	6 months	Standard duration of trial follow-up and treatment decisions
Half-cycle correction	The model does not use half-cycle correction	The cycle length (6 monthly) is sufficiently small
Discount of 3.5% for utilities and costs	Yes	As per NICE Methods Guide
Perspective (NHS/PSS)	NHS/PSS	As per NICE Methods Guide

PSS: personal social services; QALYs: quality-adjusted life years

5.3 *Intervention technology and comparators*

5.3.1 Intervention and comparator.

This submission covers the use of dapagliflozin in combination with MET and SU (triple therapy) in adults aged 18 years and older with type 2 diabetes mellitus for whom MET and SU alone does not provide adequate glycaemic control, as an alternative to current use of DPP4-is in combination with MET plus SU. The DPP4-is are considered the appropriate comparator as they represent the predominant initial add-on treatment to MET and SU therapies considered by clinicians, and like dapagliflozin are administered orally as an OD tablet. Hence, the comparators considered are the DPP4-i class of oral antidiabetic drugs; the triple therapy MET + SU + DPP4-i market leader in the UK is sitagliptin with 71% market share of prescriptions in combination with metformin and SU, with saxagliptin, vildagliptin, linagliptin and alogliptin having triple therapy market shares of 10%, 3%, 12% and 3% respectively (Patient Data, IMS Information Solutions UK Ltd, January 2016) (Table 36). The DPP4-is have been considered as a pooled class in the economic evaluation as this was the approach required to inform a robust NMA, that subsequently provides the core input data (relative treatment effects) for the model. The DPP4-is included in the analysis were treated as a class to increase the rigour of the comparisons. The non-inferiority of each of the DPP4-is to each other in the triple therapy setting is supported by published evidence (NICE 2009). For completeness we have also presented the cost-effectiveness of dapagliflozin versus other SGLT2-is (empagliflozin and canagliflozin) to demonstrate the equivalent cost and benefits of SGLT2-is as a class. All interventions were included as per their licensed dose.

Table 36: Current market share data for the use of DD4Pi as add on therapy to MET + SU

Treatment	UK Market Share, %
Saxagliptin 5mg	10
Sitagliptin 100mg	71
Vildagliptin 50mg	3
Linagliptin 5mg	12
Alogliptin 25mg	3
Patient Data, IMS Information Solutions UK Ltd, January 2016	

5.4 *Clinical parameters and variables*

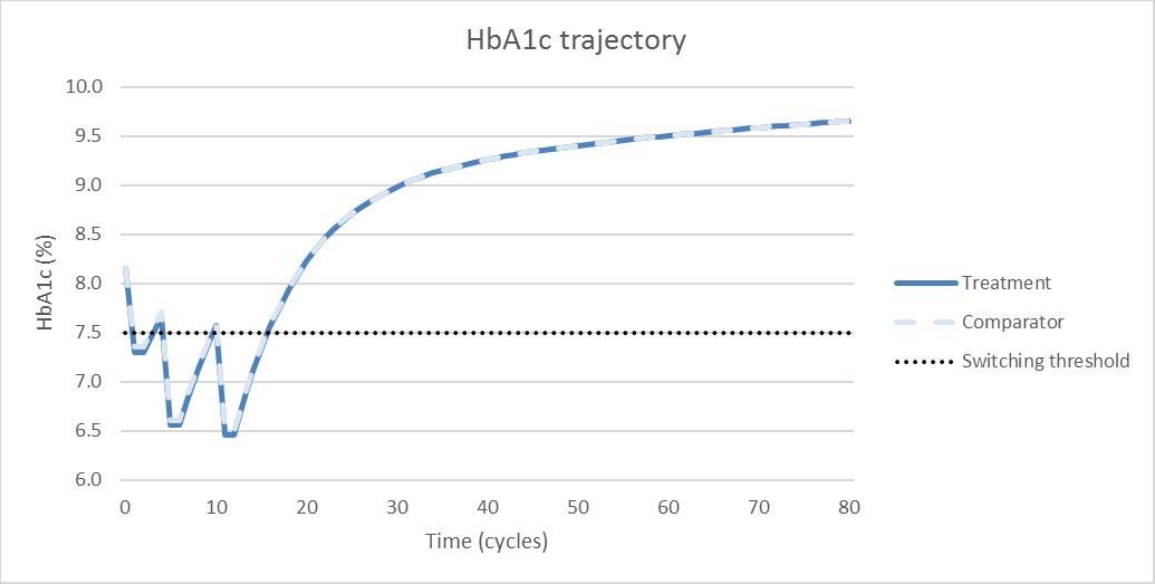
The treatment effects applied to the modifiable risk factors HbA1c %, body weight and SBP for dapagliflozin and the DPP4-is are derived from the NMA. Data was not available for treatment effects relating to lipid profiles, therefore these were not included in the analysis. The base case analysis uses NMA results from the restricted network, utilising endpoint data from the studies included in this specific NMA (assessing dapagliflozin, the DPP4is, and the other SGLT2-is only). A full description of the restricted NMA is given in Section 4.10. This methodology is similar to that submitted by the manufacturer in the NICE evaluation of empagliflozin in the same patient population.

As the model is a discrete event simulation model, transition probabilities as applied in conventional Markov models were not calculated. Instead, the occurrence of the seven diabetes-related complications and death is estimated using the risk equations of the UKPDS 68 Outcomes Model (Clarke 2004). The UKPDS health outcomes risk equations were derived using Weibull proportional hazards models utilising data for a cohort of 5,102 diabetic patients, aged 25 – 65 years in the UK (UKPDS 38 1998). From this, equations for the 10-year risk of ischemic heart disease, coronary heart failure, stroke, MI, renal failure, amputation and blindness were developed.

HbA1c natural progression

Type 2 diabetes mellitus is a progressive metabolic disorder characterised by an impaired response to insulin and a progressive deterioration in the capacity to secrete endogenous insulin resulting in chronic hyperglycaemia. Therefore, the model captures the progressive nature of type 2 diabetes mellitus by including a gradual increase in HbA1c over time. The model employs the UKPDS 68 natural trajectory of HbA1c to model HbA1c change using a slope coefficient of 0.759. In the model, the introduction of a new treatment results in a reduction in HbA1c according to the efficacy of the particular treatment, informed by the NMA. The treatment effect is applied during the first 6 months of therapy initiation and is subsequently followed by a 6 month period of maintenance (i.e. HbA1c neither increases nor decreases). After this initial 1 year reduction in HbA1c, natural progression resumes (estimated by regression analysis from the UKPDS 68 study) (Clarke 2004). When the natural trajectory of HbA1c reaches the target HbA1c threshold (7.5% in the base case) a treatment change is triggered and the 1 year treatment effect of the next therapy in the sequence is applied, followed by natural HbA1c progression until a final treatment switch is triggered through HbA1c reaching the defined switching threshold (7.5% in the base case) as presented in the figure below.

Figure 21: HbA1c change over time in the cost-effectiveness analysis



Weight progression

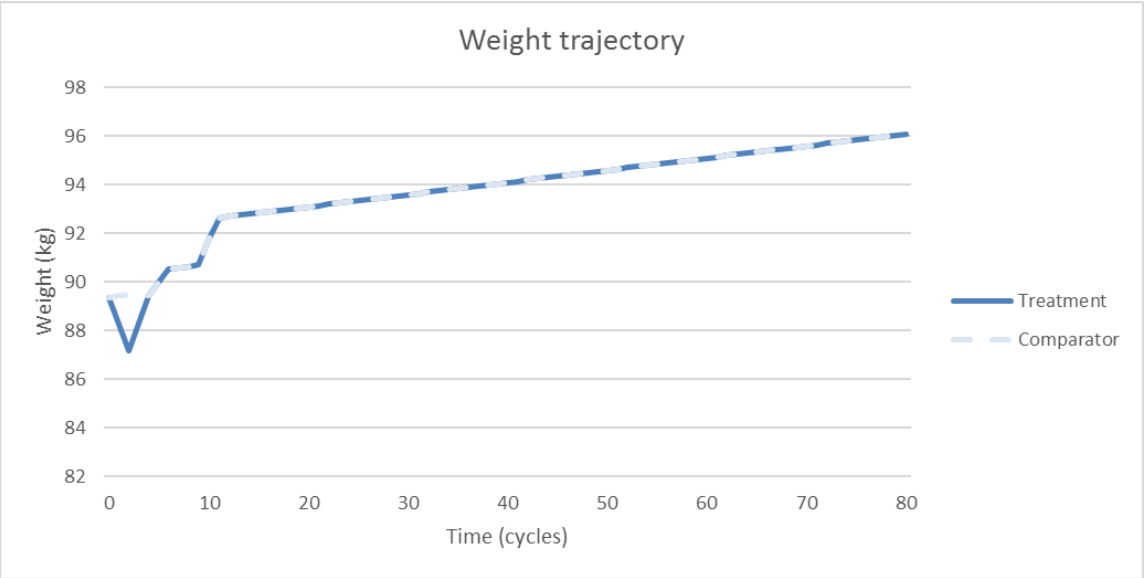
Dapagliflozin has been shown in Phase III clinical trials in dual and triple therapy contexts to be associated with significant weight loss (Bolinder 2012; Nauck 2011), and a previous NMA in dual therapy (add-on to MET) has shown significant differences in weight reduction for dapagliflozin vs. DPP4-is (Goring 2014). See also Section 4.7 for

results from study 5 in triple therapy; and section 4.10 for the NMA results informing this submission. The weight loss is associated with the SGLT2-i mechanism of action which leads to the excretion of glucose/calories in the urine (Chao 2010).The majority of the weight reduction associated with dapagliflozin has been observed to be loss of body fat, including visceral fat rather than lean tissue or fluid loss.

A key feature of the economic model is incorporation of the impact of treatment on patient weight and the modelling of weight progression over time. Weight change is associated with a HRQoL impact and may also impact the risk of CV events. CV risk is modelled using the UKPDS derived CV risk equations

For the current comparison of dapagliflozin vs. DPP4-is as add-on to MET plus SU, the treatment effects associated with weight gain/loss were derived from the NMA (see Table 38). The treatment effect was applied over the first year of therapy initiation and, conservatively, it was assumed that the treatment effect associated with both dapagliflozin and the DPP4-is was lost over the subsequent 1 year period (i.e. weight returned to its natural trajectory) (Del 2011; Del 2013). It was assumed that the weight gain associated with the insulin profiles employed for second and third therapy lines remained in place over the remainder of the simulation. A natural weight gain of 0.1kg/year was modelled. The weight trajectory is presented in Figure 22.

Figure 22: Weight change over time in the cost-effectiveness analysis



SBP, TC and HDL progression

For the estimation of complication event risk, the UKPDS 68 equations require a combination of TC and HDL parameters, in the form of a ratio (TC:HDL). Therefore the model estimates the trajectory of this ratio, rather than each individual parameter. Both SBP and TC:HDL natural trajectories are informed by the UKPDS 68 study, whilst treatment effects are applied in a similar way to HbA1c treatment effects (i.e. a 6 month treatment effect, followed by a 6 month period of maintenance and a natural trajectory thereafter). SBP treatment effects were informed by the NMA whilst the affect of treatment upon TC and HDL was not modelled due to a lack of data.

Hypoglycaemia and other adverse events

The economic analysis included assessment of hypoglycaemic episodes associated with dapagliflozin and the comparator therapies. The types of hypoglycaemic episode considered in the economic model were symptomatic, severe and nocturnal episodes as these have been shown to be associated with a treatment cost and/or a utility decrement (Clarke 2004). In addition, adverse events that may be associated with the dapagliflozin mechanism of action including UTIs and GIs, were conservatively included in the analysis. The model utilises annual inputs to derive a 6-monthly number of symptomatic hypoglycaemic events and the 6-monthly probability of a severe hypoglycaemic event or adverse event. A maximum of 1 severe hypoglycaemic event and 1 adverse event may be predicted per patient in a given cycle.

For the base case analysis, data on the number of symptomatic hypoglycaemic episodes was derived from the NMA for the comparisons with DPP4-is and SGLT2-is. The probability of a severe hypoglycaemic event; and the percentage of patients experiencing a UTI or GI adverse event were not available from the NMA; and were rather derived from RCT data using the head to head RCT comparing canagliflozin 300mg with sitagliptin (a DPP4-i) in the absence of any head to head studies for dapaglifliozin versus a DPP4-i (Schernthaner 2013b).

Discontinuations due to AEs

In a similar fashion to the incidence of complication events, the model checks for the incidence of therapy discontinuation during each cycle. Upon discontinuation, patients move to the next line of therapy. It is assumed that patients cannot discontinue the third line of therapy. Discontinuation was modelled as having being caused by adverse events using RCT data from the comparative trial of canagliflozin versus sitagliptin in the absence of any head to head studies for dapagliflozin versus a DPP4-i (Schernthaner 2013b).

Mortality

All-cause mortality events were estimated using diabetes-specific and all-cause mortality equations as described in the UKPDS 68 study (Clarke 2004). Patients may incur a fatal event during any given cycle as a function of their particular risk factor profile.

Treatment lines and HbA1c switching thresholds

The economic model is able to accommodate up to two additional therapy lines after the initial treatment line containing dapagliflozin and the comparator. For the application to triple therapy the simulation consists of a cohort of patients who receive dapagliflozin as an add-on to MET plus SU, and a cohort with the same baseline characteristics who receive a DPP4-i as an add-on to MET plus SU. The patients in each cohort will receive these therapies until their hbA1c increases to a specified threshold which represents inadequate glycaemic control, at which point they cease receiving that therapy and move on to the next therapy. Patients remain on the last therapy (third line) for the remainder of the simulation. The subsequent therapy lines are the same for both treatment arms and are assumed to consist of a switch to MET plus insulin, followed by a switch to MET plus intensified insulin (assumed to be a 50% increase in dose over the initial dose used when starting insulin treatment (NICE TA288 2013)).

NICE guidelines for type 2 diabetes mellitus management indicate a treatment switch should be considered in triple therapy when the hbA1c reaches a threshold of 7.5% (NICE 2015). Therefore, a switching threshold of 7.5% is utilised in the base case for first line to second line therapy switching and second to third line therapy switching. The effect of this assumption is investigated in scenario analyses.

5.5 *Transition probabilities*

As the model is a patient level fixed-time increment, Monte Carlo micro simulation model, transition probabilities as applied in conventional Markov models were not calculated. Instead, the occurrence of the diabetes-related complications and death is estimated using the risk equations of the UKPDS 68 Outcomes Model (Clarke 2004). The UKPDS health outcomes risk equations were derived using Weibull proportional hazards models utilising data for a cohort of 5,102 diabetic patients, aged 25 – 65 years in the UK (UKPDS 38 1998). From this, equations for the ten year risk of ischemic heart disease, coronary heart failure, stroke, MI, renal failure, amputation and blindness were developed (Stevens 2001; Kothari 2002; Clarke 2004).

Risk equations

Much of the perceived benefit in diabetes cost-effectiveness analyses relates to the avoidance of predicted long-term complications. Consequently, the choice and justification of the risk equations used to predict diabetes related complications and mortality is important. Many diabetes models utilise the UKPDS risk equations and

debate continues in the literature regarding their continued use given routine clinical practice has changed considerably since the study reported (Kengne 2010; Van Dieren 2011).

The choice of potential risk equations to use is large; a recent review (Van Dieren 2012) identified twelve cardiovascular disease risk equations developed specifically for subjects with type 2 diabetes and 33 equations from general populations with diabetes as an endpoint risk factor. While the UKPDS equations are subject to criticism they have also been the most widely studied with nine published articles externally validating them.

It is noteworthy that the avoidance of diabetes related complications is often not the key driver in cost-effectiveness analyses. This is because in many evaluations there is little (if any) difference in modifiable vascular-risk factor parameters; either by design, for example in treat-to-target trials, or because the glucose lowering properties of the therapies being compared are similar.

The Cardiff Model and the UKPDS Risk Equations

The Cardiff Diabetes Model is designed to estimate the long-term economic and health impact of managing patients with T2DM (McEwan 2006). The model is a fixed time increment (six-monthly) stochastic simulation with a 40-year time horizon; the core model is coded in C++ and linked to a Microsoft Excel front end. Development of the Cardiff Model began in 2003 and was initially based on the noninsulin dependent diabetes mellitus (NIDDM) model, published by Eastman (Eastman 1997a). This model was updated to include UKPDS 56, 60 and 68 equations in 2004 and UKPDS 82 in 2014 (Eastman 1997b).

In the previous 2012 NICE evaluation of dapagliflozin model predictions from the Cardiff Model were verified to those obtained by the CORE diabetes model (Palmer 2004a). This exercise demonstrated output across the CORE and Cardiff models was comparable when both models used identical data and similar model settings. Since the CORE and Cardiff models were compared, both have had peer-reviewed external validation results published (McEwan 2014; McEwan 2015b). These publications evaluated both the UKPDS 68 and more contemporary UKPDS 82 risk equations; the latter were found to provide a better fit to UKPDS data with slightly improved goodness of fit results recorded against external validation studies.

Impact of risk equation choice of cost-effectiveness for dapagliflozin

The UKPDS 82 equations are capable of predicting an expanded set of diabetes related endpoints compared to UKDS 68, in particular, secondary myocardial infarction, stroke and amputation events and ulcers. However, the UKPDS 82 equations require the specification of additional risk factors that are not routinely reported (albuminuria, eGFR, heart rate, LDL cholesterol and white blood cell count) and these risk factors have been shown to exert considerable influence on absolute event rate predictions (McEwan 2015b).

Importantly, absolute risk is of less relevance when considering the use of these equations to support cost-effectiveness analyses because it is the incremental difference in event rates (typically driven by risk factors reported in randomized clinical trials) that is important.

This is of particular relevance to dapagliflozin because the driver of cost effectiveness is health utility gain associated with avoiding weight loss rather than utility gains and cost

offsets associated with the avoidance of vascular complications. This was the key finding in the first (2013) HTA for dapagliflozin, in which the key driver of health economic benefit was weight change mediated via its direct relationship with health utility as opposed to indirectly via a difference in vascular event rates.

Importantly, body mass index (BMI) impacts health economic value in diabetes in two ways:

- Firstly, each unit change in BMI is associated with a utility change of 0.0061 (Bagust 2005). For a person 1.65m tall a 2.7kg weight reduction corresponds to a 1-unit change in BMI; if 1000 patients are treated and, on average, achieve a 1-unit change in BMI the total QALY gain will be 6.1 and if this is maintained for 4 years total QALY gains will be 24.4 per cohort of 1000.
- Risk equations
    - UKPDS 82: A 1-unit reduction in BMI within the UKPDS 82 risk equations maintained over 4 years would result in a reduction in 4-year risk of congestive heart failure of 0.00083; for a cohort of 1000 and a utility decrement of -0.28 for CHF this would result in a total QALY gain of 0.23. This gain would be partially offset by an increased risk of renal failure associated with the weight loss with a corresponding 0.13 QALY reduction resulting in a net gain of 0.1 QALYs.
    - UKPDS 68: A 1-unit reduction in BMI within the UKPDS 68 risk equation would result in no QALY gain at all as these equations only use BMI at baseline. Therefore any change modelled in MI over time has no impact whatsoever on risk of events (this is different to UKPDS 82 that incorporates time dependent BMI)

In summary:

- A 1-unit reduction in BMI over a 4-year time period will result in 24.4 additional QALYs per 1000 based on direct health utility gains alone.
- The UKPDS 82 equations would result in an addition 0.1 QALY per 1000 patients for 1-unit reduction in BMI maintained over 4 years.
- The UKPDS 68 equations would result in no QALY change per 1000 patients.

Consequently, the choice of risk equations employed to evaluate dapagliflozin will have a negligible impact on cost-effectiveness and therefore the utilisation of the UKPDS 68 equations within the base case will allow an assessment to be made using identical settings to those previously seen by NICE (Canagliflozin STA; Empagliflozin STA, Dapagliflozin STA, 2012) and could be considered conservative. This is because the UKPDS 68 equations do not accommodate time-dependent BMI changes and would therefore confer no additional health economic benefit for dapagliflozin compared to the small gain offered by UKPDS 82.

5.5.1 Variation of transition probabilities over time

In the simulation model the risk of occurrence of micro- or macro-vascular events in the model varies over time, dependent on age, duration of diabetes, HbA1c, SBP, TC, HDL-C, and body weight (see Section 5.3.1).

5.5.2 *Linking intermediate outcome measures to final outcomes*

Intermediate outcome measures (i.e. the modifiable risk factors) were linked to final clinical outcomes (i.e. micro- and macro-vascular fatal and non-fatal events) based on the UKPDS 82 risk equations (Hayes 2013). This is standard practise in most of the validated economic models in diabetes and is further described in Section 5.7.

5.5.3 *Clinical experts*

At the time of the initial NICE assessment of dapagliflozin in 2012, a number of advisory boards were held with clinical and health economic experts at which the initial dapagliflozin model and the input parameters were discussed in order to strengthen the model and analyses. The experts were asked to consider the clinical information included in the model (comparators, outcomes, and treatment pathways), the economic data included in the model (data sources, model approach, and health states) and the comparability of the results of the model (clinical outcomes) with those from other economic models. The Cardiff model has participated in the last five Mount Hood Challenge meetings for computer modelers of diabetes to discuss and compare models: Mount Hood 3 (2003, Oxford, UK); Mount Hood 4 (2004, Basel, Switzerland); Mount Hood 5 (2010, Malmo, Sweden), Mount Hood 6 (2012, Baltimore, USA), Mount Hood 7 (2014, Stanford, USA). Further, the model structure and input parameters have been presented by AstraZeneca in the initial STA for dapagliflozin and the recent SGLT2-i monotherapy MTA; and accepted by the ERG group.

5.6 *Summary list of variables used*

A list of baseline patient characteristics and risk factors used in the add-on to MET + SU analyses is provided in Table 37. Age, duration of diabetes and modifiable risk factor parameters change as the simulation progresses due either to treatment effects or natural progression.

Table 37: Summary of baseline variables applied in the economic model

Input parameter	Add on to MET+SU Dapa RCT (SE) (Matthaei 2015b)	Alternative population THIN data second intensification
Demographics		
Current Age (yrs)	61.00 (0.64)	65.40
Proportion female	0.51 (0.03)	0.44
Duration diabetes (yrs)	9.45 (0.43)	8.50
Height (m)	1.68 (0.00)*	1.68
Proportion AC	0.0270 (0.0008)*	0.0270
Proportion Indian	0.0270 (0.0008)*	0.0270
Proportion smokers	0.1900 (0.0019)*	0.1900*
Modifiable risk factors		
HbA1c (%)	8.15 (0.06)	7.90
Total-Cholesterol (mg/dL)	211.97 (0.21)*	211.97
HDL Cholesterol (mg/dL)	46.72 (0.06)*	46.72
SBP (mmHg)	135.40 (0.09)	143.20

Weight (kg)	**89.35 (1.15)**	**86.70**
Clinical event history		
AF	**0.0063 (0.0004)***	**0.0063**
PVD	**0.0047 (0.0003)***	**0.0047**
IHD	**0.0970 (0.0014)***	**0.0970**
MI	**0.0250 (0.0008)***	**0.0250**
CHF	**0.0230 (0.0007)***	**0.0230**
Stroke	**0.0180 (0.0006)***	**0.0180**
Amputation	**0.0040 (0.0003)***	**0.0040**
Blindness	**0.0220 (0.0007)***	**0.0220**
ESRD	**0.0100 (0.0005)***	**0.0100**

Abbreviations: AC, Afro-Caribbean; AF, atrial fibrilation; CHF, congestive heart failure; DPP4, dipeptidyl peptidase 4 inhibitor; ESRD, end-stage renal disease; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IHD, ischaemic heart disease; MET, metformin; n/a, not available; MI, myocardial infarction; NMA, network meta-analysis; PVD, peripheral vascular disease; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea;
*Values based on THIN NG28

The impact of using alternative baseline characteristics was investigated in scenario analyses. Alternative parameters were sources from a THIN database analysis facilitated for the purposes of the NG28 for UK patients on second intensification. For more details on the data please see appendix 21.

Clinical event history data were available from the THIN analysis in NG28, in which prevalence estimates where available for clinical history parameters derived from a UK general practice database. These values alongside RCT data have been used in the base case analysis. To explore the potential impact of assuming no prior history of complications a scenario analysis was performed in which prevalence estimates were set to 0 (see sections 5.9 and 5.11).

A summary of treatment effects and AE parameters applied for each treatment in the model are listed in Table 38, followed by a description of the data inputs used.

Table 38: Treatment effects and AE parameters applied in the economic model

Variable	Source	Change from baseline *			Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
		HbA1c (%)	Weight (kg)	SBP (mmHg)					
DPP4	NMA add-on to MET + SU for change from baseline & symptomatic hypoglycaemia Schernthaner 2013 for AEs except for symptomatic hypoglycaemia	-0.79	+0.12	+1.85	0.029	0.181	0.034	0.021	0.056
Dapagliflozin		-0.85	-2.20	-3.13	0.053	0.202	0.040	0.119	0.040
Empagliflozin 10mg		-0.85	-2.10	-3.30	0.053	0.148	0.040	0.119	0.040
Empagliflozin 25mg		-0.85	-2.00	-3.19	0.053	0.131	0.040	0.119	0.040
Canagliflozin 100mg		-0.867	-1.78	-4.82	0.053	0.208	0.040	0.119	0.040
Canagliflozin 300mg		-1.09	-2.06	-4.16	0.053	0.208	0.040	0.119	0.040
MET + insulin	Monami 2008	-1.1	1.084	0.00+	0.000	0.0108	0.037	0.000	0.000
Intensified insulin	Waugh 2010	-1.11	1.90	0.00+	0.000	0.616	0.022	0.000	0.000

DPP4, dipeptidyl peptidase 4 inhibitor; GI, genital infection; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hypo, hypoglycaemia; MET, metformin; NMA, network meta-analysis; SBP, systolic blood pressure; SU, sulphonylurea; sympt, symptomatic; TC, total cholesterol; TZD, thiazolidinedione; UTI, urinary tract infection.
* Effects apply to the first year after treatment initiation. Absolute change from baseline values were applied in the model.
# Probability of treatment discontinuation due to adverse events was applied during the first model cycle (= first 6 months).
^ Probabilities of adverse events were applied during every model cycle;
+ no estimate available - zero value assumed

Extrapolation of trial outcomes

The trial outcomes of HbA1c, SBP, TC, HDL and body weight were extrapolated beyond the trial periods.

The initiation of a new treatment results in a reduction in HbA1c according to the efficacy of the particular therapy, applied for one year, as described in section 5.4. After this initial 1 year reduction in HbA1c, natural progression consists of a gradual rise in HbA1c associated with a natural decline in the capacity to secrete endogenous insulin whilst patients continue on therapy (Clarke 2004). Regression analysis of the UKPDS dataset estimated a non-linear slope coefficient of 0.759 for the time varying annual risk of this HbA1c % 'creep', lagged one year. The slope of the curve is non-linear as HbA1c rises at a quicker rate immediately following the reduction (this is in line with the trajectories reported in the UKPDS 68 study) (Clarke 2004). It is assumed that a full 12 months of treatment effect (i.e. 2 model cycles) is obtained after initiating dapagliflozin or comparator treatment based on the evidence from the NMAs performed. The analysis then assumes a natural HbA1c creep commences, applied from the start of the third yearthe simulation.

Weight is included in the model as an additional modifiable risk factor and is associated with CV risk and a HRQoL impact. The treatment effect was applied over the first year of therapy initiation and, conservatively, it was assumed that the treatment effect associated with both dapagliflozin and the DPP4-is was lost over the subsequent 1 year period (i.e. weight returned to its natural trajectory). It was assumed that the weight gain associated with the insulin profiles employed for second and third therapy lines remained in place over the remainder of the simulation. A natural weight gain of 0.1kg/year was modelled. The weight trajectory is presented in Figure 22. The approach described herein is considered highly conservative as the weight loss is implemented for a shorter time period than observed in the clinical trial setting with weight loss sustainted for up to four years (Del 2015). In a real world setting, weight loss is likely to be maintained by patients receiving dapagliflozin beyond 2 years.

5.7 *Measurement and valuation of health effects*

Health-related quality-of-life data from clinical trials

5.7.1 Effects of the condition on patients' quality of life

The factors which impact the quality of life of patients with type 2 diabetes, as they relate to this economic assessment, are outlined below.

Disease progression and its consequences i.e. complications: As type 2 diabetes progresses, patients are exposed to an ever greater risk of complications, including CV disease, renal disease, amputation and retinopathy. As patients experience events, the impact on their quality of life is determined by the nature of the event and the consequences unique to that event. The occurrence of diabetes-related complications results in significant reductions in quality of life (Clarke 2002).

Body weight change: A number of antidiabetic drugs are associated with weight gain, in particular the SUs and TZDs which, as well as increasing risk of complications in patients with an already high body weight, is associated with a reduction in HRQoL. Conversely, any reductions in patient body weight, such as is apparent with dapagliflozin, can have a positive impact on HRQoL.

Attributes of the individual treatments: Fear of experiencing hypoglycaemia associated with type 2 diabetes pharmacological treatments also affects patients' quality of life.

5.7.2 Change in HRQoL over time

Type 2 diabetes is a progressive disorder. The risk of developing diabetes-related complications increases over time. Consequently, patients' HRQoL is likely to decrease over time. Upon the incidence of a complication event, assuming the patients survives, a disutility specific to that event is applied. Disutilities associated with complication events are applied in the cycle of the event and in all cycles thereafter. In contrast, disutilities associated with adverse events and hypoglycaemia are only applied in the relevant cycle and do not hold a legacy affect, the incidence of future events influences any future disutilities. All utility decrements are applied additively in the model.

In addition, HRQoL related to patients' body mass index changes over time, either through treatment effects on body weight or through natural weight progression. As time and type 2 diabetes progress, and patients move on to type 2 diabetes therapies associated with weight gain (e.g. insulin), patients' HRQoL decreases.

HRQoL data derived from clinical trials

5.7.3 Description of trial based HRQoL data

The key RCT of this appraisal (study 5) demonstrates that QOL is maintained in the short term (measured at 24 and 52 weeks) in patients receiving dapagliflozin on a background of MET + SU.

Quality of life (AstraZeneca 2013a)
Over 24 weeks patients treated with dapagliflozin had greater improvement in weight change-related HRQoL, similar obesity-specific HRQoL, and greater treatment satisfaction, compared with patients who received placebo (AstraZeneca 2013a). As measured using the EQ 5D patients receiving dapagliflozin with metformin plus SU, maintained high HRQoL scores over the 24 week trial period (0.84 score at baseline and 0.83 at 24 weeks. For placebo plus metformin and SU patients the baseline score was 0.85 at baseline and 0.83 at 24 weeks) (AstraZeneca 2013a)

Patient reported outcomes at 52 weeks (Grandy 2015; Grandy 2016)
The five-dimension EuroQol questionnaire (EQ-5D), SHIELD Weight Questionnaire-9 (WQ-9), Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were used to evaluate health status and health-related quality of life (HRQoL) at baseline and week 52. Patients treated with dapagliflozin in combination with metformin + SU were compared to patient with placebo, in combination with metformin +SU, using a repeated-measures mixed model.
The EQ-5D index score and the EQ-5D visual analogue scale score were high at baseline (0.85 and means score of 73-75, respectively). An increase in EQ-5D VAS was observed for both treatment groups and only a slight change in the mean index score was observed for both treatment groups. These changes were not statistically significant.
The IWQOL-Lite and DTSQ scores improved in the dapagliflozin and placebo groups from baseline to week 52; however, there was no significant difference between groups ($p>0.20$).
A numerically greater proportion of the dapagliflozin group reported improvement in all nine SHIELD WQ-9 items compared with placebo, and the difference was statistically significant

for physical health (p=0.017). Over 52 weeks of therapy, patients maintained their health status and HRQoL when dapagliflozin was added to the treatment.

The trial investigated the changes in QOL from baseline to 52 weeks for each of the therapy arms and demonstrated a non-significant difference, therefore was not included within the modelled analysis. Further, the application of QOL data derived over a 52 week period is unlikely to be suitable for an analysis modelling a 40 year time horizon. Disutilities associated with the complications were derived from the UKPDS 62 (Clarke 2002). Only ESRD disutilities were derived from Currie 2005. Utility related to change in body weight is described below.

Mapping clinical trial HRQoL data

5.7.4 Description of mapping exercise

Not applicable.

5.7.5 Literature search to identify HRQoL studies

A systematic search was performed to identify utility studies for HRQoL outcomes in type 2 diabetes.

This was part of a single comprehensive systematic review that also covered the identification of economic evaluations and resource utilisation studies for the selected drug interventions and specific type 2 diabetes patient population that match that included in the dapagliflozin economic model in this submission i.e. triple therapy (see section 5.1).

Further details of the single comprehensive search strategy are provided in Appendix 16.

5.7.6 HRQoL studies identified

From the searches, 15 utility studies considered of direct relevance for this submission and were selected for review. We have completed the table for 13 studies as two studies (Troelsgaard 2014) and (Copley 2013) did not report any utility values.

A summary of the methods and results from these studies are presented in Table 39.

Table 39: Utility studies reviewed from the HRQoL search

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
(Brandle 2009)	Switzerland	549; 58.9 years	Type 2 diabetes patients failing to achieve an HbA1c <7.0% with maximally effective doses of metformin and a sulfonylurea were included in the analysis	T2DM with body weight increased; Range: (-0.065,-0.044) T2DM with body weight decreased; Range: (0.02,0.032) T2DM patients with BMI (for each unit of BMI over 25 kg/m^2): –0.061
(Tunis 2010)	Canada	NR; 60.9 years	Type 2 diabetes patients inadequately controlled on metformin and a sulfonylurea were included in the analysis	T2DM with no complications: 0.783 T2DM with MI (year of event): -0.0409 T2DM with MI (subsequent year): -0.012 T2DM with Angina (year of event): -0.0412 T2DM with Angina (subsequent year): -0.024 T2DM with CHD (year of event): -0.0546 T2DM with CHD (subsequent year): -0.018 T2DM with Stroke (year of event): -0.0524 T2DM with Stroke (subsequent year): -0.04 T2DM with Peripheral vascular disease (subsequent year): -0.021 T2DM with Peritoneal or haemodialysis: -0.16 T2DM with Renal transplant (year of event): -0.03 T2DM with Severe vision loss/blindness (first year): -0.0498 T2DM with Severe vision loss/blindness (subsequent year): -0.0498 T2DM with Cataract extraction: -0.0171 T2DM with Neuropathy (year from onset): -0.0244 T2DM with Uninfected ulcer (monthly based): -0.09 T2DM with Infected ulcer (monthly based): -0.14 T2DM with amputation (year of event0: -0.266

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
				T2DM with major hypoglycaemia: -0.549
(Ray 2007)	UK	549; 58.9 years	Type 2 diabetic patients with inadequate glycaemic control (i.e. HbA1c > 7.0% and ≤ 10.0%) and treatment with metformin and sulfonylurea therapy	T2DM with Body weight increased; Range: (-0.065,-0.044) T2DM with Body weight decreased; Range: (0.02,0.032) T2DM patients with BMI (for each unit of BMI over 25 kg/m^2): –0.061
(Thompson 2014)	UK	756; 56.7 years	Type 2 diabetes patients inadequately controlled on metformin and a sulfonylurea	T2DM with Overweight-obese (each unit BMI>25 kg/m2): -0.0061 T2DM with Severe hypoglycaemia: -0.0118 T2DM with Non-severe symptomatic hypoglycaemia: -0.0036
(Mittendorf 2009)	Germany	551; 58.9 years	Type 2 diabetes patients, aged 30-75 years of age, not achieving adequate glycaemic control (defined as having an HbA1c level of 7-10%) on a combination of metformin and a sulfonylurea	T2DM with Body weight increased; Range: (-0.065,-0.044) T2DM with Body weight decreased; Range: (0.02,0.032) T2DM patients with BMI (for each unit of BMI over 25 kg/m^2): –0.0061
(Sabapathy 2015)	Canada	NR; 56.6 years	Patients with T2DM inadequately controlled on metformin and a sulfonylurea	T2DM with Age (per 10 y) : -0.235 T2DM Female : -0.093 T2DM with duration (per 10 y) : -0.0163 T2DM with Body weight increased per kg/m^2 over 25 kg/m^2 (Source A) : -0.0061 T2DM with Body weight increased per kg/m^2 over 25 kg/m^2 (Source B) : -0.00195 T2DM with Body weight increased per kg/m^2 over 25 kg/m^2 (Source C) : -0.0472 T2DM with Body weight decreased per kg/m^2 over 25 kg/m^2: -0.0171 T2DM with Myocardial infarction : -0.012

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
				T2DM with Ischaemic heart disease : -0.024 T2DM with Congestive heart failure : -0.018 T2DM with Stroke : -0.04 T2DM with Peripheral vascular disease : -0.063 T2DM with Symptomatic neuropathy : -0.084 T2DM with Diabetic foot ulcer : -0.2 T2DM with Lower extremity amputation (LEA) : -0.28 T2DM with Macro albuminuria : -0.048 T2DM with End-stage renal disease : -0.263 T2DM with eGFR 30 to 59 mL/min/1.73 m2 : -0.05 T2DM with eGFR 15 to 29 mL/min/1.73 m2 : -0.07 T2DM with eGFR <15 mL/min/1.73 m2 : -0.175 T2DM with Blindness : -0.0498 T2DM with Lower UTI : -0.00123 T2DM with Upper UTI : -0.00729 T2DM with Genital mycotic infection : -0.0046 T2DM with Non-severe symptomatic hypoglycaemia (Source A) : -0.000004767 T2DM with Severe hypoglycaemia (Source A) : -0.01 T2DM with Non-severe symptomatic hypoglycaemia (Source B) : -0.005 T2DM with Severe hypoglycaemia (Source B) : -0.06
(CADTH 2013)	Canada	NR; NR	Adults with type 2 diabetes inadequately controlled with on metformin and a sulfonylurea. When available, characteristics of simulated patients were derived from RCTs included in the systematic review and NMA	T2DM with Ischaemic heart disease: Year 1: -0.0412 T2DM with Myocardial infarction: Year 1: -0.0409 T2DM with Heart failure: Year 1: -0.0635 T2DM with Stroke: Year 1: -0.0524 T2DM with Amputation: Year 1: -0.28 T2DM with Blindness: Year 1: -0.0498

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
				T2DM with Renal failure: Year 1: -0.263 T2DM with Ischaemic heart disease: Year >=2: -0.024 T2DM with Myocardial infarction: Year >=2: -0.012 T2DM with Heart failure: Year >=2: -0.018 T2DM with Stroke: Year >=2: -0.04 T2DM with Amputation: Year >=2: -0.28 T2DM with Blindness: Year >=2: -0.0498 T2DM with Renal failure: Year >=2: -0.263
(Nielsen 2015)	Spain	NR; NR	Type 2 Diabetes Mellitus patients inadequately controlled on METFORMIN or METFORMIN + SULFONYLUREA	T2DM with No complications: 0.743 T2DM with Myocardial infarction event: -0.057 T2DM with Post myocardial infarction: 0.686 T2DM with Angina: 0.653 T2DM with Chronic heart failure: 0.635 T2DM with Stroke event: -0.324 T2DM with Post stroke: 0.419 T2DM with Peripheral vascular disease: 0.682 T2DM with Micro albuminuria: 0.743 T2DM with Gross renal proteinuria: 0.695 T2DM with Haemodialysis: 0.579 T2DM with Peritoneal dialysis: 0.539 T2DM with Renal transplant: 0.72 T2DM with Background diabetic retinopathy: 0.703 T2DM with Background diabetic retinopathy, wrongly treated: 0.703 T2DM with Proliferative diabetic retinopathy, laser treated: 0.673 T2DM with Proliferative diabetic retinopathy, no laser: 0.673 T2DM with Macular oedema: 0.703

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
				T2DM with Severe vision loss/blindness: 0.669 T2DM with Cataract : 0.727 T2DM with Neuropathy: 0.659 T2DM with Healed ulcer: 0 T2DM with Active ulcer: 0.573 T2DM with Amputation, year of event: -0.28 T2DM with Post amputation (2+ years after event): 0.463 T2DM with Severe hypoglycaemic events: –0.047 T2DM with Non-severe hypoglycaemic events: –0.014 T2DM with Depression, not treated: 0.677 T2DM with Depression, treated: 0.677 T2DM with BMI, per kg/m2 above 25 kg/m2: –0.0061
(Charokopou 2014)	UK	NR; NR	Patients with T2DM inadequately controlled on metformin and a sulfonylurea	T2DM with Ischaemic heart disease: -0.09 T2DM with Myocardial infarction: -0.055 T2DM with Congestive Heart Failure: -0.108 T2DM with Stroke: -0.164 T2DM with Blindness: -0.074 T2DM with Amputation:-0.28 T2DM with End-stage renal disease: -0.263 T2DM with For each unit decrease in BMI: ±0.0061 T2DM with Severe hypoglycaemia: -0.047 T2DM with Symptomatic hypoglycaemia: -0.0142 T2DM with Other adverse event UTI: -0.00283 T2DM with Other adverse event GI: -0.00283
(SMC 993 2014)	Scotland	NR; NR	Adults with type 2 diabetes inadequately controlled (glycosylated haemoglobin (HbA1c) ≥7% (≥7.5% in study 49) and ≤10%) on a stable	T2DM BMI per increased unit : -0.0159

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
			dose for at least 12 weeks of metformin plus sulfonylurea	
(Waugh 2010)	UK	NR; NR	The patient is assumed to have progressed from metformin, to combined metformin and sulfonylurea, but now to having poor control as defined by HbA1c level rising above 7.5%.	T2DM with Ischaemic heart disease: –0.090 T2DM with Myocardial infarction: –0.055 T2DM with Heart failure: –0.108 T2DM with Stroke: –0.164 T2DM with Amputation: –0.280 T2DM with Blindness: –0.074 T2DM with Renal failure: –0.263 T2DM with Nausea: -0.048 T2DM with Reduced fear associated with an annual severe hypoglycaemic event: 0.01
(SMC 799 2012)	Scotland	NR; NR	Patients with T2DM inadequately controlled with metformin + SU regimen	T2DM with increase/decrease in BMI: ±0.0061
(Pititto 2015)	Brazil	NR; NR	Patients with T2DM inadequately controlled with metformin + SU regimen	T2DM with age (per 10 y): –0.0235 T2DM: female: –0.093 T2DM with duration of T2DM (per 10 y): –0.016 T2DM with excess body weight (per kg/m2 over 25 kg/m2): –0.0061 T2DM with IHD: –0.028 T2DM with MI: –0.028 T2DM with CHF: –0.028 T2DM with Stroke: –0.115 T2DM with blindness: –0.057 T2DM with macro albuminuria: –0.048 T2DM with EGFR 30-59 ml/min/1.73 m2: –0.050 T2DM with EGFR 15-29 ml/min/1.73 m2: –0.070

Study	Country	Sample size (N); Age in years	Eligibility criteria	Health state and utility values
				T2DM with EGFR <15 ml/min/1.73 m2: –0.175 T2DM with symptomatic neuropathy: –0.084 T2DM with peripheral vascular disease (PVD): –0.061 T2DM with diabetic foot ulcer: –0.170 T2DM with Lower extremity amputation (LEA): –0.272 T2DM with non-severe symptomatic hypoglycaemia: –0.005 T2DM with severe hypoglycaemia: –0.060 T2DM with lower UTI: –0.00123 T2DM with upper UTI: –0.00729 T2DM with genital mycotic infection: –0.0046 T2DM with orthostatic hypotension and related AEs: –0.005 T2DM with Polyuria/pollakiuria/nocturia: –0.005

Key findings from the utility/HRQoL studies were as follows:

- The HRQoL studies identified have reported utilities or disutilities for complications of type 2 diabetes, the relationship between BMI/weight and utility in type 2 diabetes, and disutilities associated with hypoglycaemia and the fear of further hypoglycaemic episodes
- Many of the utility studies performed in type 2 diabetes have used the EQ-5D (tariff and VAS), which is consistent with the NICE reference case
- There have been several studies that have investigated the relationship between BMI and utility, demonstrating a significant correlation between increased BMI or obesity and disutility using EQ-5D and other recognised methods

A key advantage of dapagliflozin over comparator drugs used as add-on to MET, or add-on to insulin, is the weight loss potential achieved with the drug. Therefore, the relationship between change in weight associated with type 2 diabetes drugs and change in utility is an important component of the economic assessment of dapagliflozin. It is possible to use values from the literature to model the impact of a per unit increase in BMI on type 2 diabetes patient utility. However, the only study reviewed above that has specifically assessed the relationship between BMI and change in utility in type 2 diabetes patients that lose weight is the SMC for dapagliflozin which included the Bagust 2005 paper also used for this submission. Hence, for the base case of the dapagliflozin economic evaluation a bespoke utility analysis was used to inform estimates; the study obtained specific type 2 diabetes patient utilities associated with both increasing and decreasing BMI (Bagust 2005).

5.7.7 Comparison of HRQoL data

As described above, the application of QOL data derived over a 52 week period from the key clinical trial of dapagliflozin in a triple regimen is unlikely to be suitable for an analysis modelling a 40 year time horizon; and therefore this data has not been included in the economic model.

Adverse reactions

5.7.8 Impact of adverse events on HRQoL

Weight gain

Certain type 2 diabetes treatments, such as insulin and TZD, are associated with weight gain which can be considered as an adverse effect of pharmacological treatment. Dapagliflozin on the other hand reduces body weight. The effect of changes in BMI (as a measure of body weight) on quality of life has been included in the model. An increase in BMI had a negative affect on QoL and a decrease in BMI had a positive effect on QoL.

A recently published systematic review of utilities associated with weight change that covered both type 2 diabetes mellitus and non-type 2 diabetes mellitus overweight or obese patient populations found a number of studies reporting EQ-5D values that also indicated the relationship between weight gain and loss and utility is not linear (Doyle 2012). This review indicated that the values estimated by Bagust for utility associated with BMI unit change is potentially a conservative estimate of the impact of weight gain or loss on patient HRQoL/utility (Bagust 2005).

In the base case, utility estimates associated with weight change were derived from an ordinary least squares (OLS) regression analysis of EQ-5D and BMI data from an observational dataset of over 4,600 type 2 diabetes mellitus patients in the UK, Belgium,

Spain, Italy, Netherlands and Sweden (Bagust 2005). Using the UK time trade off tariff for the EQ-5D, a disutility of -0.0061 per 1 unit increase in BMI was estimated in patients with BMI >25 (SE 0.001, p<0.001). Therefore, a utility change of ±0.0061 for weight gain and loss was applied to each treatment induced weight/BMI change in the economic model (Table 41). The utility estimates from this study were used for the base case on the grounds that it has been used in previous technology appraisals of type 2 diabetes interventions performed by NICE, including the economic model used for the assessment of treatments covered by NICE Clinical Guideline 28 (NICE 2015).

Hypoglycaemia

In the base case, the annual number of symptomatic hypoglycaemic events alongside the probability of a severe event was predicted using data from the NMA; the probability of a severe event was predicted using data from the head to head RCT comparing canagliflozin with sitagliptin in the absence of head to head trials for dapagliflozin versus a DPP4-i (Table 38). Nocturnal hypoglycaemic events were not considered due to a lack of data. The disutility associated with hypoglycaemia in terms of the fear associated with different types of event (symptomatic and severe) occurring was incorporated.

Utility decrements associated with hypoglycaemic events were based on a study by Currie et al., who developed a statistical model that relates the fear of hypoglycaemia to changes in utility measured with the EQ-5D in a UK population of 1,305 patients with diabetes, conditioned upon the severity and frequency of hypoglycaemic events (Currie 2006). The published equations characterising this relationship were included in the cost-effectiveness model. For each cycle in the model, the number and the severity of hypoglycaemic events in the patients' history is determined. Each event experienced causes a loss of utility through increased fear of hypoglycaemia.

Other adverse events

The model also allows for utility decrements to be applied to the occurrence of AEs other than hypoglycaemia. Genital infections and urinary tract infections (UTIs) were considered events of special interest in the dapagliflozin development programme given that, due to its mechanism of action, dapagliflozin causes glucosuria, and that these infections are known to be more common in diabetic patients than in the general population. Therefore these two AEs were included in the model and were assumed to incur a quality of life decrement, estimated to be 0.00283 per event, derived from a published economic evaluation of care interventions for UTIs in women; this represented the highest utility decrement in the published study (Barry 1997) and is therefore a conservative assumption. The utility reported in the study by Barry et al. was presented as quality adjusted life months and was converted to QALYs. The decrements were applied only in the year in which the event occurred (Table 40).

Table 40: Utility decrements associated with hypoglycemic events and other adverse events (UTI's/GI's)

Event	Utility decrement per event	Source:
Other adverse event:		
UTI	-0.00283	(Barry 1997)
GI	-0.00283	(Barry 1997)

*due to uncertainty over the utility associated with nocturnal hypoglycaemia, a zero disutility was applied in the economic model for this

Health-related quality-of-life data used in cost-effectiveness analysis

At model initiation, patients are assigned an age-adjusted utility associated with type 2 diabetes mellitus without complications. The age adjustment was modelled using mean EQ-5D by age group in patients with no major complications obtained from the Health Survey for England 2003 (Health Survey for England. 2003). An inverse relationship between age and utility was estimated, in which utility decreases as age increases. The rate at which utility decreases varies at different stages of life. Between the ages of 30 and 60, there is a slow rate of decline, whilst in the later stages of life the rate of decrease is greater. Disutilities associated with CV and metabolic complications are subtracted from the age dependent baseline utility.

Table 41 presents the reduction in quality of life, in terms of incremental disutilities, associated with the 7 non-fatal macro and microvascular complications included in the model. These are drawn from the UKPDS 62 sub-study whereby utility values for type 2 diabetes mellitus patients experiencing complications were assessed using the EQ-5D (Clarke 2002). In this study the EQ-5D questionnaire was sent to 3,667 UKPDS patients. Tobit regression analysis was conducted on 3,192 of these patients to estimate disutilities for the complications. This source has been used in almost all validated type 2 diabetes mellitus economic models and has provided utility data for most previous technology appraisals of type 2 diabetes mellitus drugs in the UK, including the NICE NG28 (NICE 2015). Disutility values for ESRD were not available from UKPDS 62, hence data on ESRD and EQ-5D values derived from the Health Outcomes Data Repository (HODAR database) that covers type 2 diabetes mellitus patients in Wales were used (Currie 2005).

The disutilities in Table 41 are derived from UK patient populations.

The model assumes that for patients experiencing more than one complication the disutilities are additive (i.e. if stroke and MI are experienced the disutility is the sum of both subtracted from the age dependent baseline utility). The assumptions of additive properties and lifetime disutility are justified by the methods used to generate the utilities within the UKPDS sub-study 62 (Clarke 2002). After the event the disutility was assumed to apply in the first and subsequent years.

Table 41: Utility decrements associated with complications and BMI related utilities

Type 2 diabetes related complications	Utility decrements*	Source:
Ischemic Heart Disease	-0.090	(Clarke 2002)
MI	-0.055	
Congestive Heart Failure	-0.108	
Stroke	-0.164	
Blindness	-0.074	
Amputation	-0.280	
ESRD	-0.263	(Currie 2005)
For each unit decrease in BMI	±0.0061**	(Bagust 2005)

BMI, body mass index; ESRD, end stage renal disease; MI, myocardial infarction;
*The decrement applies for the first year of the event and all subsequent years, and is subtracted from age adjusted no complications utility.
**For each 1 unit increase in BMI a utility decrement of -0.0061 is applied in the economic model, and for a unit decrease in BMI a utility increase of 0.0061 is applied.

Input from clinical experts

For the initial assessment of dapaglifozin in 2012, clinical guidance was sought through ad board meetings with health economic and clinical experts. For this update, AstraZeneca followed the most recent NICE clinical guideline (NG28) to ensure the most appropriate model inputs.

HRQoL experienced in each health state

If a patient experiences a diabetes-related complication a decrement is subtracted from the age-specific baseline utility in the year in which the complication occurs, and in all subsequent years. The model assumes that for patients experiencing more than one complication the disutilities are additive (i.e. if stroke and MI are experienced the disutility is the sum of both subtracted from the age dependent baseline utility). The assumptions of additive properties and lifetime disutility are justified by the methods used to generate the utilities within the UKPDS sub-study 62 (Clarke 2002).

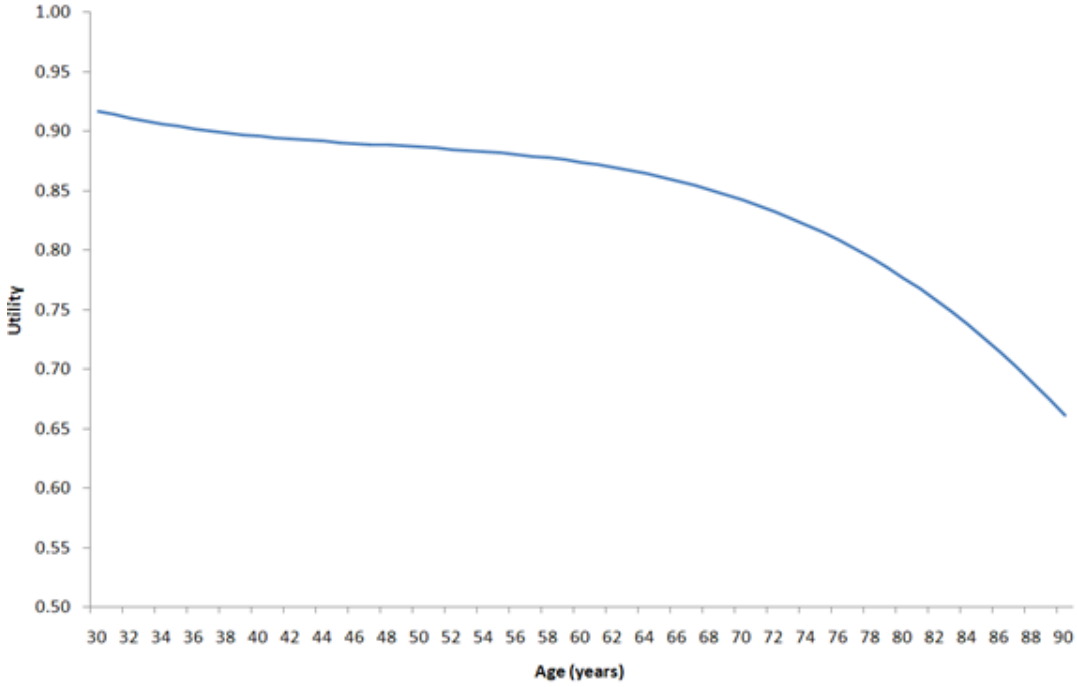
Health effects excluded from the analysis

The literature review identified studies that included an assessment of disutilities associated with type 2 diabetes macro and micro-vascular complications, the relationship between BMI/weight and obesity and utility outcomes in type 2 diabetes patients, utilities associated with the fear of hypoglycaemia and hypoglycaemic episodes and baseline utilities associated with patients not achieving glycaemic control on MET + SU. In the dapagliflozin economic analyses account has been taken of disutilities from macro/micro-vascular complications associated with lack of glycaemic control and other risk factors, such as BMI/weight, hypoglycaemia and adverse effects identified in the SGLT2-i clinical trials for add-on to MET + SU (specifically, UTIs and GIs). Hence, no significant health effects identified in the literature or clinical trials have been excluded from the dapagliflozin economic evaluation.

Baseline HRQoL

An age-dependent utility value of 0.87 corresponding with baseline age (61 years in the base case analyes) was assumed as baseline quality of life in the analyses (Figure 23). When patients grow older, their age-dependent baseline utility declines, modelled using mean EQ-5D by age group in subjects with no major complications, obtained from the DoH Health Survey for England (Health Survey for England. 2003). In case of an event, absolute disutilities (independent of patients' age, shown in Table 41) associated with complications and adverse events are deducted from patients' age-dependent baseline utility.

Figure 23: Age-dependent baseline utility function



Changes in HRQoL over time

HRQoL changes over time due to the incidence of complications, hypoglycaemia and other adverse events are modelled In addition, HRQoL changes associated with changes in body weight/BMI related to treatment effects and natural weight progression are also modelled.

5.8 *Cost and healthcare resource use identification, measurement and valuation*

Drug acquisition costs

The drug acquisition costs used to represent specific drugs and classes of drugs in the model are presented in Table 42. For dapagliflozin, the price per pack is £36.59 for 28 x 10 mg tablets, representing an annual cost of £477 or an equivalent daily cost of £1.31 for the 10 mg OD dose (BNF 2015).

In the base case a weighted average cost of the five DPP4-i products used in clinical practice in England and Wales was used, based on the relative market share of each drug when added to MET + SU (in terms of prescriptions as of January 2016). The triple therapy MET + SU + DPP4-i market leader in the UK is sitagliptin with 71% market share of prescriptions in

combination with metformin and SU, with saxagliptin, vildagliptin, linagliptin and alogliptin having triple therapy market shares of 10%, 3%, 12% and 3% respectively. (Patient Data, IMS Information Solutions UK Ltd, January 2016). The weighted average cost of the DPP4-is was estimated at £424.50 per year (Table 42).

The lowest non-proprietary cost of MET was included in the model and the cost of SU was based on the price of gliclazide (BNF 2015). The lowest cost available for the human neutral protamine hagedorn (NPH) insulin regimen was applied (Insuman Basal). The cost of insulin in the model was applied as a cost per kg per day based on the estimated baseline weight of 86.7 kg from the THIN NG28 second intensification data. All the drug acquisition costs applied in the model are summarised in Table 42.

Table 42: Drug acquisition costs applied in the model for the add-on to MET + SU

Therapy	Price per pack	Tablets per pack	Price per tablet Φ	Dose per tablet	Daily dose	Annual cost (£)
Dapagliflozin	£36.59	28	£1.31	10 mg	10 mg	£476.92
DPP4-is:						
Sitagliptin	£33.26	28	£1.19	100 mg	100 mg	£433.57
Saxagliptin	£31.60	28	£1.13	5 mg	5 mg	£411.92
Vildagliptin	£33.35	56	£0.60	50 mg	100 mg	£434.74
Linagliptin	£33.26	28	£1.19	5 mg	5 mg	£433.57
Alogliptin	£26.60	28	£0.95	25 mg	25 mg	£346.75
Weighted average of DPP4-is*	£33.12	-	-	-	-	£424.50
SGLT2s:						
Canagliflozin	£39.2	30	£1.31	100/300 mg	100/300 mg	£476.93
Empagliflozin	£36.59	28	£1.31	10/25 mg	10/25 mg	£476.98
Other:						
SU (Gliclazide)	£1.13	28	£0.04	80 mg	160 mg	£29.46
MET	£1.94	56	£0.03	850 mg	1900 mg	£25.29
Insulin (Insuman basel) – add-on to MET	£17.50	5Ɣ	£0.0055 per kg/day**			
Intensified insulin – add-on to MET	£17.50	5Ɣ	£0.0082 per kg/day**			

Φ pack price/tablets per pack
*Weighted cost based on prescription estimates for UK with 71% sitagliptin, 10% saxagliptin, 12% linagliptin 3% vildagliptin and 3% alogliptin (AstraZeneca 2013b)
Ɣ Injection pens per pack
**based on a dose per injection pen of 300 units and a daily dose of 40 IU for Insulin (Insuman basel), and 60 IU for intensified insulin for an 86.7kg patient (the average weight from the THIN NG28 second intensification) representing a daily dose per kg of 0.47 and 0.70 respectively.

Drug administration and monitoring

As dapagliflozin and the primary comparators are oral antidiabetic drugs, no administration costs have been assumed. In addition, insulin is assumed to be self-administered.

As the efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients with moderate impairment and absent in patients with severe impairment it is not recommended for use in patients with moderate to severe renal impairment (SPC Forxiga

2013). Patient monitoring, including renal monitoring, is part of the routine clinical management of type 2 diabetes mellitus. However, we have included in the economic analysis the incremental cost associated with introducing renal monitoring on initiation of dapagliflozin treatment. This is estimated to include one GP visit (unit cost of £45, from (Curtis 2013) and a 24 hour urine creatinine clearance test (unit cost of £2 NHS ref cost 2013/14). The cost of monitoring has been added to the total cost of the dapagliflozin treatment arms. The cost of MET + SU is the same for each cohort, therefore only the cost of the add-on treatment has been considered in the economic analysis (Table 43). Additionally, a one-off cost of £45 (a single GP visit) was applied to patients that discontinued therapy.

Table 43: Unit costs associated with the technology in the economic model

Items	Dapagliflozin	DPP4-i	Other SGLT2
Technology cost	£477/year	£424.50/year	£477/year
Administration cost	NA	NA	NA
Monitoring cost	£45	NA	£45
Tests	£2	£0	£2
Discontinuation due to AE	£45	£45	£45

AE: adverse event; NA: Not applicable

Health-state unit costs and resource use

5.8.1 A summary of the costs included in each health state are given below. Provide a rationale for the choice of values used in the cost-effectiveness model.

Complications costs

The annual costs of complications used in the economic model are presented in Table 44. The costs for fatal and non-fatal macrovascular (IHD, MI, CHF, and stroke) and microvascular events (blindness, ESRD and amputation) were primarily derived from the UKPDS sub-study (Clarke 2003) The original cost estimates are for the 2000 financial year for all outcomes except inpatient renal failure, source year for inpatient renal failure was 1996; all costs have been updated to 2012-2013. The cost data used in the base case are aligned with cost data used in the NICE clinical guidelines (NICE 2015). The UKPDS 65 study estimated the first year event cost and the subsequent annual maintenance costs for patients who survived until the end of the simulation. Although dated, these estimates have been used as the basis for the cost of complications in all of the main validated type 2 diabetes models, including the UKPDS health outcomes model.

The cost of blindness can only be incurred once as patients were assumed to incur severe vision loss/blindness in both eyes simultaneously.

A scenario with costs inflated to 2014/2015 costs has been included in the scenario analysis and utilises the more contemporary UKPDS 84 cost study (Alva 2015).

Table 44: Annual direct medical complication costs included in the model

Event	Fatal	Non-fatal	Maintenance	Reference
No complication	NA	£465	NA	UKPDS [65]
Ischaemic heart disease	NA	£3,346	£1,105	
MI	£1,695	£6,451	£1,062	
Congestive heart failure	£3,731	£3,731	£1,308	
Stroke	£4,977	£3,946	£746	
Amputation	£12,847	£12,847	£742	
Blindness	NA	£1,685	£714	
End stage renal disease	£35,715	£35,715	£35,631	

MI, myocardial infarction;
* Prices were indexed to 2012 using the Hospital and Community Health Services Pay & Prices index reported in UKPDS 84

Adverse reaction unit costs and resource use

Costs associated with hypoglycemia

Resource use and unit costs for severe hypoglycaemic episodes were largely based on Hammer et al (Hammer 2009). The paper included a UK sample of non-randomly selected people with type 2 diabetes on insulin-based treatment options. Of 147 people, 19 reported having at least 1 severe hypoglycaemic episode in the previous 1 year. Approximately 53% of the 19 people reporting a severe hypoglycaemic episode were treated by the NHS. Weighted estimated costs of managing severe hypoglycaemic events using community and hospital episode statistics were inflated to 2012-13 prices (£380). The Guideline Development Group for the recent NG28 NICE guideline felt such a cost was not unrealistic. A scenario analysis using 2014/2015 costs has been evaluated.

The Hammer et al study was used as it represents the most recent assessment of health care costs associated with hypoglycaemia. It covers a wide range of direct health care costs including primary care visits, hospital costs, and out of hospital health care professional contacts, ambulance services and drug treatment.

UTI and GI adverse event and treatment discontinuation costs

A cost was included for the management of each UTI and GI event, assumed to consist of the cost of a GP visit at £45, derived from Curtis, 2013 (Curtis 2013). This does not include the costs of antibiotics, urine analysis or other drugs/tests.

Treatment discontinuation associated with AEs was assumed to incur a GP visit at a cost of £45. Table 45 summarises the hypoglycaemic and UTI/GI costs included in the model.

Table 45: Costs of hypoglycaemic episodes and UTI/GI AEs included in the economic model

Adverse event	Cost per episode	Source
Severe hypoglycaemic episode	£380	Hammer 2009
UTI or GI	£45	Cost of GP visit (12 min consultation), from (Curtis 2013) NG28

Miscellaneous unit costs and resource use

Treatment discontinuation was assumed to incur the cost of a visit to the GP (£45; (Curtis 2013).

5.9 *Summary of base-case de novo analysis inputs and assumptions*

Univariate sensitivity analysis

In order to investigate the affect of individual parameter groups on cost-effectiveness outcomes, a number of univariate sensitivity analyses were performed. Univariate sensitivity analysis was undertaken for the comparison of dapagliflozin versus DPP4-is only. The affects of varying the following parameters was assessed:

- Discounting (0% and 6%)
- Model time horizon (5 and 20 years)
- Age (±25%)
- Proportion female (0% and 100%)
- Current smoking status (0% and 100%)
- Baseline hbA1c (±25%)
- Baseline TC (±25%)
- Baseline HDL (±25%)
- Baseline SBP (±25%)
- Baseline weight (±25%)
- HbA1c treatment effect (±25%)
- Weight treatment effect (±25%)
- Non-severe hypoglycaemia rates (±25%)
- Severe hypoglycaemia rates (±25%)
- Adverse event rates (±25%)
- Event costs (±25%)
- BMI costs (±25%)
- Baseline utility (±25%)
- Event disutility (±25%)
- BMI-related utility (±25%)

Scenario analysis

In addition to the univariate sensitivity analyses, a number of scenario analyses were performed to assess the impact of alternate data sources on cost-effectiveness outcomes (Table 46).

Table 46: Scenario analyses performed

Scenario	Base case	Alternative value
Baseline patient characteristics	Taken from Matthaei 2015	Patient population based on THIN database (NG28)
		Patient population based on NMA full network
		Patient population based on NMA restricted network
Baseline HbA1c	Taken from Matthaei 2015	HbA1c baseline value to 7.5% (according to NG28)
		HbA1c baseline value to 7.9% (according to THIN database) + weight maintenance dapagliflozin 2 years
		HbA1c baseline value to 8.24% (according to MET + SU NMA 2016)
HbA1c threshold for treatment switch	7.5% (59 mmol/mol)	HbA1c threshold 1st-2nd line: 7.5% and 2nd-3rd line: 8.0%
		HbA1c threshold 1st-2nd line: 8.0% and 2nd-3rd line: 9.0%
Treatment effect	NMA restricted	NMA full network
Health care Cost	NG28	UKPDS 84
BMI cost	None	Include BMI costs according to UK Counterweight Project Team data (2008)
Disutilities weight gain	Disutilities weight gain 0.061 per BMI point (Bagust)	Disutilities weight gain 0.014 per BMI point (1)
		Disutilities weight gain 0.0038 per BMI point (2)
Disutilities for AE		No disutilities for AE
Disutilities for AE	Based on Barry 2007	lower limit of -0.0104 for GTI and UTI
Disutilities for AE	Based on Barry 2008	Upper limit -0.000657 for GTI and UTI
Risk equation	Risk equations UKPDS 68	Risk equations UKPDS 82
Discontinuation of treatment	RCT	No discontinuation
		Discontinuation of DPP4 set equal to dapagliflozin
Prior CV history	THIN NG28	No prior CV history (values set to 0)
Drug costs in 2nd and 3rd line	Costs for insulin	Costs for MET, SU and DPP4/Dapa added to insulin costs
Weight trajectory	Treatment effect and subsequent loss over 2 years	Treatment effect maintained over simulation period

AE: adverse event; BMI: body mass index; GTI, genital tract infection; SU: sulphonylurea

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted by simulating 5,000 cohorts of 5,000 patients in which values of key parameters were drawn randomly and independently from their parameter distributions. If SEs were available, then these were used to vary the parameter around the mean. If an SE was not available then it was assumed to be 20% of

the mean. For probabilities, missing SEs were calculated assuming that the probability estimate had been determined based on 100 subjects. In general, beta distributions were used for utilities and probability estimates, gamma distributions were used for costs, and normal distributions were used for the other parameters. Details on the parameters, SEs and assumptions are provided in Table 47.

Table 47: Model parameters and parameter distributions varied in the PSA

PSA parameter	Mean	SE	Distribution
Baseline patient characteristics			
Current Age (years)	61.000	0.642	Normal
Proportion female	0.509	0.034	Beta
Duration diabetes (years)	9.450	0.431	Normal
Height (m)	1.680	0.000	NA
Proportion AC	0.027	0.001	Beta
Proportion Indian	0.027	0.001	Beta
Proportion smokers	0.190	0.002	Beta
Baseline clinical risk factors			
HbA1c (%)	8.150	0.061	Normal
Total cholesterol (mg/dl)	211.969	0.206	Normal
HDL cholesterol (mg/dl)	46.718	0.056	Normal
SBP (mmHg)	135.400	0.089	Normal
Weight	89.350	1.149	Normal
Baseline clinical history			
Atrial fibrilation	0.006	0.038	Beta
Peripheral vascular disease	0.005	0.033	Beta
Ischaemic heart disease	0.097	0.014	Beta
Myocardial infarction	0.025	0.075	Beta
Congestive heart failure	0.023	0.072	Beta
Stroke	0.018	0.064	Beta
Amputation	0.004	0.030	Beta
Blindness	0.022	0.071	Beta

End-stage renal disease	0.010	0.048	Beta
Complication costs			
No complications	465	0.00	Gamma
IHD – Non fatal	3,346	669.20	Gamma
IHD – Maintenance	1,105	221.00	Gamma
MI – Fatal	1,695	339.00	Gamma
MI – Non fatal	6,451	1290.20	Gamma
MI – Maintenance	1,062	212.40	Gamma
Stroke – Fatal	4977	995.40	Gamma
Stroke – Non fatal	3946	789.20	Gamma
Stroke – Maintenance	746	149.20	Gamma
CHF – Fatal	3731	746.20	Gamma
CHF – Non fatal	3731	746.20	Gamma
CHF – Maintenance	1308	261.60	Gamma
Amputation – Fatal	12847	2569.40	Gamma
Amputation – Non fatal	12847	2569.40	Gamma
Amputation – Maintenance	742	148.40	Gamma
Blindness – Fatal	0	0.00	Gamma
Blindness – Non fatal	0	0.00	Gamma
Blindness – Maintenance	714	142.80	Gamma
ESRD – Fatal	35715	7143.00	Gamma
ESRD – Non fatal	35715	7143.00	Gamma
ESRD – Maintenance	35631	7126.20	Gamma
Symptomatic hypoglycaemia	45	9.00	Gamma
Severe hypoglycaemia	380	76	Gamma

Utilities			
IHD	0.0900	0.0180	Beta
MI	0.0550	0.0110	Beta
CHF	0.1080	0.0216	Beta
Stroke	0.1640	0.0328	Beta
Amputation	0.2800	0.0560	Beta
Blindness	0.0740	0.0148	Beta
ESRD	0.2630	0.0526	Beta
BMI (unit decrease)	0.0061	0.0012	Beta
BMI (unit increase)	0.0061	0.0012	Beta
UTI disutility	0.0028	0.0006	Beta
GI disutility	0.0028	0.0006	Beta
Dapagliflozin treatment effects			
HbA1c (%)	-0.854	0.184	Normal
SBP (mmHg)	-3.130	4.328	Normal
Weight (kg)	-2.201	0.875	Normal
Annual no. symptomatic hypoglyceaemia	0.202	0.054	Normal
Probability of severe hypoglycaemia	0.040	0.020	Beta
Probability of UTI	0.119	0.032	Beta
Probability of GI	0.040	0.020	Beta
DPP4-is treatment effects			
HbA1c (%)	-0.793	0.064	Normal
SBP (mmHg)	1.848	5.171	Normal
Weight (kg)	0.120	0.332	Normal
Annual no. symptomatic hypoglyceaemia	0.181	0.017	Normal

Probability of severe hypoglycaemia	0.034	0.0181	Beta
Probability of UTI	0.021	0.014	Beta
Probability of GI	0.056	0.030	Beta
Empagliflozin 10mg treatment effects			
HbA1c (%)	-0.849	0.188	Normal
SBP (mmHg)	-3.304	4.088	Normal
Weight (kg)	-2.103	0.740	Normal
Annual no. symptomatic hypoglyceaemia	0.148	0.071	Normal
Probability of severe hypoglycaemia	0.040	0.020	Beta
Probability of UTI	0.119	0.032	Beta
Probability of GI	0.040	0.020	Beta
Empagliflozin 25mg treatment effects			
HbA1c (%)	-0.849	0.189	Normal
SBP (mmHg)	-3.191	4.117	Normal
Weight (kg)	-1.998	0.746	Normal
Annual no. symptomatic hypoglyceaemia	0.131	0.071	Normal
Probability of severe hypoglycaemia	0.040	0.020	Beta
Probability of UTI	0.119	0.032	Beta
Probability of GI	0.040	0.020	Beta
Cangliflozin 100mg treatment effects			
HbA1c (%)	-0.867	0.129	Normal
SBP (mmHg)	-4.823	0.031	Normal
Weight (kg)	-1.778	0.835	Normal
Annual no. symptomatic hypoglyceaemia	0.208	0.071	Normal
Probability of severe hypoglycaemia	0.040	0.020	Beta

Probability of UTI	0.119	0.032	Beta
Probability of GI	0.040	0.020	Beta
Cangliflozin 300mg treatment effects			
HbA1c (%)	-1.095	0.105	Normal
SBP (mmHg)	-4.162	3.163	Normal
Weight (kg)	-2.059	0.669	Normal
Annual no. symptomatic hypoglyceaemia	0.208	0.071	Normal
Probability of severe hypoglycaemia	0.040	0.020	Beta
Probability of UTI	0.119	0.032	Beta
Probability of GI	0.040	0.020	Beta

BMI: body mass index; CHF: congestive heart failure; DPP4-i: dipeptidyl peptidase 4 inhibitor; ESRD: end stage renal disease; GI: genital infection; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; hypo: hypoglycaemia; IHD: ischaemic heart disease; MET: metformin; MI: myocardial infarction; n/a: not available; NMA: network meta-analysis; SBP: systolic blood pressure; SU: sulphonylurea; sympt: symptomatic; TC: total cholesterol; TZD: thiazolidinedione; UTI: urinary tract infection.

5.9.1 Summary of assumptions used

- Long-term CV outcomes studies are now available for empagliflozin (EMPA-REG), saxagliptin (SAVOR); and sitagliptin (TECOS); however the results of these studies have not yet been incorporated into economic models for type 2 diabetes patients. Instead, it is assumed that valid lifetime predictions of events can be made by using the UKPDS 68 risk equations (Clarke 2004). The UKPDS is widely considered to be the gold standard in long-term diabetes trials and contains the most relevant risk data to use to date.
- Several assumptions were made regarding extrapolation of treatment effects on body weight. For the current comparison of dapagliflozin vs. DPP4-is as add-on to MET plus SU progression in weight over the first year was derived from the treatment effect recorded for each therapy from the NMA performed for triple therapy (see Table 38). In the dapagliflozin cohort patient weight was assumed to converge back in year 2. At this point in the model it is assumed that patients will regain all the weight back to the baseline trajectory in a linear manner over the course of one year. The approach described here for the weight trajectory of dapagliflozin patients is considered highly conservative as the weight loss is implemented for a shorter time period than that observed in the clinical trial programme.
- Treatment effects on SBP were applied during the first year. After year 1, the model assumes that patient's progress according to the UKPDS 68 panel regression throughout the rest of the modelled time horizon. This means that the SBP difference established at commencement of therapy is maintained over time. This could be to the benefit of dapagliflozin, which has a more favourable effect on SBP following treatment. The comparative long term effects of these treatments on SBP are yet to be established.
- As data relating to certain modifiable risk factors (i.e. lipids) were not available from the NMA, these were set as equal between the treatments in the model.
- Disutilities within the model are treated additively. This assumption is generally appropriate considering the data sources used to inform the disutility values.
- The model includes a large selection of diabetes-related events however, due to a lack of evidence and appropriate data, may not include all complication outcomes that are influenced by the incidence of type 2 diabetes. As the model includes the most common and most impactful complications, this is unlikely to alter evaluation conclusions.

5.10 *Base-case results*

The base case results for dapagliflozin as an add-on to MET plus SU compared to DPP4-is estimated that treatment initiated with dapagliflozin would be cost-saving, based on a cost difference of-£122. Additionally, it was expected that dapagliflozin would result in a QALY gain of 0.03, resulting in dominance (Table 48).

The QALY gain estimated is driven by the superior weight reduction outcome and its impact on health related quality of life for dapagliflozin relative to the DPP4-is.

When compared to other SGLT2-is, treatment with dapagliflozin was estimated to result in very similar cost and QALY outcomes resulting in a mix of dominant, cost-effective and dominated outcomes. Across the four comparisons, incremental costs ranged from -£192 to

£66, whilst incremental QALYs ranged from -0.001 to 0.006; as such these differences can be considered negliglible. Incremental costs and QALYs are driven by a combination of factors, the most significant being weight gain/loss profiles and the timing of therapy initiation.

Table 48: Summary of results from the cost-effectiveness analysis

Treatment	Costs (£)	LYG	QALYs	ICER (£/QALY)
Absolute results (per patient)				
MET + SU + Dapagliflozin	**20,417**	**11.60**	**9.62**	
MET + SU + DPP4-i	**20,529**	**11.57**	**9.58**	
Canagliflozin (100mg)	**20,351**	**11.61**	**9.62**	
Canagliflozin (300mg)	**20,610**	**11.60**	**9.61**	
Empagliflozin (10mg)	**20,456**	**11.60**	**9.61**	
Empagliflozin (25mg)	**20,410**	**11.60**	**9.61**	
Incremental results (per patient)				
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	**-112**	**0.026**	**0.032**	**Dapagliflozin Dominates**
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	**66**	**-**	**-0.001**	**Canagliflozin 100mg Dominated**
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	**-192**	**-**	**0.003**	**Dapagliflozin Dominates**

MET + SU + Dapagliflozin versus Empagliflozin (10mg)	**-38**	**0.000**	**0.005**	**Dapagliflozin** **Dominates**
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	**8**	**0.000**	**0.006**	**£1,354** **Cost-effective**
LYG, life year gained; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio				

Clinical outcomes from the model

5.10.1 Summary of clinical outcomes from the model

Lifetime clinical outcomes associated with the comparison of dapagliflozin and DPP4-i as an add-on to MET + SU are presented in Table 49. Treatment with dapagliflozin is expected to result in a reduction in the number of clinical complications as a result of a favourable clinical risk factor profile.

Table 49: Lifetime predicted cumulative number of events per 1,000 patient: MET + SU + dapagliflozin vs MET + SU + DPP4-i

Variable	DPP4-i		Empagliflozin 10mg		Empagliflozin 25mg		Canagliflozin 100mg		Canagliflozin 300mg		Dapagliflozin	
	Non-Fatal	*Fatal*	*Non-Fatal*	*Fatal*	*Non-Fatal*	*Fatal*	*Non-Fatal*	*Fatal*	*Non-Fatal*	*Fatal*	*Non-Fatal*	*Fatal*
Macrovascular events												
IHD	**84.1**	**0.0**	**83.4**	**0.0**	**83.4**	**0.0**	**83.1**	**0.0**	**83.2**	**0.0**	**83.4**	**0.0**
MI	**108.6**	**145.4**	**107.2**	**144.3**	**107.2**	**144.3**	**106.8**	**143.9**	**107.2**	**143.5**	**107.2**	**144.3**
CHF	**78.4**	**8.6**	**77.7**	**8.5**	**77.7**	**8.5**	**77.5**	**8.5**	**77.3**	**8.4**	**77.7**	**8.5**
Stroke	**64.6**	**18.8**	**62.8**	**18.5**	**62.8**	**18.5**	**62.3**	**18.4**	**62.5**	**18.3**	**62.9**	**18.5**
Microvascular events												
Blindness	**47.1**	**0.0**	**47.1**	**0.0**	**47.1**	**0.0**	**47.1**	**0.0**	**46.8**	**0.0**	**47.1**	**0.0**
Nephropathy	**22.9**	**2.5**	**22.1**	**2.5**	**22.1**	**2.5**	**21.9**	**2.4**	**22.1**	**2.4**	**22.1**	**2.5**
Amputation	**28.7**	**3.3**	**28.3**	**3.3**	**28.3**	**3.3**	**28.1**	**3.3**	**27.7**	**3.2**	**28.3**	**3.3**
Fatal Adverse events												
Macrovascular		**172.8**		**171.3**		**171.4**		**170.9**		**170.2**		**171.3**
Microvascular		**5.8**		**5.8**		**5.8**		**5.7**		**5.7**		**5.8**
Other		**821.4**		**822.9**		**822.9**		**823.4**		**824.1**		**822.9**

Abbreviations: CHF, congestive heart failure; DPP4, dipeptidyl peptidase 4 inhibitor; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; sympt, symptomatic; UTI, urinary tract infection.

5.10.2 state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable.

5.10.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

For each simulated patient within a cohort, after every cycle, the model verifies whether micro-vascular or macro-vascular events, hypoglycaemic events or other AEs have occurred, and notes whether BMI changed over the cycle period. The appropriate utility decrements are then applied. The simulation continues until the end of the time horizon or until the subject dies. Once all individuals have been simulated summary statistics of QALYs over time are calculated for that particular cohort. Utilities are applied additively and baseline quality of life is estimated from an age-adjusted source.

5.10.4 Life years and QALYs accrued for each clinical outcome

The model is not set up to report life years and QALYs accrued for individual clinical outcomes, therefore they are not presented here.

Disaggregated results of the base case incremental cost effectiveness analysis

The model is not set up to report disaggregated incremental QALYs by health state; therefore they are not presented here.

Per patient costs by category for the dapagliflozin versus DPP4-i comparison are presented below (Table 50).

Table 50: Lifetime discounted costs per patient cohort: MET + SU + dapagliflozin vs MET + SU + DPP4-i (£)

Variable	DPP4-i	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin
Macrovascular						
IHD	**1,849**	**1,843**	**1,843**	**1,840**	**1,844**	**1,843**
MI	**1,511**	**1,489**	**1,490**	**1,483**	**1,490**	**1,490**
CHF	**923**	**914**	**914**	**911**	**912**	**914**
Stroke	**619**	**600**	**601**	**595**	**599**	**601**
Microvascular						
Blindness	**403**	**404**	**404**	**404**	**403**	**404**
Nephropathy	**6,167**	**5,990**	**5,993**	**5,942**	**5,983**	**5,995**
Amputation	**376**	**367**	**367**	**365**	**361**	**367**
Hypoglycaemia	**40**	**40**	**39**	**45**	**66**	**45**
Other						
Adverse Events	**8**	**16**	**16**	**16**	**22**	**16**
Treatment	**3,253**	**3,398**	**3,349**	**3,352**	**3,535**	**3,349**
Other Costs (Renal monitoring and no complication background cost)	**5,382**	**5,394**	**5,394**	**5,398**	**5,396**	**5,394**
Total	20,529	20,456	20,410	20,351	20,610	20,417

Abbreviations: AE. Adverse event; CHF, congestive heart failure; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; SU, sulphonylurea.

5.11 *Sensitivity analyses*

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results

The scatterplot and cost-effectiveness acceptability curves from the PSA are presented below. As is to be expected when comparative therapies achieve similar degrees of efficacy, the scatter plots appear to vary around incremental costs of £0 and incremental and QALYs of 0, with the probability of cost-effectiveness within the range of 40-60% at all thresholds across all comparisons. At a willingness to pay of £20,000 the probability that dapagliflozin is cost-effective compared to DPP4-is in triple therapy is 56.98%. When compared to the other SGLT2s, this probability ranged from 49.12-51.32%.

Figure 24: Scatterplot for incremental costs and QALYs (versus DPP4-i)

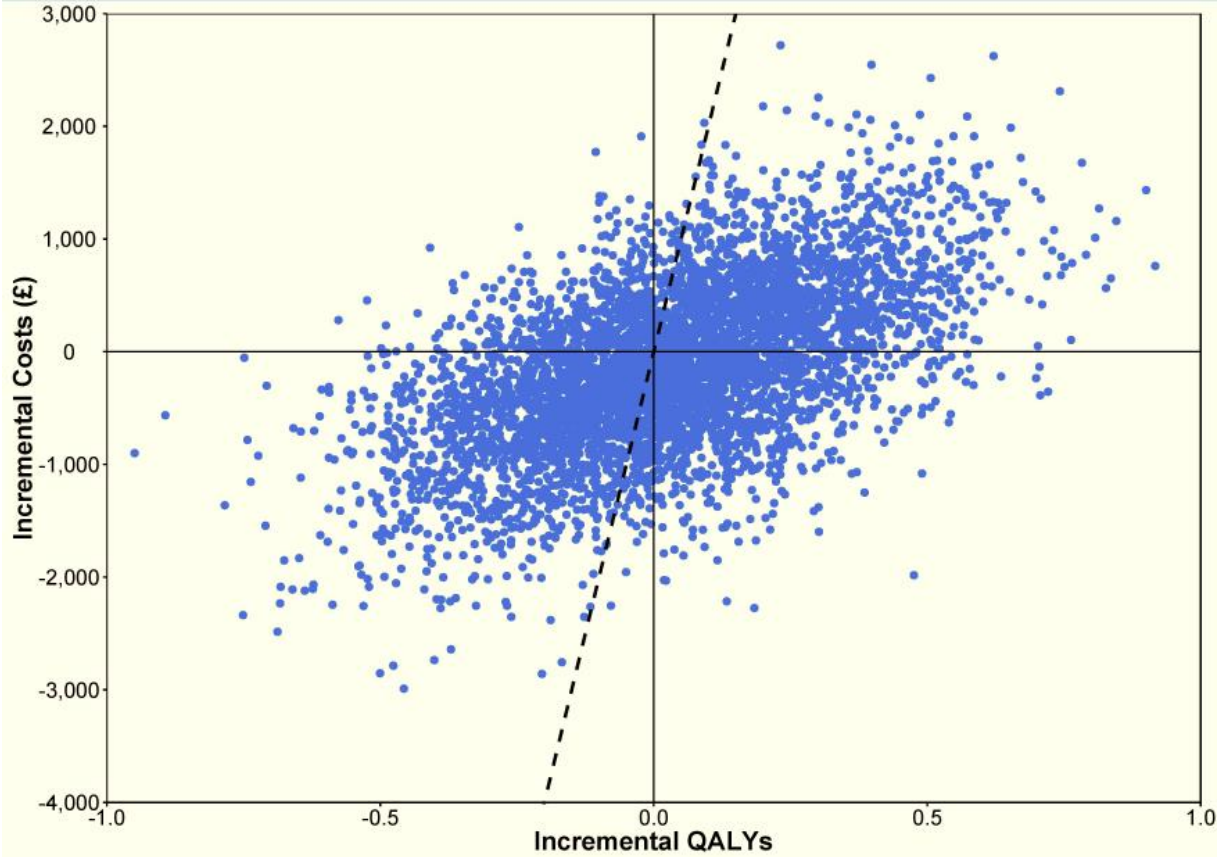


Figure 25: Scatterplot for incremental costs and QALYs (versus Empagliflozin 10mg)

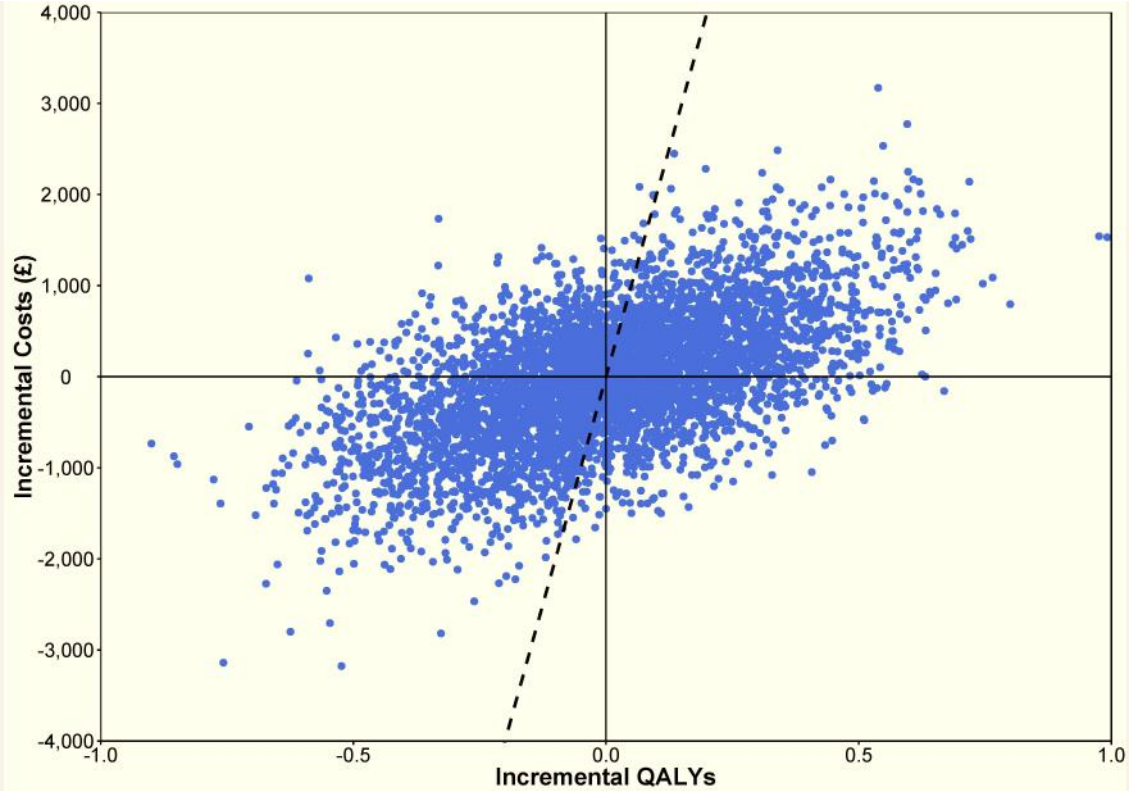


Figure 26: Scatterplot for incremental costs and QALYs (versus Empagliflozin 25mg)

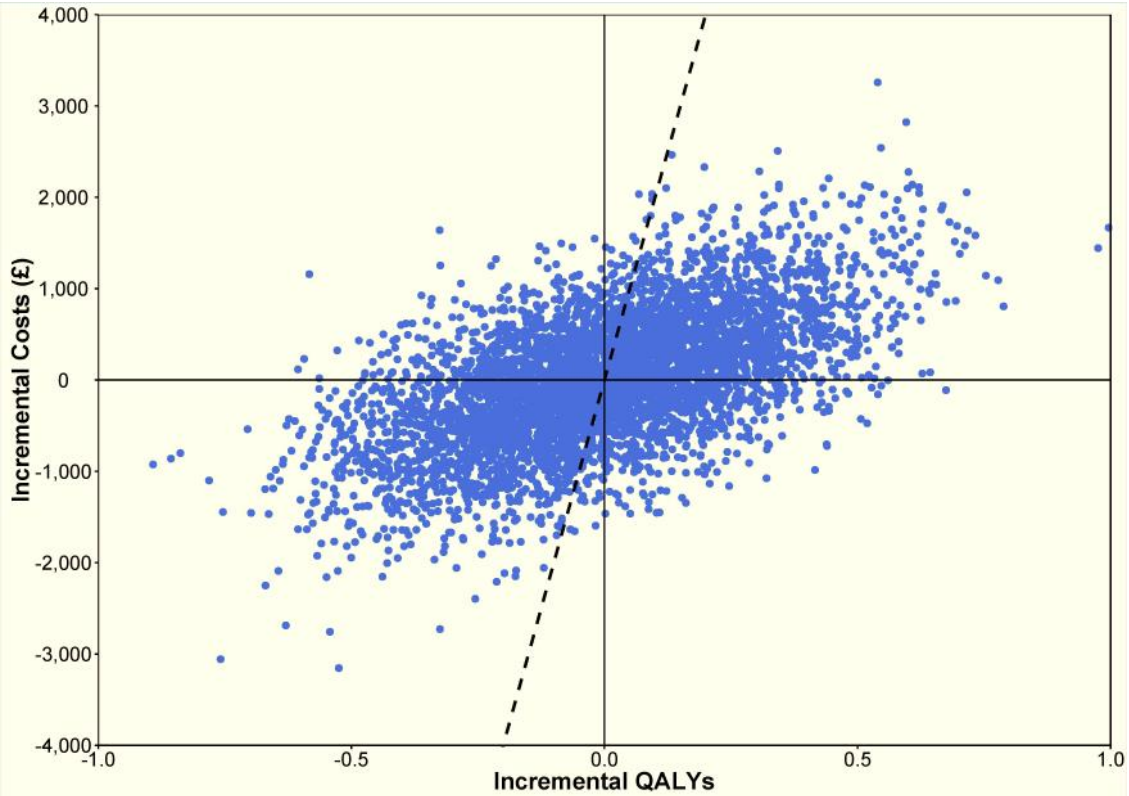


Figure 27: Scatterplot for incremental costs and QALYs (versus Canagliflozin 100mg)

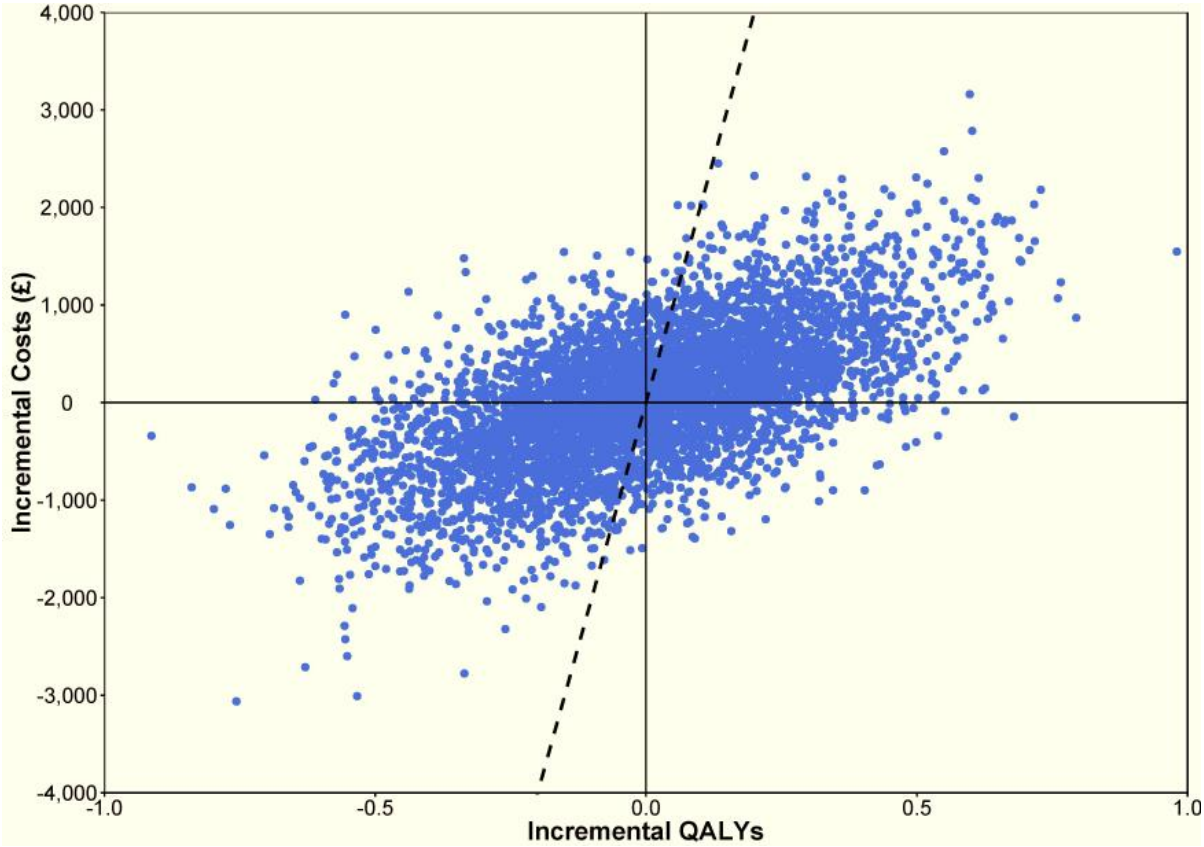


Figure 28: Scatterplot for incremental costs and QALYs (versus Canagliflozin 300mg)

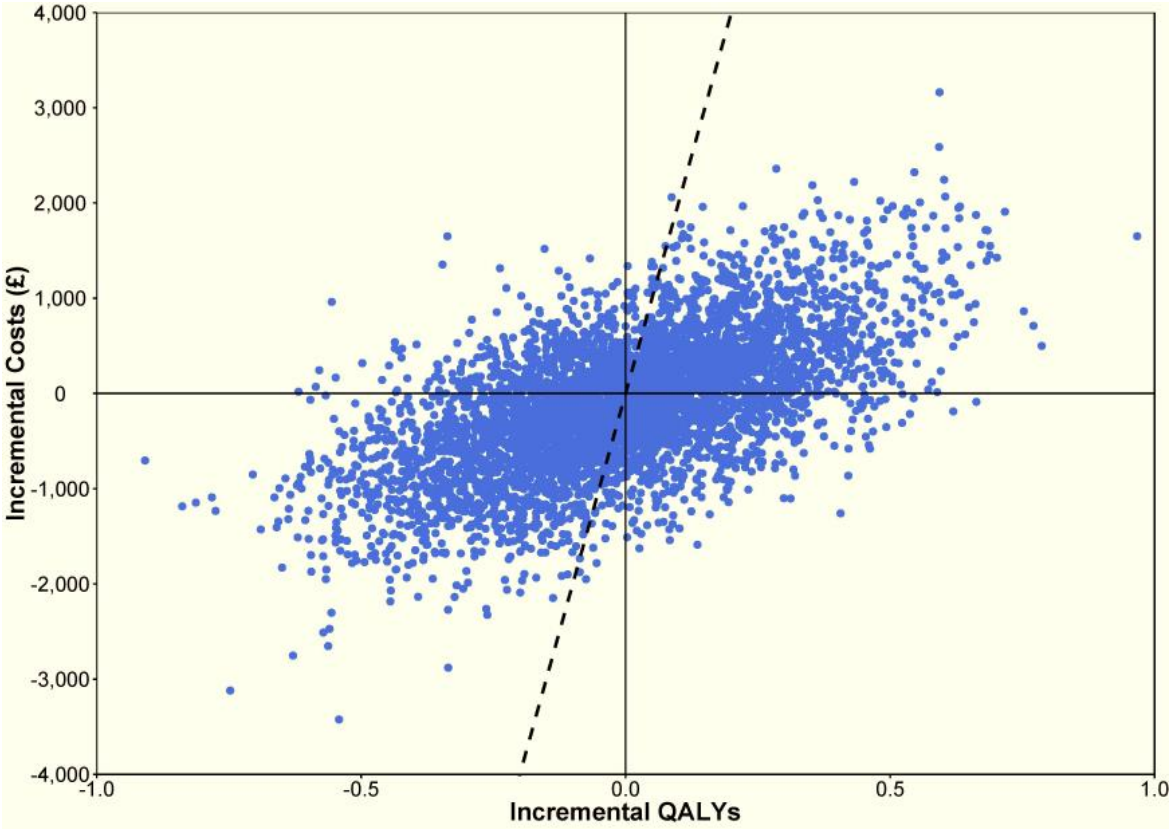


Figure 29: Cost-effectiveness acceptability curve for dapagliflozin vs DPP4-i in triple therapy

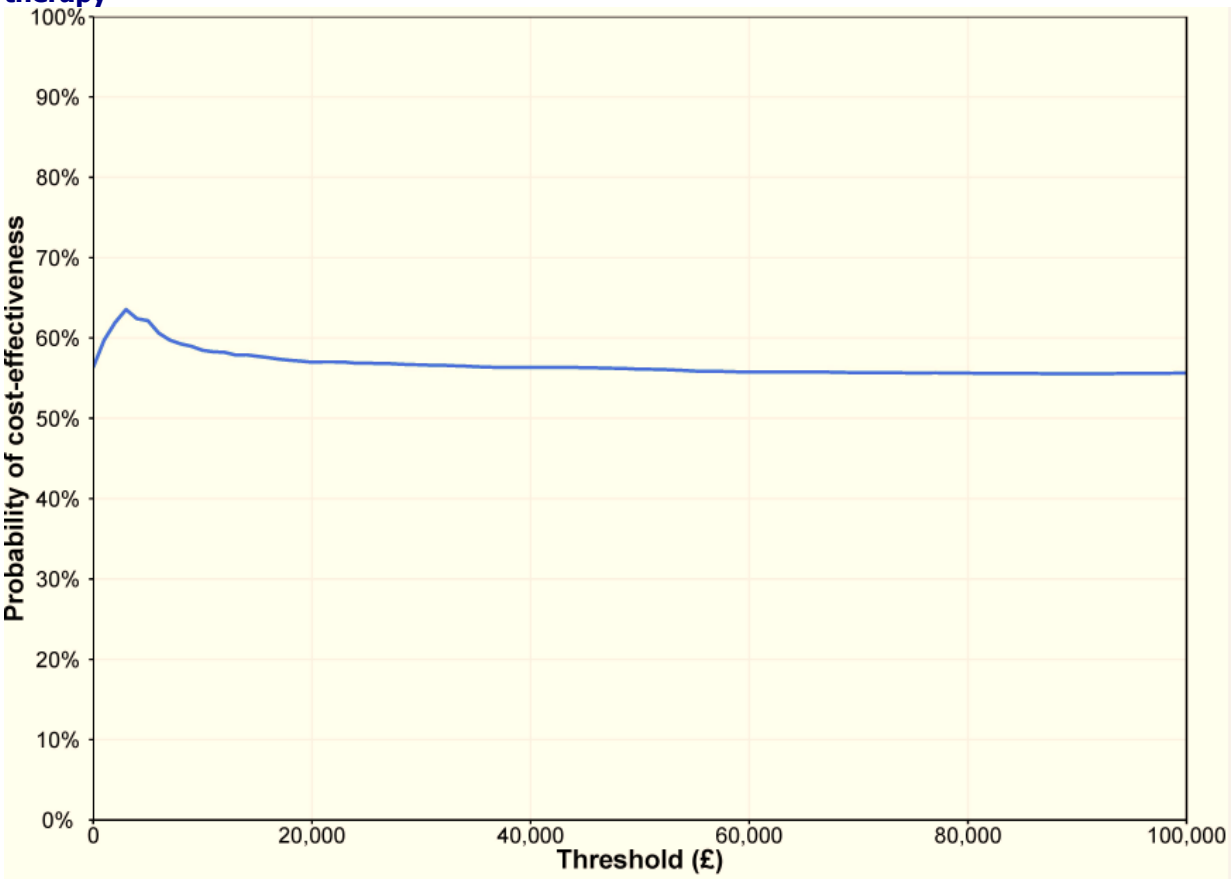


Figure 30: Cost-effectiveness acceptability curve for dapagliflozin vs Empagliflozin 10mg in triple therapy

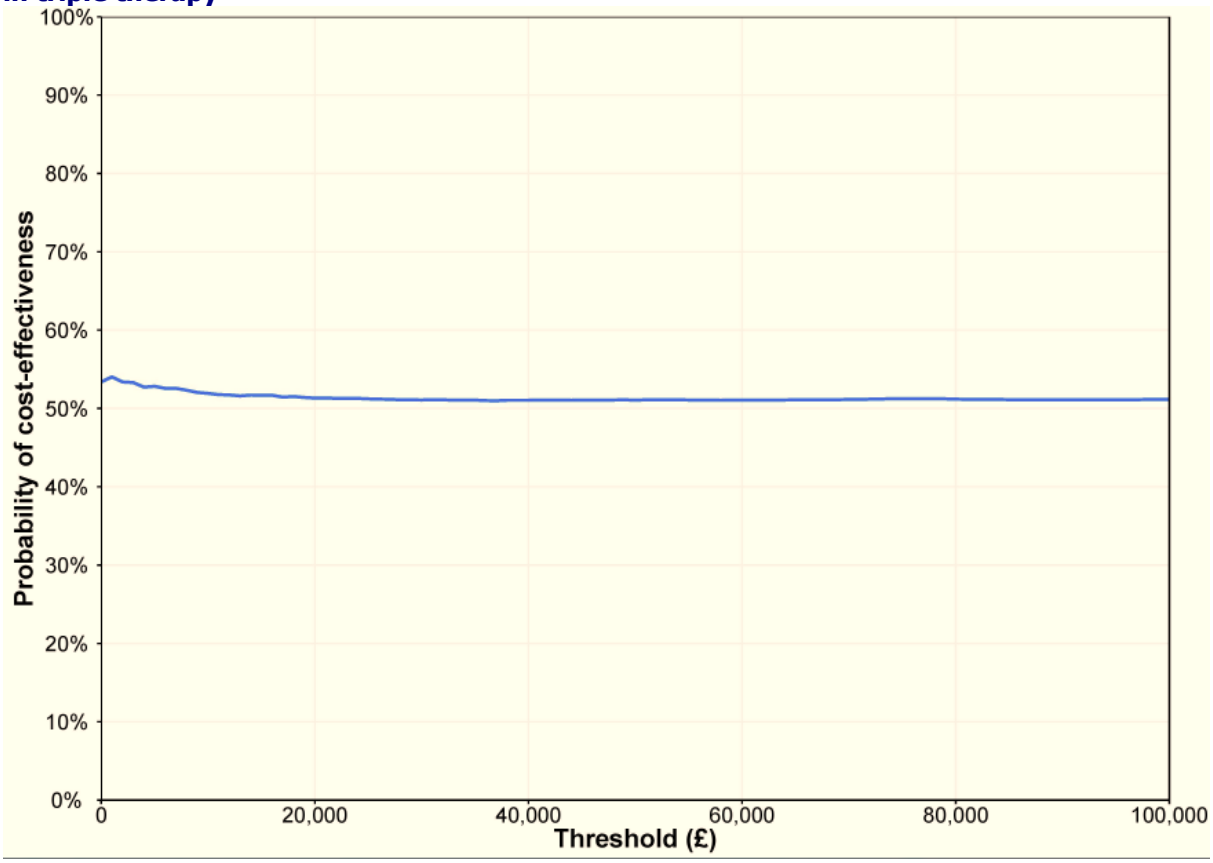


Figure 31: Cost-effectiveness acceptability curve for dapagliflozin vs Empagliflozin 25mg in triple therapy

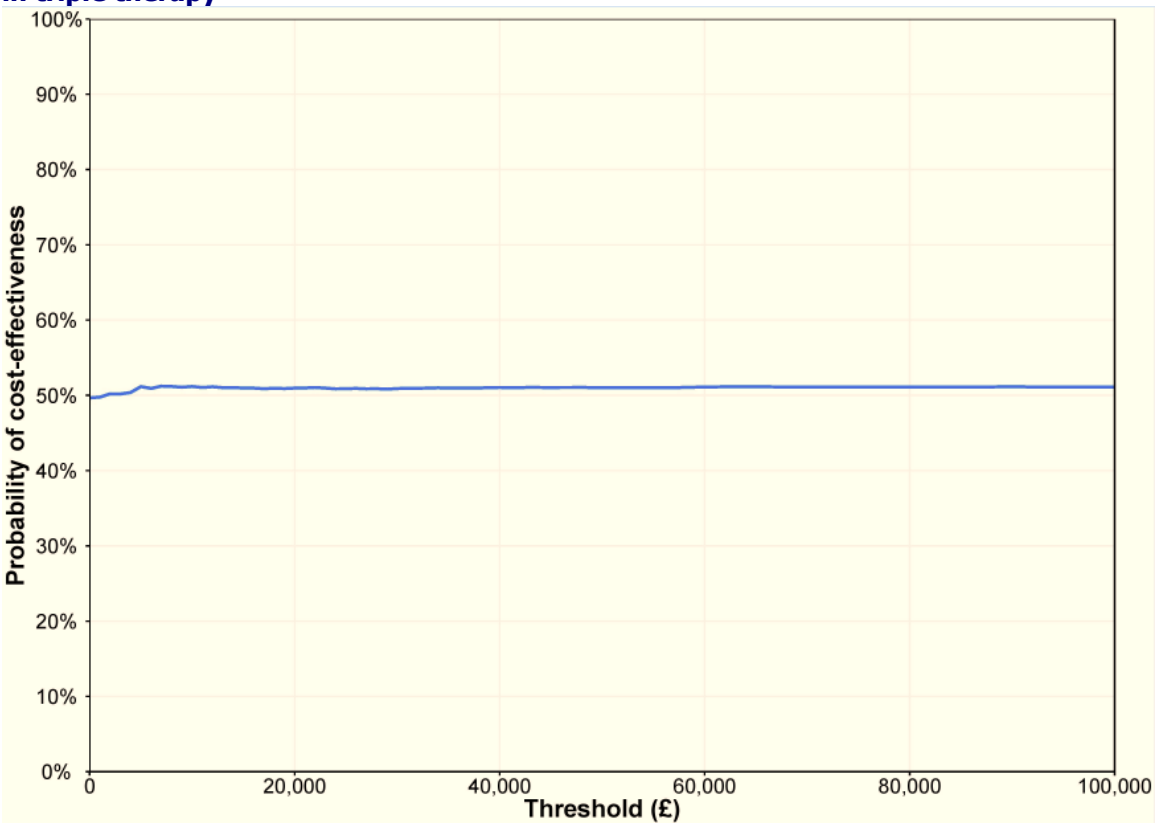


Figure 32: Cost-effectiveness acceptability curve for dapagliflozin vs Canagliflozin 100mg in triple therapy

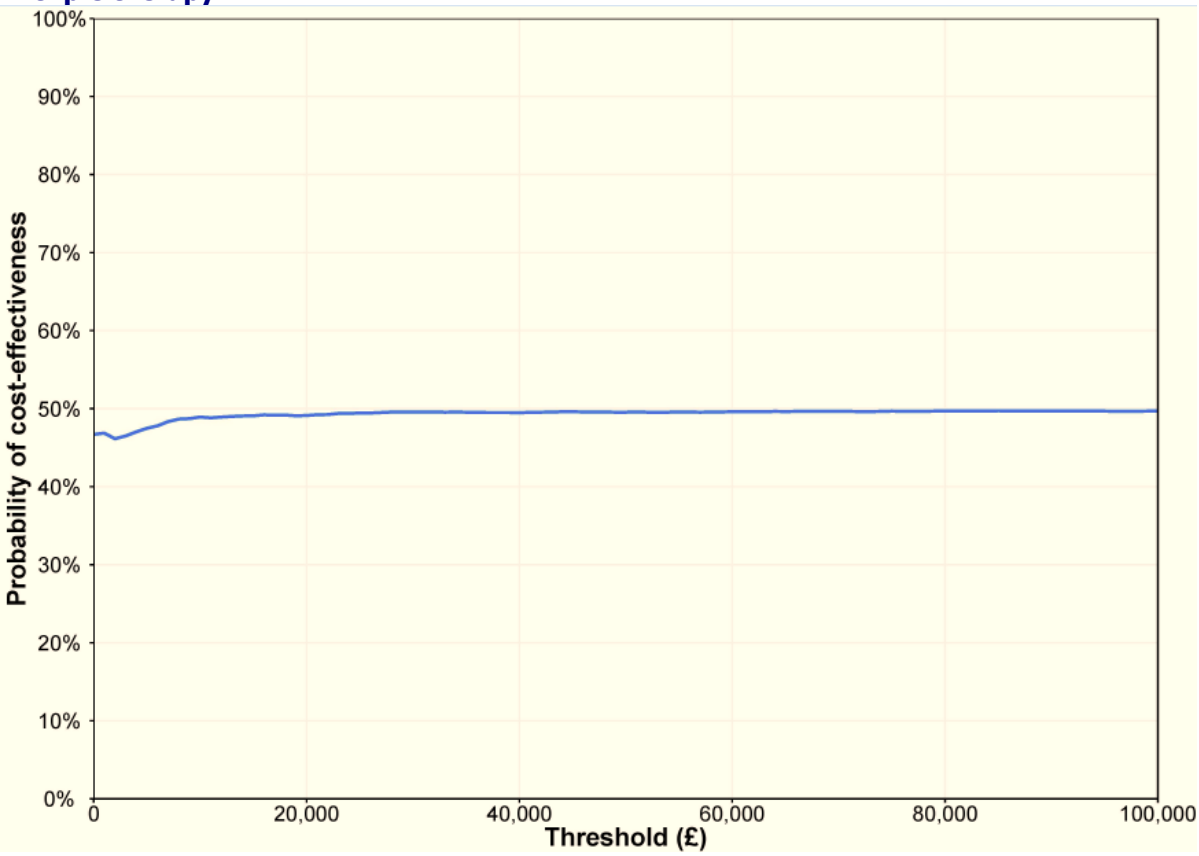
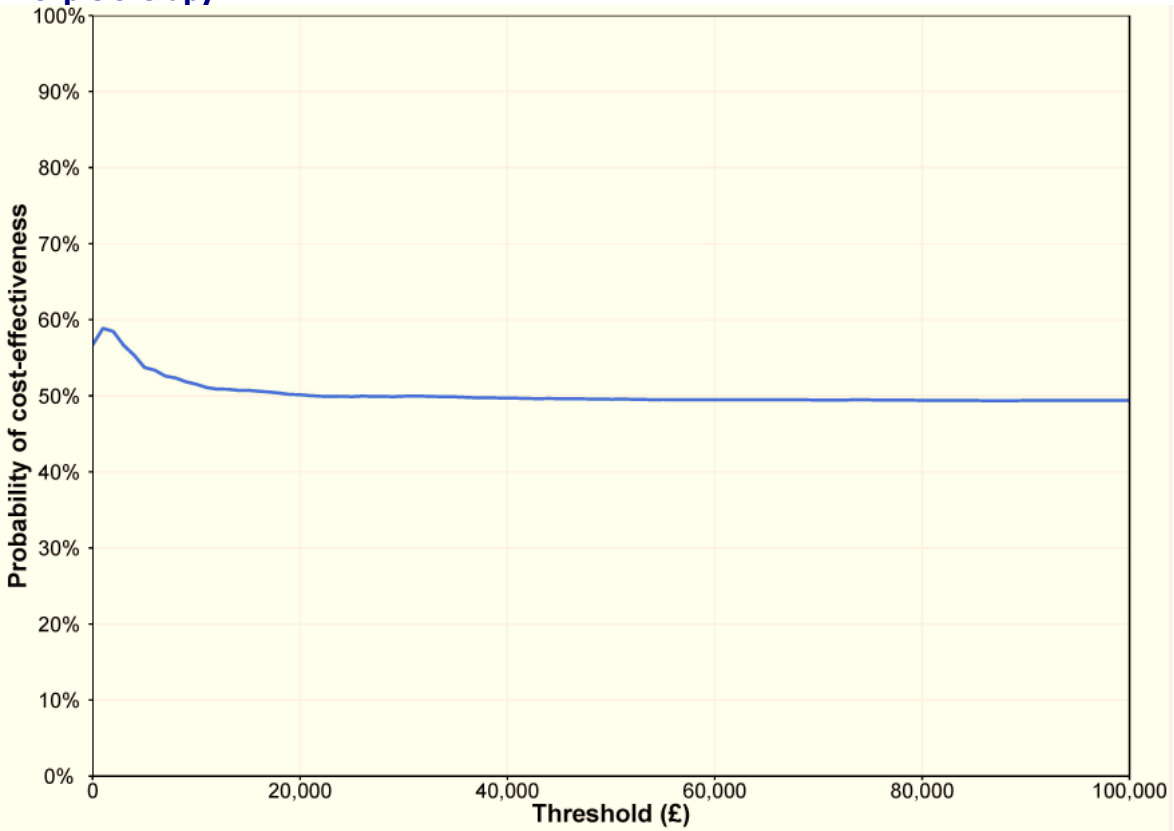


Figure 33: Cost-effectiveness acceptability curve for dapagliflozin vs Canagliflozin 300mg in triple therapy



Scenario analysis

The scenario analysis demonstrated that cost-effectiveness outcomes were relatively insensitive to alternative data assumptions (Table 51). The majority of scenarios investigated resulted in no change in the conclusion that dapagliflozin was dominant compared to the DPP4-is, with exceptions including alternative sources for hbA1c thresholds, baseline hbA1c, the use of UKPDS 82 equations and the inclusion of DPP4 costs in the second and third therapy lines. When these alternative data sources were utilised, ICER estimates increased to a maximum of £13,514, remaining cost-effective at a £20,000/QALY threshold. Of further note, dapagliflozin as a triple therapy regimen with MET + SU remained the dominant treatment option when the treatment effect associated with the full network of the NMA was utilised.

Table 51: Summary of scenario analyses: MET + SU + dapagliflozin vs MET + SU + DPP4-i

Scenario	Base case	Alternative value	Inc. Cost	Inc. QALYs	ICER
Baseline patient characteristics	Taken from Matthaei 2015	Patient population based on THIN database (NG28)	-£51	0.039	Dapagliflozin Dominates
		Patient population based on NMA full network	-£261	0.089	Dapagliflozin Dominates
		Patient population based on NMA restricted network	-£108	0.028	Dapagliflozin Dominates
Baseline HbA1c	Taken from Matthaei 2015	HbA1c baseline value to 7.5% (according to NG28)	£240	0.02	£12,256 Cost-effective
		HbA1c baseline value to 7.9% (according to THIN database) + weight maintenance dapagliflozin 2 years	-£51	0.029	Dapagliflozin Dominates
		HbA1c baseline value to 8.24% (according to MET + SU NMA 2016)	-£112	0.032	Dapagliflozin Dominates
HbA1c threshold for treatment switch	7.5% (59mmol/mol)	HbA1c threshold 1st-2nd line: 7.5% and 2nd-3rd line: 8.0%	-£104	0.032	Dapagliflozin Dominates
		HbA1c threshold 1st-2nd line: 8.0% and 2nd-3rd line: 9.0%	£7	0.028	£246 Cost-effective
Treatment effect*	NMA restricted	NMA full network	-£75	0.027	Dapagliflozin Dominates
Health care Cost	NG28	UKPDS 84	-£142	0.032	Dapagliflozin Dominates
		Include BMI costs according to UK Counterweight Project Team data (2008)	-£122	0.032	Dapagliflozin Dominates
Disutilities weight gain	Disutilities weight gain 0.061 per BMI point (Bagust)	Disutilities weight gain 0.014 per BMI point (1)	-£112	0.037	Dapagliflozin Dominates
		Disutilities weight gain 0.0038 per BMI point (2)	-£112	0.030	Dapagliflozin Dominates

Scenario	Base case	Alternative value	Inc. Cost	Inc. QALYs	ICER
Disutilities for AE		No disutilities for AE	-£112	0.032	Dapagliflozin Dominates
Risk equation	Risk equations UKPDS 68	Risk equations UKPDS 82	£71	0.018	£3,914 Cost-effective
Discontinuation of treatment	RCT	No discontinuation	-£104	0.034	Dapagliflozin Dominates
		Discontinuation of DPP4 set equal to dapagliflozin	-£107	0.033	Dapagliflozin Dominates
Prior CV history	THIN NG28	No prior CV history (values set to 0)	-£111	0.031	Dapagliflozin Dominates
Drug costs in 2nd and 3rd line	Costs for insulin	Costs for MET, SU and DPP4/Dapa added to insulin costs	£431	0.032	£13,514 Cost-effective
Disutilities for AE	Based on Barry 2007	Lower limit of -0.0104 for GTI and UTI	-£112	0.031	Dapagliflozin Dominates
Disutilities for AE	Based on Barry 2008	Upper limit -0.000657 for GTI and UTI	-£112	0.032	Dapagliflozin Dominates
Weight	Weight effect lost by end of second year	Weight effect maintained	-£115	0.035	Dapagliflozin Dominates

GTI, genital tract infection

Univariate sensitivity analysis

The univariate analyses have been conducted varying key parameters by arbitrary amounts to assess their impact on modelled outcomes. Incremental costs, incremental QALYs and ICER values are reported as outcomes of interest (Figure 34, Figure 35, Figure 36). The results of the univariate sensitivity analysis demonstrate that cost-effectiveness estimates are most sensitive to assumptions around smoking status, baseline hbA1c and age. Further, when considering either incremental costs or incremental QALYs alone, baseline SBP, baseline weight, hbA1c treatment effect and time horizon were additionally predicted to be influential.

Care should be taken when interpretting the results of the univariate sensitivity analysis. As the difference in incremental costs and incremental QALYs is very small, resultant ICER

estimates have a tendency to fluctuate significantly. However, the analysis presented here demonstrates that it would take significantly different data assumptions to alter the conclusions of the base case analysis of dapagliflozin versus DPP4-is.

Figure 34: Univariate sensitivity analyses: Incremental cost tornado plot: MET + SU + dapagliflozin vs MET + SU + DPP4-i.

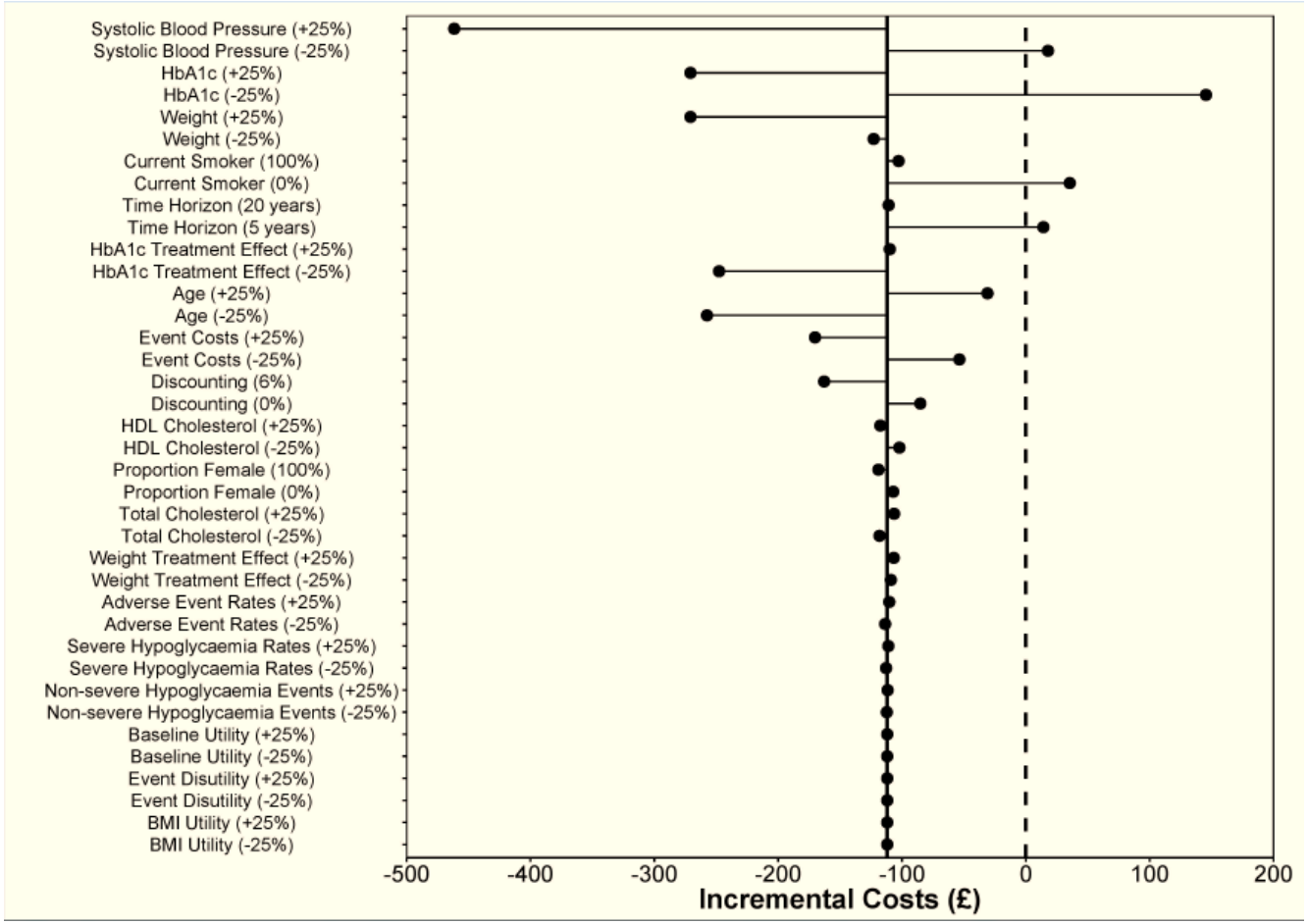


Figure 35: Univariate sensitivity analyses: Incremental QALY tornado plot: MET + SU + dapagliflozin vs MET + SU + DPP4-i.

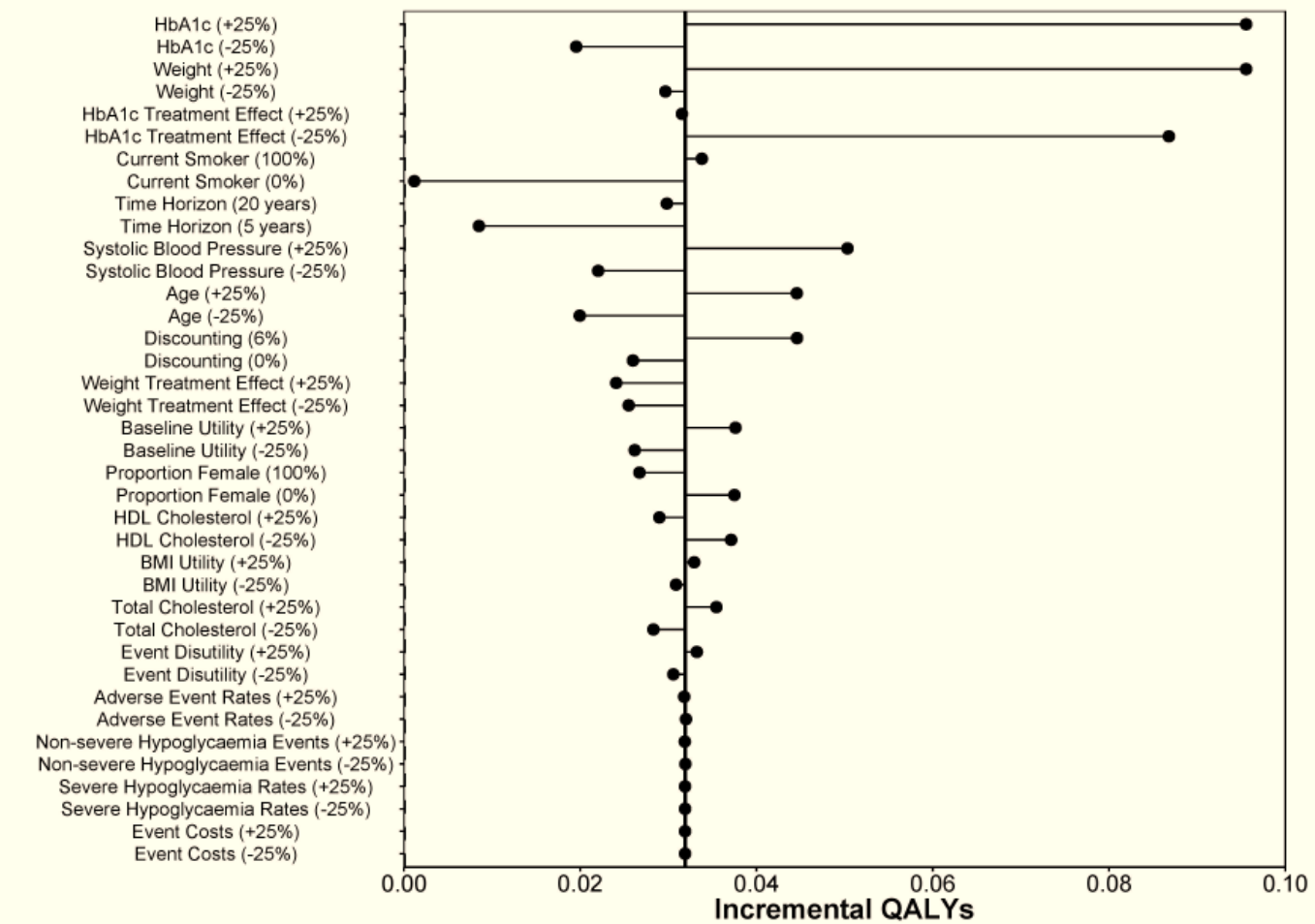
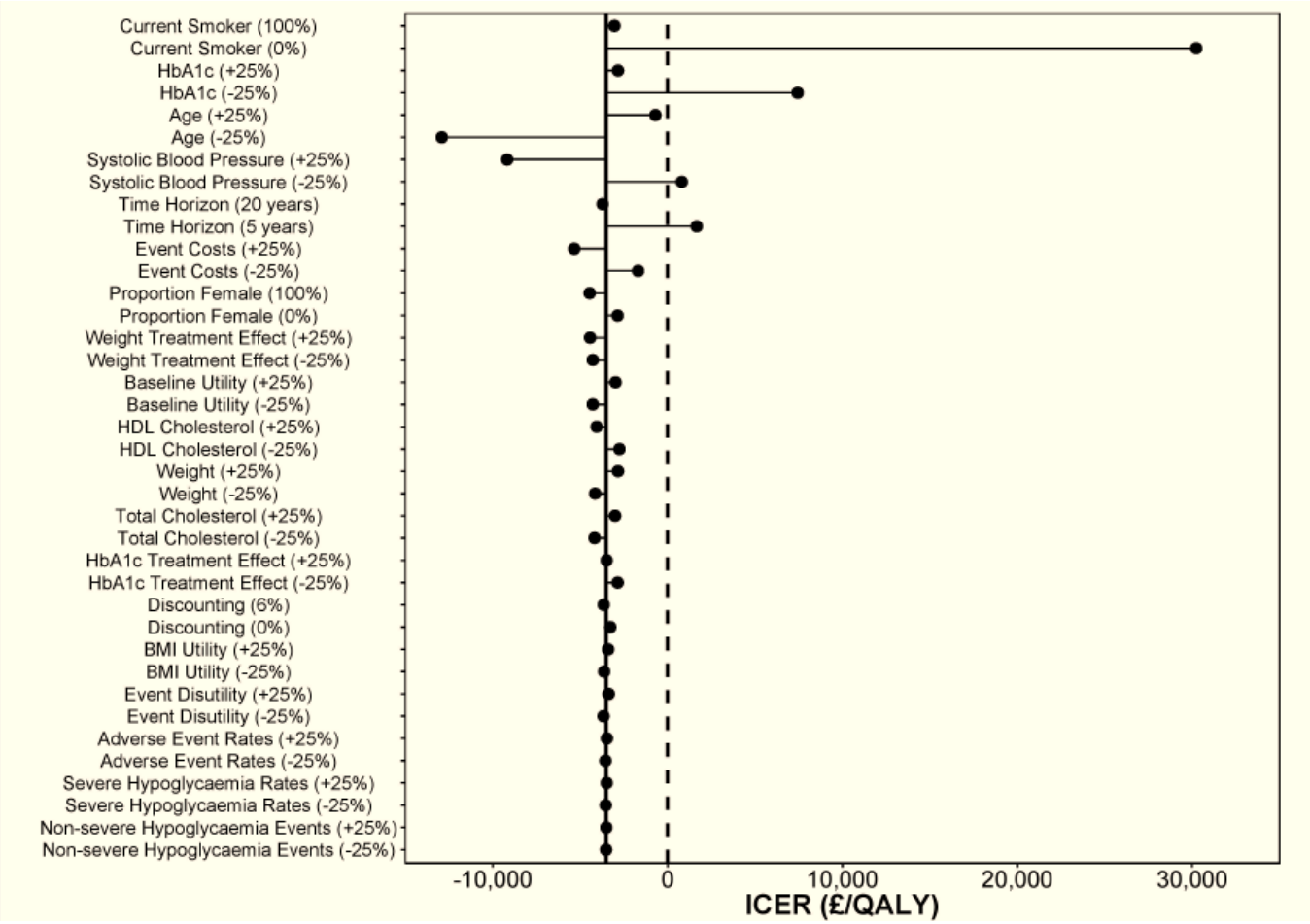


Figure 36: Univariate sensitivity analyses: Incremental ICER tornado plot: MET + SU + dapagliflozin vs MET + SU + DPP4-i.



Summary of sensitivity analyses results

5.11.1 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results

See deterministic sensitivity analysis section above.

5.12 *Subgroup analysis*

No further exploration of sub-groups is considered in the cost effectiveness assessment.

5.13 *Validation*

See Section 5.5

Validation of de novo cost-effectiveness analysis

5.13.1 When describing the methods used to validate and quality assure the model, provide:

- ***the rationale for using the chosen methods***
- ***references to the results produced and cross-references to the evidence identified in the clinical evidence, measurement and valuation of health effects, and cost and healthcare resource sections***

5.14 *Interpretation and conclusions of economic evidence*

5.14.1 Comparison with published economic literature

The systematic review conducted for this submission identified two published studies for the cost-effectiveness of dapagliflozin as included in the SMC assessment (see section 5.1). The methodology for the economic analysis used in this submission is similar as that used in these two publications. The dapagliflozin models do not deviate from the relatively standardised approach to diabetes modelling using a similar structure as other models, making similar use of the UKPDS dataset. The dapagliflozin model is a modified version of a validated economic model that has been used in previous economic evaluations of drug interventions for type 2 diabetes mellitus. As in other economic analyses, important drivers of outcome in the dapagliflozin analysis are the improvement in HbA1c and other modifiable risk factors such as SBP. Diabetes models tend also to take account of the impact of weight change on HRQoL outcomes. This is of particular importance in the dapagliflozin model as a driver of cost-effectiveness due to the significant weight loss benefits associated with the drug relative to DPP4-is.

5.14.2 Relevance of the economic evaluation to all patient groups

The dapagliflozin economic analysis can be considered relevant for all type 2 diabetes patients who have failed to achieve adequate glycaemic control on add-on to MET + SU.

5.14.3 Strengths and weaknesses of the evaluation

Strengths

- The dapagliflozin economic analyses use a validated and previously published economic modelling structure, with long term outcomes driven by well accepted UKPDS risk equations
- Most of the data inputs are standard to other validated diabetes models used and accepted in the current NICE diabetes management guidelines (NG28)

These strengths mean that we believe the model is producing valid and robust results with the main uncertainties in key data inputs such as the relationship between BMI and utility addressed in probabilistic and scenario analysis.

Weaknesses

- As there were no comparative head to head data against relevant comparators, an indirect comparison was necessary. To be as robust as possible this was performed as a Bayesian NMA.
- The UKPDS dataset contains newly diagnosed patients and the appropriateness of using equations derived from such a patient population when modelling a treatment experienced cohort has not been evaluated
- Probabilistic sensitivity analysis undertaken with the Cardiff model does not account for parameter relationships and samples all variables independently

As with all economic evaluations in type 2 diabetes, there are some limitations in the data used to provide inputs for the model, which may lead to uncertainty, however this has been addressed through comprehensive sensitivity/scenario analysis.

5.14.4 Further analyses

Additional investigation in to the relationship between increasing/decreasing BMI and EQ-5D derived utilities could be useful to verify the results found from the TTO study.

6 Assessment of factors relevant to the NHS and other parties

- We expect the number of patients diagnosed with type 2 diabetes mellitus to rise to 3.7 million in 2020
- The usage of SGLT2-i is expected to increase up to 2020. Within the SGLT2 class, dapagliflozin as the first-to-launch in the class currently has the largest market share yet this is expected to drop between now and 2020
- Overall the annual net budget impact for dapagliflozin used on a background of MET plus SU is expected to be £1,084,462 in 2016 rising to £5,232,755 in 2020

6.1 *How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years*

We expect the number of patients diagnosed with type 2 diabetes mellitus to be 3.4 million in 2016, rising to 3.7 million in 2020. The figures have been derived from the UK population growth, estimates of the prevalence of diabetes (YHPHO 2015), and the proportion of patients prescribed oral anti-diabetic therapy and/or a GLP1 (Patient data, IMS Information Solutions UK Ltd, Dec 15) . Based on uptake figures we expect the uptake of SGLT2-is in a triple therapy treatment regimen to be 7% in 2016 (Year 1), rising to 19% in 2020 (Year 5). The uptake of dapagliflozin as an add on therapy to MET + SU is 15% in 2016 (Year 1), rising to 32% in 2020 (Year 5). The number of patients expected to be treated with dapagliflozin in this indication is 20,665 in 2016 (Year 1), rising to 99,714 in 2020 (Year 5).

6.2 *What assumption(s) were made about current treatment options and uptake of technologies?*

Estimates of the uptake of dapagliflozin are presented in Table 52. Dapagliflozin's displacement of existing therapies was derived from consultations with clinicians in both England and Wales and for simplicity we assume constant annual proportions of patient switching from the DPP4-i therapies and other SGLT2-i.

Table 52: Epidemiology analysis in England and Wales

	2016	2017	2018	2019	2020
Diabetes population in England & Wales, n	3,784,491	3,860,348	3,936,204	4,012,061	4,087,917
Type 2 diabetes population in England & Wales, n	3,406,042	3,474,313	3,542,584	3,610,855	3,679,125
Type 2 diabetes population receiving OAD/GLP1, n	3,167,619	3,231,111	3,294,603	3,358,095	3,421,587
Uptake of SGLT2, %	7.3	10.3	12.9	16.1	19.3
Potential number of SGLT2 patients, n	232,086	332,220	425,765	541,403	661,430
Proportion of patient on Forxiga, %	59	54	48	46	47
Number of patients on Forxiga, n	137,768	178,078	205,127	251,287	311,605
Proportion of patient on Forxiga add on to MET + SU, %	15	19	24	28	32
Patient on Forxiga add on to MET + SU	20,665	34,280	48,205	69,732	99,714

OAD: oral antidiabetic

6.3 *What assumption(s) were made about market share (when relevant)?*

As above, of patients receiving dapagliflozin, 15% in year 1 rising to 32% by year 5 are expected to recieved dapagliflozin in a triple regimen.

6.4 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning)*

There are no other significant costs associated with treatment with dapagliflozin in the treatment of type 2 diabetes mellitus.

6.5 *What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?*

The unit costs applied in the budget impact analysis are the same as those used in the cost utility model regarding drug costs. Details of these costs can be found in Section 5.8.

6.6 *Were there any estimates of resource savings? If so, what were they?*

There are no additional resource savings expected from using dapagliflozin in the treatment of type 2 diabetes mellitus.

6.7 *What is the estimated annual budget impact for the NHS in England and Wales?*

The estimated net annual budget impact for the NHS in England and Wales following the introduction of dapagliflozin in triple therapy is estimated to be just over £1m in the first full year following introduction, rising to £5.2m in year 5 (Table 53).

Table 53: Budget impact analysis for England and Wales

Budget Impact (£)	2016	2017	2018	2019	2020
Type 2 diabetes population receiving OAD/GLP1, n	3,167,619	3,231,111	3,294,603	3,358,095	3,421,587
Uptake of SGLT2, %	7.3	10.3	12.9	16.1	19.3
Potential number of SGLT2 patients, n	232,086	332,220	425,765	541,403	661,430
Proportion of patient on dapagliflozin, %	59	54	48	46	47
Number of patients on dapagliflozin, n	137,768	178,078	205,127	251,287	311,605
Proportion of patient on dapagliflozin add on to MET + SU, %	15	19	24	28	32
Patient on dapagliflozin add on to MET + SU, n	20,665	34,280	48,205	69,732	99,714
Cost of dapagliflozin, £	£9,856,786	£16,350,802	£22,992,576	£33,260,588	£47,561,043
Less cost of displaced medicines (DPP4), £	£8,772,324	£14,551,856	£20,462,890	£29,601,196	£42,328,289
Net cost of dapagliflozin, £	£1,084,462	£1,798,946	£2,529,686	£3,659,392	£5,232,755

OAD: oral antidiabetic

6.8 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

All the opportunities for resource savings have been identified.

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Appendices (Please see the separate appendices document)

Appendix 1: European public assessment report, SmPC/IFU, scientific discussion or drafts (Section 2.2)

Appendix 2: Search strategy for relevant studies (Section 4.1.2)

Appendix 3: Quality assessment of randomised controlled trials (RCTs) (Section 4.6)

Appendix 4: Sub-group analysis

Appendix 5: Excluded studies from the systematic review

Appendix 6: Data extractions for included studies on a background of MET + DPP4i (Section 4.10)

Appendix 7: Search strategy for indirect and mixed treatment comparisons (Section 4.10.1)

Appendix 8: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison (Section 4.10.9–10)

Appendix 9: Programming language used in the analysis (Section 4.10.13)

Appendix 10:: Search strategy for section 6.8 (Non-RCT evidence)

Appendix 11: Search strategy for adverse reactions (Section 4.12.3)

Appendix 12: Quality assessment of adverse reaction data (Section 4.12.3)

Appendix 13: Heterogeneity and inconsistency assessment results for NMA base case

Appendix 14: Sensitivity analyses for NMA base case

Appendix 15: Meta-regression for NMA base case

Appendix 16: Search strategy for cost-effectiveness studies (Section 5.1.1)

Appendix 17: Quality assessment of cost-effectiveness studies (Section 5.1.3)

Appendix 18: Search strategy for measurement and valuation of health effects (Section 5.4.3)

Appendix 19: Summary of study 4 (dapagliflozin vs glipizide as add onto metformin: 4-year data)

Appendix 20: Sub-group analyses: Triple regimen data from supportive studies

Appendix 21: Baseline THIN data used to populate economic model in the recent NICE guideline (NG28)

Appendix 22: UKPDS 82 coded equations

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Single technology appraisal

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]

Dear Zavy

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 12th April 2016 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by **5pm** on **23rd June. 2016**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

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

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

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact) [redacted] Any procedural questions should be addressed to [redacted] at TACommA@nice.org.uk

Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question:** The submission states that 62% of patients on triple therapy with metformin and a sulfonylurea have a DPP4 inhibitor as the third drug. Please state the third drug added to the metformin and sulfonylurea combination for the remaining 38% of patients, with percentages for each combination.

A2. **Priority question:** There was some gender imbalance in Matthaei with 57.4% female in the dapagliflozin arm and 44.4% in the placebo arm. Please provide weight, BMI, SBP and HbA1c changes for men and women separately for this study.

A3. **Priority question:** On page 92, the submission states that there is published evidence that the DPP4 inhibitors are non-inferior to each other. Please provide supporting references.

A4. **Priority question:** On page 57, the last paragraph mentions two RCTs, MB 102073 and BM102077. If these are published, please provide references for these trials.

A5. **Priority question:** Please explain why the following outcomes were not included in the network meta-analysis:

   a. BMI (given both the gender imbalance in study 5 and that the economic modelling requires the patient BMI)

   b. Discontinuation rates

A6. **Priority question:** Tables 26, 27, 28 and 29 provide 4 different results sets for key outcomes for the NMA (24 week results, 52 week results, "study endpoint" results and "base case" results). However, it is not clear how the "base case" values relate to the other values in the table. Furthermore, it is noted that the "study endpoint" values and the "base case" values of tables 26, 27, 28 and 29 differ, yet on page 78, the submission states that CrIs of the 52 week data provide the "…rationale to use the endpoint network as the base case" (which suggests that the "base case" values should be the same as the "study endpoint" values). Please provide a more detailed explanation of any relationship between the 4 different result sets, and please describe how the "base case" values in table 26, 27, 28 and 29 were derived.

A7. **Priority question:** The NMA results of tables 26, 27, 28 and 29 are all stated relative to dapagliflozin. Please provide the central estimates and 95% CIs for the changes from baseline for dapagliflozin for both the fixed effects model and the random effects model for the 24 week, 52 week, study endpoint and base case analyses of tables 26, 27, 28 and 29. Please then describe the methodology used to derive the values used in the economic model (table 38) for HbA1c change from baseline, weight change from baseline, SBP change from baseline and the number of symptomatic

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hypoglycaemia events. This can be supplied in Excel if this is easier. Please provide answers for both the full network and the restricted network as available.

A8. **Priority question:** Please provide a more detailed explanation of the sources and arithmetic underlying the treatment specific estimates of UTI rates, GTI rates, discontinuation rates and probabilities of hypoglycaemic events being severe within table 38.

A9. On pages 78 onwards, some NMA results are given for the expanded network and some for the restricted network. However, it is unclear from the company submission which studies were used in the different models presented. Table 8 lists 14 trials in the restricted network for the base case NMA, though one trial (NCT0159771) appears to be unpublished and was not provided. In the results for HbA1c, weight and SBP, which studies were added in the "expanded networks"?

A10. The NMAs included evidence from drug classes and individual drugs within the same network. Was any assessment undertaken to look at these separately (i.e. classes in a NMA and individual drugs in another NMA)? If so, please provide the results.

A11. The company submission does not discuss whether a sensitivity analysis was undertaken on the different elements in the NMA models, specifically whether prior distributions, link functions and priors for parameters were examined. Please describe and provide results for any sensitivity analyses undertaken for these.

A12. The company submission does not present any diagnostic plots or summary measures regarding model convergence (i.e. history plots, Brooks-Gelman-Rubin plots/statistics, Monte-Carlo error). Also, no mention is made of whether autocorrelation was assessed, or if it was a concern. Please provide more detail about whether these were undertaken and whether they were considered appropriate.

A13. Measures assessing model fit are provided for decisions regarding the use of a fixed-effect or random-effects model, however these are not provided for any other models (e.g. meta-regression or sensitivity analyses). Please provide these if available.

A14. The company submission presents a meta-regression for HbA1c only, despite noting that other factors are likely to cause heterogeneity. Were other factors included in a meta-regression analysis? If so, please provide these outcomes.

A15. The NMAs synthesize relatively sparse evidence. Were the effects of the sparse evidence base assessed and were other approaches considered to overcome any subsequent problems?

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A16. Table 19: Lui is missing from the Table, and Seino is incorrectly included. Please provide a corrected table.

A17. Table 20: Hong is missing from the Table. Please provide a corrected Table.

A18. Table 38: Monami 2008 is cited, but this has not been included in the reference list, nor in the folder of references. Please provide the correct reference for Monami 2008.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Dapagliflozin has a QALY gain compared with DPP4 inhibitors. Please describe the source of the QALY gain, including what contributions are from weight, HbA1c, SBP, lipids and hypoglycaemia events.

B2. **Priority question:** Table 38 of the submission gives figures for "Intensified insulin". Please explain the company's interpretation/definition of "intensified insulin", and the source of the figures given for intensified insulin (particularly for hypoglycaemia). It is noted that in the cited reference (Waugh 2010) there is a figure of 1.11% for reduction in HbA1c (Table 38 of the HTA report), however this result is for glargine. Intensified insulin therapy usually refers to a basal bolus regimen.

B3. Please outline how the baseline QoL value of 0.87 has been calculated and why this is preferred over the 0.85 baseline mean of study 5. Please also provide the VBA code for the age adjusted utility value in the absence of complications.

B4. Appendix 22 outlines the code for the UKPDS 82 equations. Please:

a. provide the corollary for the event equations for the UKPDS 68 for both complications and deaths, and any other equations qualifying these equations, together with their sources.

b. provide a detailed explanation of how deaths are modelled when UKPDS 68 is selected for the model, the degree to which this corresponds with equations 8, 9 and 10 of UKPDS 68, and how this is qualified when the life tables check box is selected within the model.

c. outline if equation 14 of the UKPDS 68 has been applied, and if so how.

B5. **Priority question:** Within the model it appears that in some instances, patients do not immediately switch treatments when HbA1c rises above the set threshold, but instead continue treatment for six months (or more) before changing therapy. For example, in the model, in the Biannual Risk Factor Input worksheet, in cells AM5:AM6, the switch to 2nd line therapy appears to be delayed by one cycle, suggesting that those in the DPP4-inhibitor arm remain on the more expensive triple therapy for too long. Cells AR6:AR8 suggest that there is no parallel delay in the

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dapagliflozin arm. Is this an error, or does the model assume that treatment switches occur at year ends (which would obviate the need for a six month cycle)?

B6. From the data in visual basic, it appears that the evolution of HbA1c, when applying the UKPDS 68 equation, is deterministic. Please state whether the modelled evolutions of HbA1c, SBP and TC:HDL ratio within the PSA are deterministic or probabilistic in terms of the UKPDS 68 parameters.

B7. **Priority question:** UKPDS 68 equations 11, 12 and 13 clearly differentiate between values at diagnosis and values lagged by one year; e.g. HBA1C_BASE and LHBA1C. However, in the model, the clinical risk factors that appear when clicking on the Select Patient Profile button of the Simulation worksheet do not appear to make this distinction. Please outline what the HbA1c, SBP, TC and HDL values are at diagnosis and what the values are at baseline and where these values can be found within the model.

B8. **Priority question:** When using the UKPDS 82 modelling, please:

a. provide more detail about the assumptions used for the evolution of HbA1c, SBP, TC:HDL ratio, smoking status, BMI, eGFR, haemoglobin, albuminuria, WBC and heart rate.

b. clarify whether secondary events are simulated during a UKPDS 82 based analysis.

c. outline how to run the model to replicate the scenario analysis of the UKPDS 82 equations.

B9. For the disutility associated with hypoglycaemia, both the NICE diabetes clinical guideline (NG28) and the Assessment Group report for SGLT2-inhibitor monotherapy for diabetes (TA390) note that non-severe hypoglycaemia event rates need to be converted to 3-monthly rates (due to the recall period in Currie et al before the 1.773 HFS coefficient can be applied). Please confirm if this assumption has been used in the current modelling. It also appears that the model does not include the Insulin use 2.668 coefficient of Currie et al, despite patients intensifying to insulin at different time points as determined by a treatments' initial HbA1c effect. Please confirm if this is the case, and if so, what would be the probable impact of including the 2.668 coefficient?

B10. The control arm does not have the £47 one off costs of renal functioning and creatinine clearance monitoring. Please confirm if this assumption was also used within the base case modelling. Please also confirm if the costs in cells B110:B119 are additional to those of cells B8:B40; i.e. would a patient with blindness maintenance have an annual cost of £714+£512 applied?

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B11. **Priority question:** In the probabilistic sensitivity analyses, what were the central estimates of the costs and QALYs, and what is the variance reduction? Please also clarify whether figure 33 presents the likelihood of dapagliflozin being more cost effective than canagliflozin 300mg or the likelihood of canagliflozin 300mg being more cost effective than dapagliflozin.

Section C: Textual clarifications and additional points

C1. On page 119, the company submission states "For the purposes of this analysis, a total of 5,000 simulations, each containing 5,000 patients, were undertaken". However, it is unclear how this relates to the results of the base case, the PSA results and the model inputs in the Simulation worksheet:

a. Does the Simulation worksheet number of runs correspond to the number of monte carlo trials each patient is run through, or to the number of PSA iterations when second order sampling is being explored?

b. When running the model with the Mean Value Analysis selected with a cohort size of 5,000 and a number of runs of 5,000, how many monte carlo trials is each of the 5,000 patients subject to; i.e. how many times is each of the 5,000 patients run through the model?

c. When running the model with the Probabilistic Sensitivity Analyses selected with a cohort size of 5,000 and a number of runs of 5,000, how many PSA iterations are each of the 5,000 patients subject to; i.e. how many sets of parameter values are sampled with the model being run once for each of these parameter sets, and for each model PSA iteration and parameter set, how many monte carlo trials is each of the 5,000 patients subject to?

d. Do the results of table 48 correspond to a Mean Value Analysis or a Probabilistic Sensitivity Analyses?

e. Do the results of table 51 correspond to a Mean Value Analysis or a Probabilistic Sensitivity Analyses?

C2. Please describe what effect the "Number of years at or below target" variable has upon the model.

C3. Please clarify if the scenario analysis of no AE disutility values applies only to UTIs and GTIs, or also to hypoglycaemic events.

C4. Please clarify if the disutility for BMI is applied only when a patient's BMI is above 25kg/m^2 or is applied more generally to weight gains and losses relative to the patient's baseline BMI.

C5. Please expand table 37 to provide the baseline characteristics for the UKPDS 82 modelling. The UKPDS 82 specific modifiable risk factors and the proportions with a

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clinical history are the same for the base case and the THIN scenario analysis. What are the sources of these estimates?

C6. When the baseline characteristics are sampled, are they sampled independently or is there an underlying variance-covariance structure?

C7. Are the discontinuation rates only applied during the 1st cycle of treatment? What is assumed to happen to those who discontinue?

C8. Please clarify if the adverse event rates of table 38 are annual, six monthly or something else. Please also clarify if the electronic model treats these and the rates of hypoglycaemic events as being annual, six monthly or something else.

C9. Please provide the spreadsheet estimating daily insulin costs of £0.0055 per kg/day and £0.0082 per kg/day.

C10. Is there any cost consideration of self-monitoring of blood glucose for those intensifying to insulin?

C11. Within the T2 events of the model what does TTG stand for, how is it calculated and why does it fall to zero between year 9 and year 10?

C12. Please provide the technical report for the model.

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Single technology appraisal
Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]
AstraZeneca Response to Clarification Questions

SUMMARY

Thank you for the opportunity to respond to the clarification questions.

In responding to the questions, we have run two further NMA analyses regarding discontinuations; and several additional economic model scenarios.

The results of these analyses fully support the conclusions of the initial evidence submission:

- Treatment with dapagliflozin in a triple therapy regimen provides higher QALYs at lower cost than the DPP4-is.
- There are no meaningful differences in safety or efficacy between dapagliflozin and the other SGLT2-is (canagliflozin and empagliflozin) used in triple therapy regimens
- Cost effectiveness analyses for the comparison of dapagliflozin versus empagliflozin (10mg and 25mg regimens) and canagliflozin (100mg and 300mg regimens) demonstrate negligible cost and QALY differences with ICER estimates.

Section A: Clarification on effectiveness data

A1. **Priority question:** The submission states that 62% of patients on triple therapy with metformin and a sulfonylurea have a DPP4 inhibitor as the third drug. Please state the third drug added to the metformin and sulfonylurea combination for the remaining 38% of patients, with percentages for each combination.

Response:

IMS data Patient Data, IMS Information Solutions UK Ltd, December 2015 show that 31,968 patients who were previously prescribed metformin and sulfonylurea are currently prescribed triple therapy (the relevant population of this appraisal). The numbers of patients and corresponding percentages for each triple regimen is shown in Table 1.

Table 1: Triple therapy regimens in patients who were previously prescribed metformin and sulfonylurea

Triple therapy	31,968	
met+SU+DPP	19,665	62%
met+SU+SGLT2	4,567	14%
met+SU+ins	3,775	12%
met+SU+GLP	1,957	6%
SU+met+TZD	1,631	5%

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Other triple	140	0%
met+TZD+DPP	93	0%
met+TZD+SGLT2	47	0%
met+DPP+SGLT2	47	0%

A2. **Priority question:** There was some gender imbalance in Matthaei with 57.4% female in the dapagliflozin arm and 44.4% in the placebo arm. Please provide weight, BMI, SBP and HbA1c changes for men and women separately for this study.

Response:

There is no evidence of sex effects on the efficacy of dapagliflozin from the Matthaei study or from the broader dapagliflozin clinical trial programme.

Table 2 shows the change in baseline in HbA1c by gender over the 24-week short-term double-blind treatment period in the Matthaei study. Statistically significant results for change in HbA1c versus placebo were found for both male and female subjects (p-value of 0.5575 for the treatment-by-subgroup interaction). No further analyses by gender were conducted in this study.

A retrospective, post-hoc analysis of ten studies pooled from the dapagliflozin clinical programme (excluding the Matthaei study) has demonstrated that dapagliflozin significantly reduced HbA1C, body weight and systolic blood pressure from baseline in men and women of all ages with no apparent sex differences. (Reusch et al, Poster presented at ADA 2015 attached for reference).

Table 2: HbA1C by gender over the 24-week short-term double-blind treatment period in the Matthaei study

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Table 11.2.2.3.3

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HbA1c (Percent) Longitudinal Repeated Measures Analysis by Gender
Over the 24-Week Short-term Double-blind Treatment Period
Excluding Data After Rescue
Full Analysis Set

SUBGROUP / STATISTICS		PLA + MET + SU N=108	DAPA 10MG + MET + SU N=108
P-VALUE (*): 0.5575			
GENDER: MALE SUBJECTS			
DESCRIPTIVE STATISTICS	N#	60	46
	BASELINE MEAN (SD)	8.19 (0.935)	8.08 (0.843)
	WEEK 24 MEAN (SD)	7.81 (0.930)	7.13 (0.813)
OVERALL ST TREATMENT PERIOD	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-0.22 (0.0714)	-0.83 (0.0805)
	95% CONFIDENCE INTERVAL FOR ADJUSTED MEAN	(-0.36, -0.08)	(-0.99, -0.67)
	DIFFERENCE VS. PLA (SE)		-0.62 (0.1076)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE		(-0.83, -0.40)
GENDER: FEMALE SUBJECTS			
DESCRIPTIVE STATISTICS	N#	48	62
	BASELINE MEAN (SD)	8.30 (0.773)	8.07 (0.967)
	WEEK 24 MEAN (SD)	8.10 (0.938)	7.34 (0.795)
OVERALL ST TREATMENT PERIOD	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-0.10 (0.0796)	-0.62 (0.0699)
	95% CONFIDENCE INTERVAL FOR ADJUSTED MEAN	(-0.25, 0.06)	(-0.76, -0.49)
	DIFFERENCE VS. PLA (SE)		-0.53 (0.1061)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE		(-0.74, -0.32)

N is the number of subjects in the full analysis set.
N# is the number of subjects in the full analysis set with non-missing baseline and at least one post-baseline value.
MIXED model: post-baseline = baseline treatment week subgroup week*treatment week*baseline treatment*subgroup
(*) P-value for the treatment-by-subgroup interaction.
(Categorical subgroups with less than 10 subjects in any treatment group are not included in interaction model)
Program Source: /gbs/prod/clin/programs/mb/102/116/stcsr01/rpt/rt-lb-lonrepmsubgpst-v02.sas 05MAR2013: 2:56:26

A3. **Priority question:** On page 92, the submission states that there is published evidence that the DPP4 inhibitors are non-inferior to each other. Please provide supporting references.

Response:

A published network meta-analysis of DPP4is as a triple therapy regimen with metformin plus sulfonylurea concluded that there were no statistically significant differences between sitagliptin, linagliptin and vildagliptin (Craddy et al, 2014 – please see attached reference). This is also in line with the current NICE type 2 diabetes guideline (NG28) where no distinction between DPP4i is made.

A4. **Priority question:** On page 57, the last paragraph mentions two RCTs, MB 102073 and BM102077. If these are published, please provide references for these trials.

Response:

These studies have been published. Pdf copies of the following references are attached:

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Study MB102077: Weber et al. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol 2016; 4: 211–20

Study MB102073: Weber et al. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin–angiotensin system blockade. Blood Pressure 2016; Vol 25, No 2: 93-103

A5. **Priority question:** Please explain why the following outcomes were not included in the network meta-analysis:

a. BMI (given both the gender imbalance in study 5 and that the economic modelling requires the patient BMI)

b. Discontinuation rates

Response:

a) Change from baseline in BMI was rarely reported by the included studies in the systematic review.

The base case, restricted NMA was not feasible for this outcome as only one study included in the restricted network criteria reported change from baseline BMI (Nogueria 2014). Further, it should be noted that only seven of the forty studies included in the expanded network reported change in BMI demonstrating that change in total body weight was a more appropriate outcome using the available evidence.

In order to assess whether change in BMI could be calculated, studies were reviewed to see if change in weight by gender was reported. Only one study reported change in weight by gender, so an NMA using this method was not feasible.

b) New analyses have been carried out for discontinuations due to AEs and 'withdrawals due to any reason' as these were the outcomes on this matter most commonly reported by the trials included in the systematic review.

NMA results for withdrawals due to any reason and discontinuations due to AEs for the restricted, base case network have been presented in Table 3. The results show no statistically significant differences between dapagliflozin and the DPP4-is; and between dapagliflozin and the other SGLT2-is.

Figure 1: Network diagram for withdrawals due to any reasons

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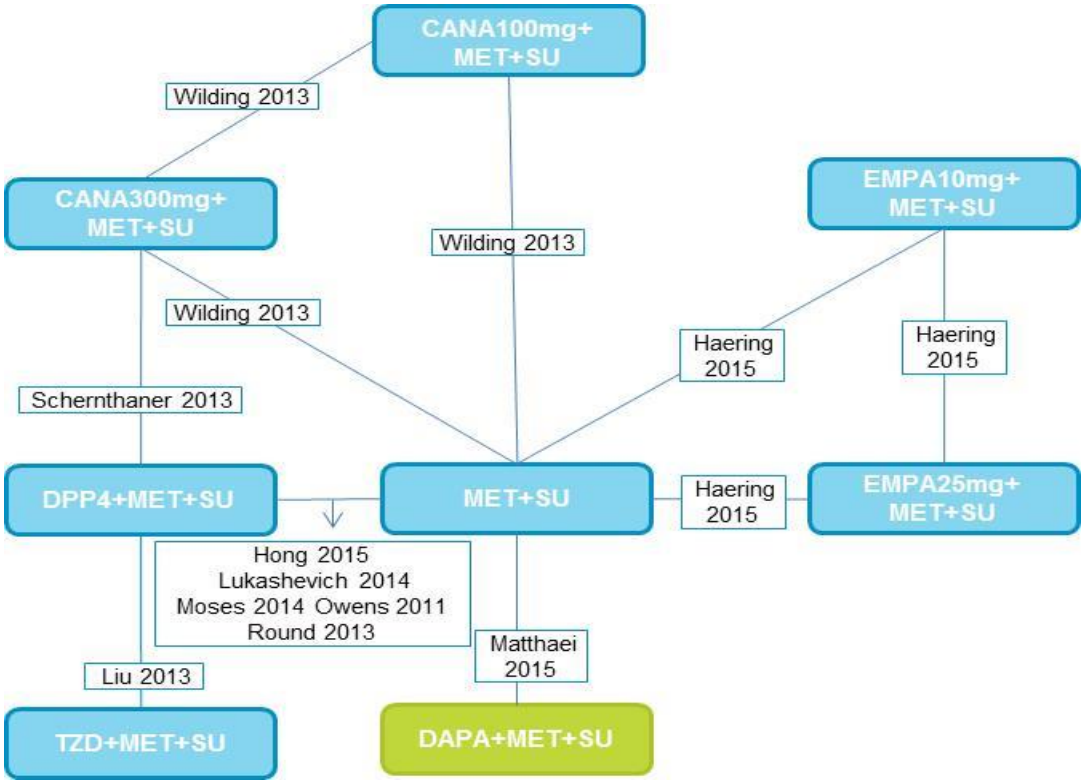

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Figure 2: Network diagram for discontinuations due to AEs

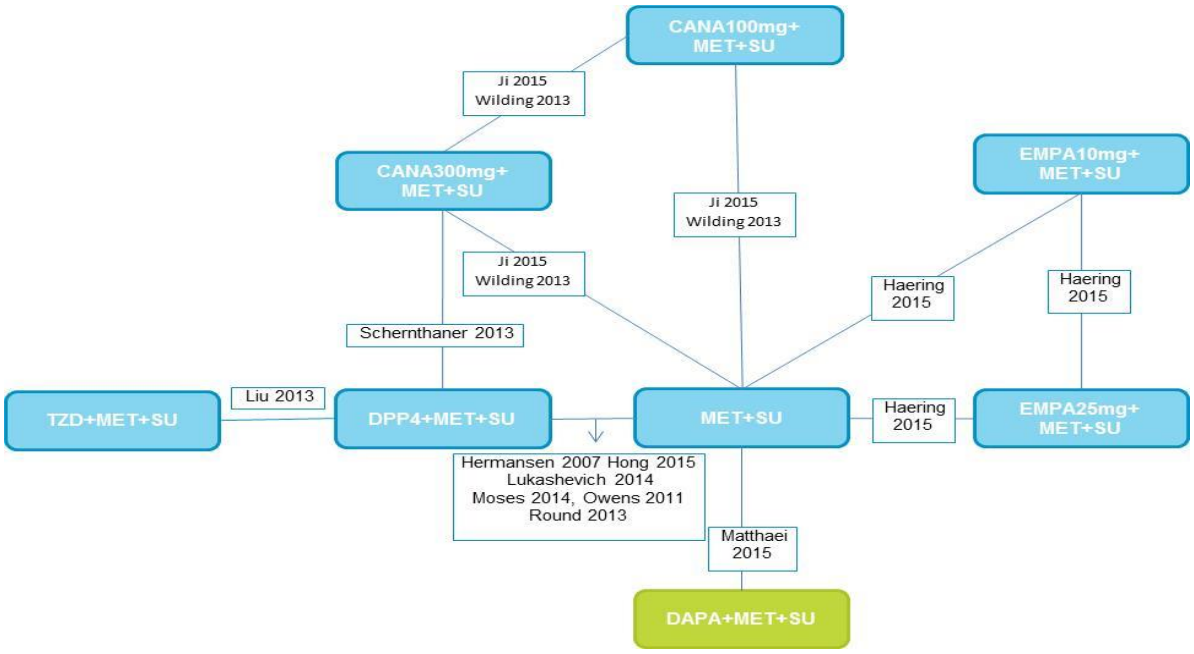

Table 3: NMA results for withdrawals due to any reason and discontinuations due to AEs

	Withdrawals due to any reason		Discontinuations due to adverse events	
MET + SU + dapagliflozin vs.	**Fixed effect model OR (95% CI)**	**Random effect model OR (95% CI)**	**Fixed effect model OR (95% CI)**	**Random effect model OR (95% CI)**
MET+SU	0.92 (0.41-2.04)	0.93 (0.28-3.11)	0.45 (0.05-2.53)	0.46 (0.05-3.06)
CANA100mg+MET+SU	1.53 (0.62-3.80)	1.54 (0.32-7.22)	0.24 (0.03-1.62)	0.23 (0.02-1.99)
CANA300mg+MET+SU	1.69 (0.72-3.95)	1.67 (0.39-6.74)	0.23 (0.02-1.44)	0.23 (0.02-1.80)
EMPA10mg+MET+SU	1.34 (0.52-3.43)	1.34 (0.27-6.66)	0.75 (0.08-5.12)	0.77 (0.06-7.43)
EMPA25mg+MET+SU	1.15 (0.45-2.93)	1.14 (0.23-5.72)	0.46 (0.05-3.04)	0.47 (0.04-4.35)
DPP4+MET+SU	1.05 (0.45-2.41)	1.05 (0.28-3.73)	0.45 (0.05-2.74)	0.48 (0.05-3.64)

Values less than 1 favours intervention (dapagliflozin)

Table 4: Model fit statistics for withdrawals due to any reason and discontinuations due to AEs

	Withdrawals due to any reason		Discontinuations due to adverse events	
	Fixed	**Random**	**Fixed**	**Random**
Deviance information criterion	161.612	162.479	129.912	131.933
Mean total residual deviance (SD)	28.12 (6.024)	25.65 (6.753)	22.99 (6.379)	23.5 (6.57)
Between-studies standard deviation		0.3551		0.3284

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A6. **Priority question:** Tables 26, 27, 28 and 29 provide 4 different results sets for key outcomes for the NMA (24 week results, 52 week results, "study endpoint" results and "base case" results). However, it is not clear how the "base case" values relate to the other values in the table. Furthermore, it is noted that the "study endpoint" values and the "base case" values of tables 26, 27, 28 and 29 differ, yet on page 78, the submission states that CrIs of the 52 week data provide the "…rationale to use the endpoint network as the base case" (which suggests that the "base case" values should be the same as the "study endpoint" values). Please provide a more detailed explanation of any relationship between the 4 different result sets, and please describe how the "base case" values in table 26, 27, 28 and 29 were derived.

Response:
To clarify, a definition of the four networks is described below:

- 24 weeks: Results refer to expanded network (including available evidence from all included studies in the systematic review) at 24 weeks
- 52 weeks: Results refer to expanded network (including available evidence from all included studies in the systematic review) at 52 weeks
- Study endpoint: Results refer to expanded network (including available evidence from all included studies in the systematic review) at study endpoint (varying study durations)
- Base-case: Results refer to restricted network (including available evidence from studies of dapagliflozin and the key comparators DPP4-is; canagliflozin and empagliflozin) at study endpoint (varying study durations)

<u>Rationale for base case</u>

The restricted network was chosen for the base case to include the evidence for the most relevant comparators to dapagliflozin for this appraisal (DPP4-is, canagliflozin and empagliflozin) – i.e. those treatments typically used by the NHS to treat the population of this appraisal's scope: adults with type 2 diabetes who are inadequately controlled on dual therapy with MET with a SU.

Study endpoint was chosen for the base case (rather than 52 or 24 weeks) to maximise use of available evidence across all outcomes resulting in more robust estimates of relative effectiveness.

To further clarify, studies included in the restricted network and the expanded network are presented in the tables below for each outcome (Table 5 to Table 8).

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Table 5: Studies included in NMA for HbA1c

Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Base case/Restricted study endpoint network
Hermansen et al., 2007	✓	x	✓	✓
Haering 2015	✓	✓	✓	✓
Hong et al., 2015	✓	x	✓	✓
Lukashevich 2014	✓	x	✓	✓
Ji et al., 2015	✓	x	✓	✓
Liu et al., 2013	✓	x	✓	✓
Matthaei et al., 2015	✓	✓	✓	✓
Moses et al., 2014	✓	x	✓	✓
NCT01590771	✓	x	✓	✓
Nogueira et al., 2014	✓	x	✓	✓
Owens et al., 2011	✓	x	✓	✓
Round et al., 2013	✓	x	✓	✓
Schernthaner et al., 2013	✓	✓	✓	✓
Wilding et al., 2013	✓	✓	✓	✓
Aljabri et al., 2004	x	x	✓	x
Bergenstal et al., 2009	✓	x	✓	x
Charpentier and Halimi, 2009	✓	x	✓	x
Davies et al., 2013	x	x	x	x
Derosa et al., 2009	x	x	✓	x
Derosa et al., 2010	✓	x	✓	x
Diamant et al., 2014	x	x	✓	x
Heine et al., 2005	x	x	x	x
Home et al., 2015	✓	✓	✓	x
Hartemann-Heurtier et al., 2009	✓	x	✓	x
Holman et al., 2007	✓	✓	✓	x
Giorgino et al., 2015	✓	✓	✓	x
Kendall et al., 2005	✓	x	✓	x
Lu et al., 2013	x	x	✓	x
Lam et al., 1998	✓	x	✓	x
Nauck et al., 2007	✓	✓	✓	x
Nomoto et al., 2015	x	x		x
Pan et al., 2014	x	x	x	x
Russell-Jones et al., 2009	✓	x	✓	x
Rosenstock et al., 2014	✓	x	✓	x
Standl et al., 2001	✓	x	✓	x
Strojek et al., 2009	✓	x	✓	x
Seino et al., 2014	x	x	✓	x

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Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Base case/Restricted study endpoint network
Wu et al., 2011	x	x	✓	x
Yang et al., 2013	✓	x	✓	x
Yiangou et al., 2013	x	x	x	x

Table 6: Studies included in NMA for body weight

Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Hermansen et al., 2007	✓	x	✓	✓
Haering 2015	✓	✓	✓	✓
Hong et al., 2015	✓	x	✓	✓
Lukashevich 2014	x	x	x	x
Ji et al., 2015	✓	x	✓	✓
Liu et al., 2013	✓	x	✓	✓
Matthaei et al., 2015	✓	✓	✓	✓
Moses et al., 2014	✓	x	✓	✓
NCT01590771	x	x	x	x
Nogueira et al., 2014	✓	x	✓	✓
Owens et al., 2011	✓	x	✓	✓
Round et al., 2013	✓	x	✓	✓
Schernthaner et al., 2013	✓	x	✓	✓
Wilding et al., 2013	x	x	x	x
Aljabri et al., 2004		x	✓	x
Bergenstal et al., 2009	✓	x	✓	x
Charpentier and Halimi, 2009	x	x	x	x
Davies et al., 2013	x	x	x	x
Derosa et al., 2009	x	x	✓	x
Derosa et al., 2010	✓	x	✓	x
Diamant et al., 2014	x	x	x	x
Heine et al., 2005	✓	x	✓	x
Home et al., 2015	✓	✓	x	x
Hartemann-Heurtier et al., 2009	✓	x	✓	x
Holman et al., 2007	✓	✓	✓	x
Giorgino et al., 2015	✓	✓	✓	x
Kendall et al., 2005	✓	x	✓	x
Lu et al., 2013	x	x	✓	x
Lam et al., 1998	✓	x	✓	x
Nauck et al., 2007	✓	✓	✓	x
Nomoto et al., 2015	x	x	✓	x
Pan et al., 2014	x	x	x	x

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Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Russell-Jones et al., 2009	✓	x	✓	x
Rosenstock et al., 2014	✓	x	✓	x
Standl et al., 2001	x	x	x	x
Strojek et al., 2009	x	x	x	x
Seino et al., 2014	x	x	✓	x
Wu et al., 2011	x	x	✓	x
Yang et al., 2013	✓	x	✓	x
Yiangou et al., 2013	x	x	x	x

Table 7: Studies included in NMA for SBP

Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Hermansen et al., 2007	x	x	x	x
Haering 2015	✓	✓	✓	✓
Hong et al., 2015	x	x	x	x
Lukashevich 2014	x	x	x	x
Ji et al., 2015	✓	x	✓	✓
Liu et al., 2013	✓	x	✓	✓
Matthaei et al., 2015	✓	✓	✓	✓
Moses et al., 2014	x	x	x	x
NCT01590771	x	x	x	x
Nogueira et al., 2014	✓	x	✓	✓
Owens et al., 2011	x	x	x	x
Round et al., 2013	x	x	x	x
Schernthaner et al., 2013	x	✓	✓	✓
Wilding et al., 2013	✓	✓	✓	✓
Aljabri et al., 2004	x	x	✓	x
Bergenstal et al., 2009	x	x	x	x
Charpentier and Halimi, 2009	x	x	x	x
Davies et al., 2013	x	x	x	x
Derosa et al., 2009	x	x	✓	x
Derosa et al., 2010	✓	x	✓	x
Diamant et al., 2014	x	x	x	x
Heine et al., 2005	x	x	x	x
Home et al., 2015	x	x	x	x
Hartemann-Heurtier et al., 2009	x	x	x	x
Holman et al., 2007	x	x	✓	x
Giorgino et al., 2015	x	x	✓	x
Kendall et al., 2005	x	x	x	x
Lu et al., 2013	x	x	x	x

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Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Lam et al., 1998	x	x	x	x
Nauck et al., 2007	x	x	✓	x
Nomoto et al., 2015	x	x	✓	x
Pan et al., 2014	x	x	x	x
Russell-Jones et al., 2009	✓	x	✓	x
Rosenstock et al., 2014	x	x	x	x
Standl et al., 2001	x	x	x	x
Strojek et al., 2009	x	x	x	x
Seino et al., 2014	x	x	x	x
Wu et al., 2011	x	x	x	x
Yang et al., 2013	x	x	x	x
Yiangou et al., 2013	x	x	x	x

Table 8: Studies included in NMA for any hypoglycaemia

Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Hermansen et al., 2007	✓	x	✓	✓
Haering 2015	✓	x	✓	✓
Hong et al., 2015	✓	x	✓	✓
Lukashevich 2014	✓	x	✓	✓
Ji et al., 2015	✓	x	✓	✓
Liu et al., 2013	✓	x	✓	✓
Matthaei et al., 2015	✓	✓	✓	✓
Moses et al., 2014	✓	x	✓	✓
NCT01590771	x	x	x	x
Nogueira et al., 2014	x	x	x	x
Owens et al., 2011	✓	x	✓	✓
Round et al., 2013	✓	x	✓	✓
Schernthaner et al., 2013	x	✓	✓	✓
Wilding et al., 2013	✓	✓	✓	✓
Aljabri et al., 2004	x	x	✓	x
Bergenstal et al., 2009	✓	x	✓	x
Charpentier and Halimi, 2009	✓	x	✓	x
Davies et al., 2013	✓	x	✓	x
Derosa et al., 2009	x	x	x	x
Derosa et al., 2010	x	x	x	x
Diamant et al., 2014	✓	x	x	x
Heine et al., 2005	x	x	x	x
Home et al., 2015	x	✓	✓	x
Hartemann-Heurtier et al., 2009	✓	x	✓	x

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Primary reference	Expanded 24 week network	Expanded 52 week network	Expanded study endpoint network	Restricted study endpoint network
Holman et al., 2007	x	✓	✓	x
Giorgino et al., 2015	x	✓	✓	x
Kendall et al., 2005	✓	x	✓	x
Lu et al., 2013	x	x	✓	x
Lam et al., 1998	x	x	x	x
Nauck et al., 2007	x	✓	x	x
Nomoto et al., 2015	x	x	x	x
Pan et al., 2014	✓	x	✓	x
Russell-Jones et al., 2009	✓	x	✓	x
Rosenstock et al., 2014	✓	x	✓	x
Standl et al., 2001	x	x	x	x
Strojek et al., 2009	✓	x	✓	x
Seino et al., 2014	x	x	✓	x
Wu et al., 2011	x	x	x	x
Yang et al., 2013	✓	x	✓	x
Yiangou et al., 2013	x	x	x	x

A7. **Priority question:** The NMA results of tables 26, 27, 28 and 29 are all stated relative to dapagliflozin. Please provide the central estimates and 95% CIs for the changes from baseline for dapagliflozin for both the fixed effects model and the random effects model for the 24 week, 52 week, study endpoint and base case analyses of tables 26, 27, 28 and 29. Please then describe the methodology used to derive the values used in the economic model (table 38) for HbA1c change from baseline, weight change from baseline, SBP change from baseline and the number of symptomatic hypoglycaemia events. This can be supplied in Excel if this is easier. Please provide answers for both the full network and the restricted network as available.

Response:

To provide economic model inputs on the absolute scale for each NMA outcome (i.e. absolute change in HbA1c, weight and SBP, and the absolute probability of hypoglycemia), the relative effect outputs from the NMA were combined with an estimate for the absolute change in the reference treatment – in this analysis, placebo plus MET plus SU. The meta-analyzed baseline response in the placebo arms (provided in the Excel sheet attached) were used as anchor values for each outcome and combined additively to the relative effect estimates for each agent (for hypoglycemia, this was done on the natural log scale).

The Excel sheet attached (Dapa TOT CE model inputs) shows the values based on the best-fitting NMA model (RE or FE), which were incorporated into the base case economic model. Further, effects of uncertainty in treatment estimates were

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investigated in sensitivity analyses. The standard error associated with each treatment effect, as estimated by the NMA, was incorporated within the PSA in order to estimate the variability of results as a function of the uncertainty in the mean absolute treatment effect (in combination with the uncertainty of other model parameters). Univariate sensitivity analysis was also undertaken to assess the influence of treatment effects upon predicted outcomes relative to other model parameters. Whilst results of the univariate sensitivity analyses demonstrated that treatment effect parameters often had the largest impact upon incremental results, it should be noted that the range of estimated ICERs produced by varying such parameters remained highly cost-effective or dominant throughout. Please see Figures 24-36 in the original submission.

Relative results for all treatments versus placebo plus MET + SU for the base case NMA restricted network for the fixed and random effects models are shown below in Table 9.

Additionally, relative results versus placebo plus MET + SU are shown for dapagliflozin in the dossier in tables 26, 27, 28 and 29 for each outcome for each of the four networks for both fixed and random effects. Should results also be required for the absolute values for each of these results (i.e. by applying the placebo 'anchoring' method described above; and available in the attached Excel sheet), please let us know, and we can provide these.

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Table 9: Data from NMA for HbA1c, body weight, SBP, any hypoglycaemia for all comparators versus placebo (plus MET+SU)

REGIMEN (Comparator vs placebo+MET+SU)	HbA1c		Body weight		SBP		Any hypoglycaemia	
	Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
DAPA+MET+SU	**-0.70(-0.97 , -0.44)**	**-0.70(-1.06 , -0.34)**	**-1.90(-30 , -0.79)**	**-1.90(-3.61 , -0.18)**	-2.07(-6.29 , 2.14)	-2.04(-10.51 , 6.45)	2.09(0.90 , 5.19)	2.08(0.28 , 16.39)
CANA300mg+MET+SU	**-0.97(-1.09 , -0.85)**	**-0.94(-1.13 , -0.71)**	**-1.77(-2.64 , -0.89)**	**-1.76(-3.07 , -0.45)**	**-3.06(-5.62 , -0.51)**	-3.07(-9.39 , 3.01)	**2.17(1.63 , 2.91)**	2.49(0.80 , 8.20)
CANA100mg+MET+SU	**-0.73(-0.91 , -0.55)**	**-0.72(-0.96 , -0.45)**	**-1.49(-2.54 , -0.44)**	-1.48(-3.12 , 0.15)	**-3.74(-6.29 , -1.20)**	-3.73(-9.81 , 2.52)	**2.16(1.47 , 3.19)**	2.42(0.65 , 9.42)
EMPA25mg+MET+SU	**-0.70(-0.97 , -0.42)**	**-0.70(-1.07 , -0.33)**	**-1.7(-2.26 , -1.15)**	**-1.70(-3.16 , -0.23)**	**-2.10(-4.03 , -0.15)**	-2.10(-10.26 , 5.88)	1.25(0.78 , 2.01)	1.25(0.18 , 8.38)
EMPA10mg+MET+SU	**-0.70(-0.98 , -0.42)**	**-0.70(-1.07 , -0.33)**	**-1.8(-2.36 , -1.25)**	**-1.80(-3.25 , -0.35)**	**-2.20(-4.14 , -0.26)**	-2.21(-10.32 , 5.70)	1.44(0.91 , 2.29)	1.44(0.21 , 9.8)
DPP4+MET+SU	**-0.64(-0.71 , -0.57)**	**-0.64(-0.76 , -0.53)**	**0.37(0.13 , 0.60)**	0.42(-0.20 , 1.10)	2.94(-0.28 , 6.13)	2.94(-7.43 , 12.84)	**1.83(1.45 , 2.32)**	**2.20(1.06 , 5.21)**
TZD+MET+SU	**-0.87(-1.21 , -0.53)**	**-0.87(-1.30 , -0.45)**	**1.97(1.05 , 2.89)**	**2.04(0.33 , 3.78)**	2.45(-1.64 , 6.50)	2.44(-10.79 , 15.20)	1.48(0.38 , 5.54)	1.78(0.17 , 19.91)
Basal insulin+MET+SU	**-0.74(-1.41 , -0.07)**	**-0.74(-1.47 , -0.03)**	0.75(-8.43 , 9.83)	0.68(-8.22 , 10.02)	7.44(-6.2 , 21.01)	7.47(-10.46 , 24.96)	-	-

*Statistically significant values have been highlighted in bold

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A8. **Priority question:** Please provide a more detailed explanation of the sources and arithmetic underlying the treatment specific estimates of UTI rates, GTI rates, discontinuation rates and probabilities of hypoglycaemic events being severe within table 38.

Response:

Table 10 presents sources and assumptions associated with base case model inputs describing treatment specific rates of UTI, GI, discontinuation and hypoglycaemia.

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Table 10: Therapy-specific discontinuation, hypoglycaemia and adverse event inputs applied in the base case and sources

Variable	Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
Mean input value					
DPP4	0.029	0.181	0.034	0.021	0.056
Dapagliflozin	0.053	0.202	0.04	0.119	0.04
Empagliflozin 10mg	0.053	0.148	0.04	0.119	0.04
Empagliflozin 25mg	0.053	0.131	0.04	0.119	0.04
Canagliflozin 100mg	0.053	0.208	0.04	0.119	0.04
Canagliflozin 300mg	0.053	0.208	0.04	0.119	0.04
MET + insulin	0	0.0108	0.037	0	0
Intensified insulin	0	0.616	0.022	0	0
Details of source					
DPP4	Taken from Table 2 of Schernthaner 2013 (Sitagliptin 100). Assumed that therapy is comparable.	Inputs were derived from the treatment effects NMA. Please see response to A7 for description of input derivation.	Taken from the Safety section of Schernthaner 2013 (Sitagliptin 100). Assumed that therapy is comparable.	Taken from Table 2 of Schernthaner 2013 (Sitagliptin 100). Assumed that therapy is comparable.	Taken from Table 2 of Schernthaner 2013 (Sitagliptin 100). Assumed that therapy is comparable.
Dapagliflozin	Taken from Table 2 of Schernthaner 2013 (Canagliflozin 300). Assumed that therapy is comparable. Discontinuation was	Inputs were derived from the treatment effects NMA. Please see response to A7 for description of input derivation.	Taken from the Safety section of Schernthaner 2013 (Canagliflozin 300), assumed all therapies have the same rate due to lack of data.	Taken from Table 2 of Schernthaner 2013 (Canagliflozin 300), assumed all therapies have the same rate due to lack of data.	Taken from Table 2 of Schernthaner 2013 (Canagliflozin 300), assumed all therapies have the same rate due to lack of data.
Empagliflozin 10mg					

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Variable	Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
Empagliflozin 25mg	modelled as having been caused by adverse events using RCT data from the comparative trial of canagliflozin versus sitagliptin in the absence of any head to head studies for dapagliflozin versus a DPP4-i				
Canagliflozin 100mg					
Canagliflozin 300mg					
MET + insulin	Assumed to be 0.	Inputs were sourced from previous NICE submissions and publications. We have been unable to derive all input values utilised from the original sources (Monami 2009, Waugh 2010), however it is worth noting that these values have previously been scrutinised and subsequently accepted by NICE (see TA288). Further, we have endeavoured to provide further reassurance of the robustness of results by providing additional sensitivity analyses, see the response to B2 for more details.		Assumed to be 0.	Assumed to be 0.
Intensified insulin	Assumed to be 0.			Assumed to be 0.	Assumed to be 0.

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A9. On pages 78 onwards, some NMA results are given for the expanded network and some for the restricted network. However, it is unclear from the company submission which studies were used in the different models presented. Table 8 lists 14 trials in the restricted network for the base case NMA, though one trial (NCT0159771) appears to be unpublished and was not provided. In the results for HbA1c, weight and SBP, which studies were added in the "expanded networks"?

Response:
Please see the response for question A6. To our knowledge, trial NCT01590771 is not published. This trial was retrieved from a search of clinicaltrials.gov. The attached pdf includes the results from the clinicaltrials.gov website.

A10. The NMAs included evidence from drug classes and individual drugs within the same network. Was any assessment undertaken to look at these separately (i.e. classes in a NMA and individual drugs in another NMA)? If so, please provide the results.

Response:
Within the submission, we have compared dapagliflozin to other SGLT2i to show clinical equivalence of all licenced SGLT2i. An analysis of dapagliflozin versus pooled SGLT2i was not undertaken.

In addition, dapagliflozin versus DPP4i was also undertaken, this was a pooled analysis and no evaluation of individual drugs within this class was undertaken. Published evidence supports the approach taken to pool the DPP4-is. A network meta-analysis of DPP4is as a triple therapy regimen with metformin plus sulfonylurea concluded that there were no statistically significant differences between sitagliptin, linagliptin and vildagliptin (Craddy et al, 2014 – please see attached reference). This is also in line with the current NICE type 2 diabetes guideline (NG28) where no distinction between DPP4i is made.

A11. The company submission does not discuss whether a sensitivity analysis was undertaken on the different elements in the NMA models, specifically whether prior distributions, link functions and priors for parameters were examined. Please describe and provide results for any sensitivity analyses undertaken for these.

Response:

Sensitivity analyses were performed on the prior distributions in two ways: analyses were performed to compare different 'uninformative' priors and to assess the effect of using informative priors. The effect of uninformative priors was assessed by changing the breadth of uniform distributions (changing the range from 0-5 to 0-10). The assessment of informative priors involved the use of lognormal priors, as recommended

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by Turner et al. In both these scenarios, the effect estimates were similar, but the uncertainty of the posterior estimates was increased. As a result, it was judged that the model was sensitive to avoidable uncertainty introduced by unrealistically broad priors, but was robust to different shaped priors. Based on this analysis, we selected fixed effects model as more suitable model over uninformative priors random effects model.

For HbA1c CFB, Body weight CFB and SBP CFB, REM model was selected on the basis of low DIC and total residual deviance. No sensitivity analysis was performed on priors as random effects model was more suitable model based on modelling parameters like DIC, and residual deviance.

For any hypoglycaemia, REM has very large standard deviation for effect estimates. One evident reason for this was the small number of studies contributing to network meta-analysis. For this outcome, prior testing was performed at U (0,5) and U(0,10) to assess the impact of vague priors on between study variability (Please refer Table 25; page 78 in submission). Changing the prior distribution has no impact on the model fit, but SD for treatment effect increases largely as we increase value of "b" in U(0,b).

Informative log-normal priors as suggested by Turner et. al. were also tested. There was considerable reduction in between study SD from 0.85 to 0.35 suggesting that results of random effects model are overwhelmed by priors. Considering the limited number of studies contributing to the network and sensitivity of results to priors a fixed effect model was considered as the most suitable model for any hypoglycaemia.

A12. The company submission does not present any diagnostic plots or summary measures regarding model convergence (i.e. history plots, Brooks-Gelman-Rubin plots/statistics, Monte-Carlo error). Also, no mention is made of whether autocorrelation was assessed, or if it was a concern. Please provide more detail about whether these were undertaken and whether they were considered appropriate.

Response:

In addition to visual inspection of chains for mixing, Brooks-Gelman-Rubin plots were produced (presented in Appendix – Graphs for Model NMA Diagnostics). Autocorrelation was present in the model, primarily when comparing dapagliflozin plus metformin plus sulfonylurea with basal insulin plus metformin plus sulfonylurea. However, the autocorrelation observed declined consistently across lags and did not appear to cause problems with convergence. We did re-run the analyses with a larger thin value, but it did not improve the convergence rate or alter the results and so we kept the thin at 1 for the base case analyses.

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BGR, time series and auto-correlation plots are shown for each outcome in the attached appendix.

A13. Measures assessing model fit are provided for decisions regarding the use of a fixed-effect or random-effects model, however these are not provided for any other models (e.g. meta-regression or sensitivity analyses). Please provide these if available.

Response: Measures of model-fit for fixed and random effect models for all sensitivity analysis have been provided below.

Table 11: Measures of model fit for sensitivity analyses

Sensitivity analysis	Outcome	Fixed		Random	
		Deviance information criterion	Mean total residual deviance	Deviance information criterion	Mean total residual deviance
Excluding poor quality studies	HbA1c	-30.13	30.92	-30.61	26.21
	Body weight	23.51	24.97	19.98	18.22
	SBP	48.96	11.03	50.62	11.83
	Any hypoglycaemia	155.18	29.67^	154.92	25.27^
Excluding subgroup studies	HbA1c	-33.24	25.13	-31.80	24.69
	Body weight	32.42	23.55	30.41	19.06
	SBP	57.46	14.02	57.49	14.01
	Any hypoglycaemia	161.22	37.9*	149.90	22.30*
Removing heterogeneous studies	HbA1c	-32.34	31.57	-32.02	28.37
	Any hypoglycaemia	166.15	31.71$	165.86	27.30$

^23 data points; *22 data points; $25 data points

Highlighted values for best fit model. Please see the response to A11 to explain why FE was the best fitting model for any hypoglycaemia.

A14. The company submission presents a meta-regression for HbA1c only, despite noting that other factors are likely to cause heterogeneity. Were other factors included in a meta-regression analysis? If so, please provide these outcomes.

Response:
There was a challenge in this analysis in that the evidence network overall was comparatively sparse. We attempted to balance the need to account for observed heterogeneity against the need to avoid overfitting or adding avoidable uncertainty to the model. We did this by investigating, for each likely covariate, whether there was a correlation between the covariate and the dependent variable and, if so, whether there was sufficient information available to incorporate that covariate into the full statistical model.

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Feasibility was checked for meta-regression for baseline BMI and disease duration. Meta regression for BMI was not feasible for SBP as only 7 studies contributed to the network. Similarly, meta-regression for disease duration as a covariate was not feasible for body weight, SBP, and any hypoglycaemia. As stated in Bornstein et al sufficiently large ratio of studies to covariates is required in order to perform meaningful analysis. Also, according to the Cochrane handbook meta-regression should generally not be considered when there are fewer than ten studies in a meta-analysis.
For other combinations of covariates and outcomes (refer to table), exploratory analyses were conducted.

One of the major assumptions of meta-regression is that there should be a correlation between a dependent variable and explanatory variable. To check the correlation, scatterplots were drawn. The plots indicate lack of correlation between dependent and independent variable as the pattern is fairly random. In addition, the value of R2 indicates poor goodness of fit for the regression equations.

Hence, it was concluded that the baseline BMI and disease duration have no significant impact on the outcomes and no meta-regressions were performed.

Table 12: Studies reporting BMI and disease duration at baseline

	Body mass Index (no. of studies)	Disease duration (no. of studies)
HbA1c	13	10
Body weight	11	8
SBP	7	6
Any hypoglycaemia	12	9

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Figure 3: Scatter plot to show relationship between HbA1c and baseline BMI

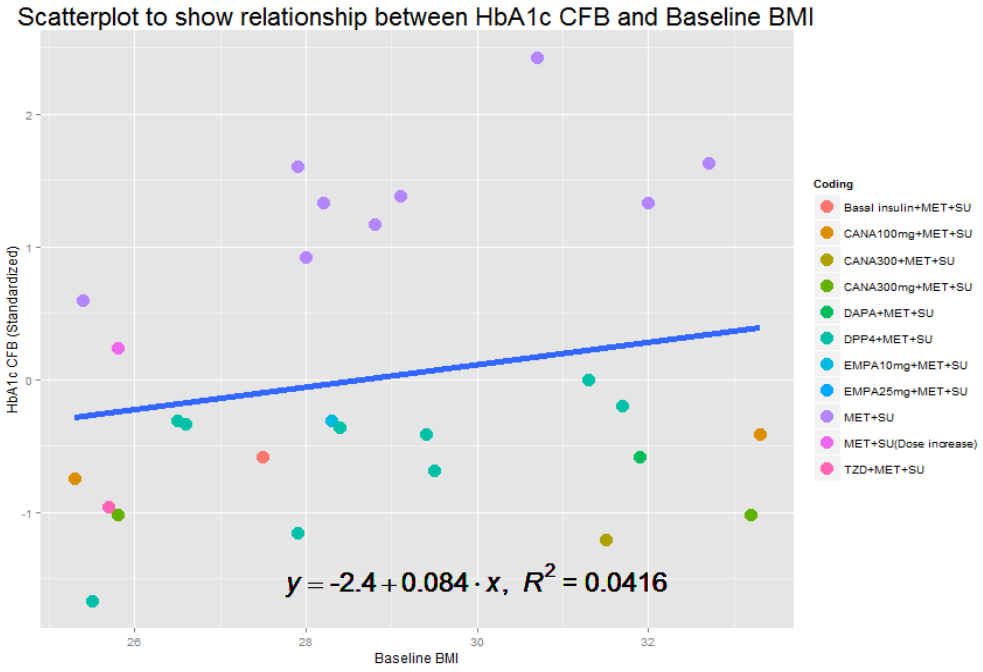

Figure 4: Scatter plot to show relationship between HbA1c and disease duration

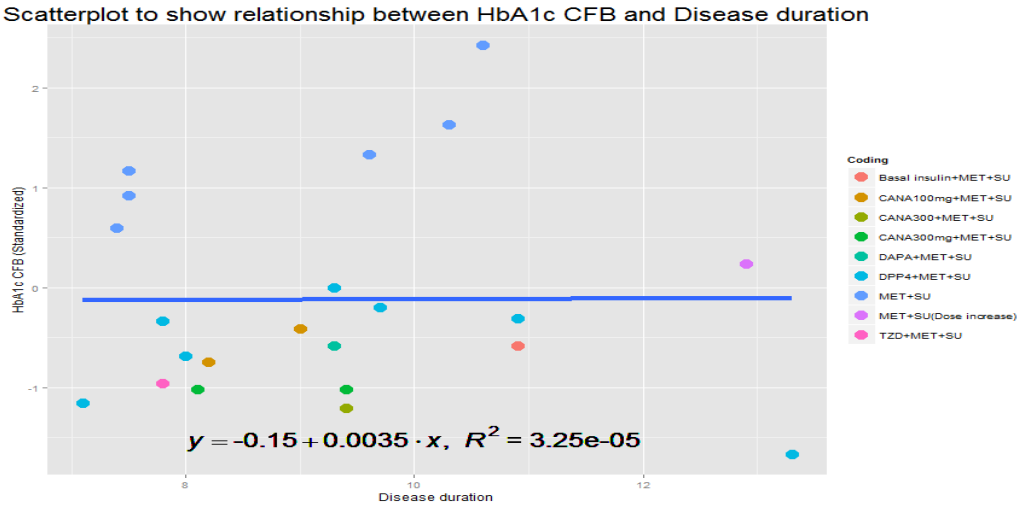

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Figure 5: Scatter plot to show relationship between body weight and baseline BMI

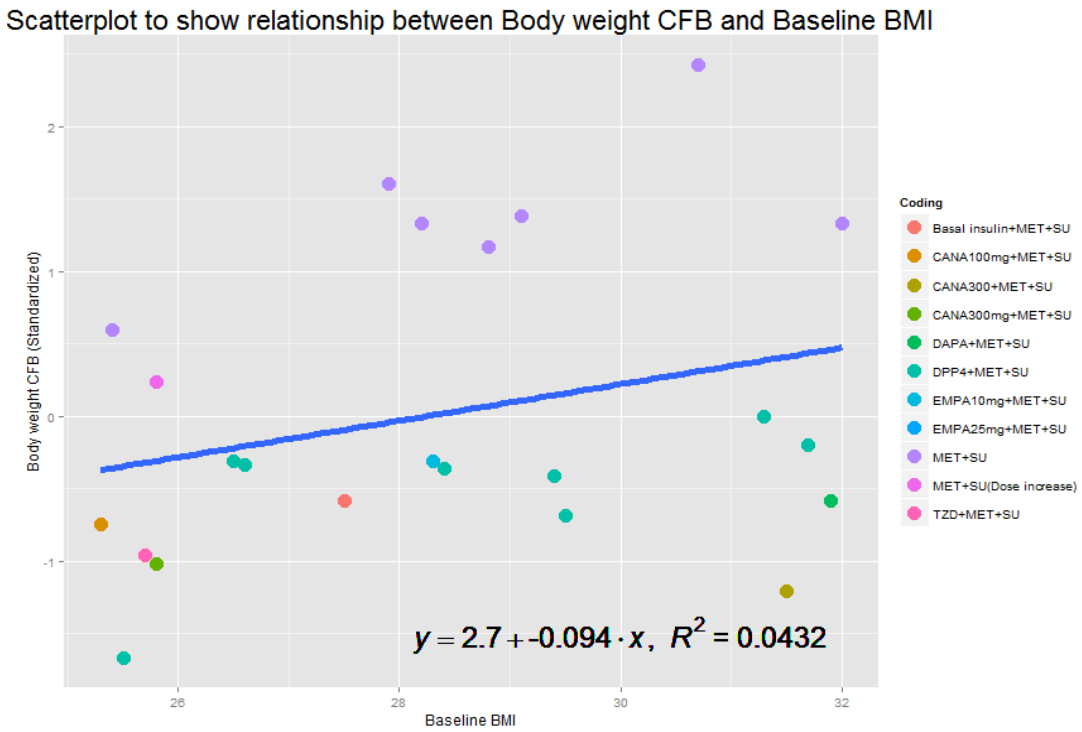
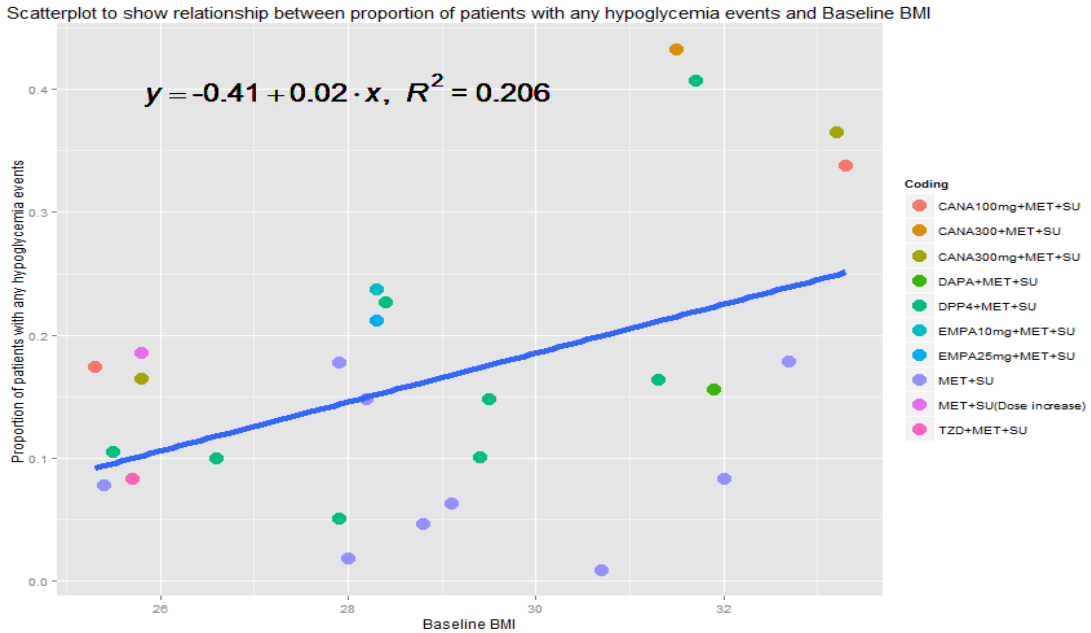


Figure 6: Scatter plot to show relationship between any hypoglycaemia and baseline BMI



A15. The NMAs synthesize relatively sparse evidence. Were the effects of the sparse evidence base assessed and were other approaches considered to overcome any subsequent problems?

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Response:
The restricted network (base-case) included only 14 studies; however we also performed analyses using the expanded network, which included all relevant data from broad literature searches. The majority of results from the expanded network were in line with those from the restricted network.

A16. Table 19: Lui is missing from the Table, and Seino is incorrectly included. Please provide a corrected table.

Response: Please see the corrected table below with the data for Liu highlighted in yellow

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Table 13: Baseline mean, SU as per inclusion criteria, and duration of stable therapy of studies included in the base case NMA

First Author	Year	Mean dose (mg/day) of combination therapy, at baseline/screening			Allowable SU and dose as per study criteria	Duration of stable combination therapy prior to study entry (months)
		MET	SU			
		(mg/day)	Agent	Dose (mg/day)		
Haering	2015	≥1,500 mg/day or MTD or MD according to local label	NR	NR	Greater than or equal to half the MRD, or the MTD, or the MD according to local label	≥3 (≥12 weeks)
Hermansen	2007	NR	Glimepiride	NR	Any OAD, or no agent at all	≥2.3
Hong	2015	1,100-1,200	Glimepiride	NR	Glimperide and Gliclazide for 12 weeks. In one of the group dose of SU was increased by 25% at random and further 25% at week 12 follow up if HbA1c was not within target level (<7%)	3
			Gliclazide	4 mg		
			Gliclazide	60 mg		
Ji	2015	MET, ≥1,500 mg/day	NR	SU, at least half-maximal labelled dose	NR	3 (4-week AHA adjustment period followed by an 8-week AHA dose-stable period)
Lukashevich	2014	≥1,500 mg	glimepiride	≥4 mg	glimepiride up to 4 mg	3
Liu	2013	1713 ± 247 (Pioglitazone)	Glimepiride	6.5 ± 1.3 (Pioglitazone)	Pre-trial SU without dose adjustment	≥2 (10 weeks)
		1717 ± 246		6.5 ± 1.5 (Sitagliptin)		

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		(Sitagliptin)		90 ± 30 (Pioglitazone)		
			Gliclazide	95 ± 29.5 (Sitagliptin)		
				half MD		
			Glimepiride			
			Glyburide			
Moses	2014	≥1,500	NR	Greater than equal to 50% of the MRD	Any SU - ≥ half maximal recommended dose	≥1.85
Nogueira	2014	2.4 ± 0.3 x 2.3 ± 0.6	Glyburide	17.6 ± 3,1 x 18.1 ± 4.1	Glyburide	NR
NCT01590771	2015	≥1,500	gliclazide glimepiride	NR	Gliclazide or glimepiride according to the China drug label	≥2
Owens	2011	Daily dose of ≥ 1,500 mg MET (or the MTD, if lower)	NR	MTD of SU	Any oral glucose-lowering drug	≥2 (≥10 weeks)
Round	2013	MET ≥1,500 mg/day	Glimiperide, Gliclazide	Glimiperide ≥2 mg, Gliclazide (≥50% of maximum registered dose)	Glimiperide ≥2 mg, Gliclazide (≥50% of maximum registered dose)	2.3

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Schernthaner	2013	≥2,000 mg/day or ≥1,500 mg/day if unable to tolerate a higher dose	Glipizide	minimum daily dose required at randomisation: 20 mg	SU - Half-maximal labeled dose or more	NR
Seino	2014	1.6-2.0 g/day mean dose	Glibenclamide, Glibomet, Gliclazide, Glimeperide, Glipizide, Tolbutamide	NR	NR	3
Wilding	2013	≥2,000 mg/day or ≥1,500 mg/day if unable to tolerate a higher dose	Glipizide	minimum daily dose required at randomisation: 20 mg	Any SU- maximally or near-maximally effective dos	NR
			Glyburide/glibenclamide	minimum daily dose required at randomisation: 10 mg		
			Glimepiride	minimum daily dose required at randomisation: 4 mg		
			Gliclazide	minimum daily dose required at randomisation: 160 mg daily		
			Gliclazide modified release	minimum daily dose required at randomisation: 60 mg daily		
			Glipizide extended release	minimum daily dose required at randomisation: 10 mg		

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A17. Table 20: Hong is missing from the Table. Please provide a corrected Table.

Response: Please see the corrected table below with the data for Hong highlighted in yellow.

Table 14: Study inclusion/exclusion criteria

Author, Year	Inclusion Criteria	Exclusion Criteria
Haering et al., 2015	Eligible patients were aged ≥18 years; BMI ≤45 kg/m^2) with inadequately controlled type 2 diabetes (HbA1c ≥ 7 to ≤10%) despite a diet and exercise program and a stable regimen (unchanged for ≥12 weeks prior to randomisation) of MET immediate release plus a SU. Patients with HbA1c >10% were eligible to participate in an open label treatment arm	Exclusion criteria included uncontrolled hyperglycemia (glucose level >13.3 mmol/L) after an overnight fast, confirmed by a second measurement), acute coronary syndrome, stroke or transient ischemic attack within 3 months prior to consent, indication of liver disease, impaired kidney function (estimated glomerular filtration rate [eGFR] ,30 mL/min/1.73 m^2) during screening or run-in, contraindications to MET or SU according to the local label, gastrointestinal surgeries that induce chronic malabsorption, history of cancer (except basal cell carcinoma) or treatment for cancer within 5 years, bloody scrasias or any disorders causing hemolysis or unstable erythrocytes, treatment with antiobesity drugs 3 months prior to consent, use of any treatment at screening that leads to unstable body weight, treatment with systemic steroids at time of consent, change in dosage of thyroid hormones within 6 weeks of consent, alcohol or drug abuse within 3 months of consent, and investigational drug intake within 30 days of the trial
Hermansen et al., 2007	Men and women, ≥18 and ≤75 years of age, with Type 2 diabetes were recruited for this study. Only the following patients were eligible to be screened: (i) already taking glimepiride alone (at any dose) or in combination with MET (at any dose), (ii) taking another OAD in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any OADs over the prior 8 weeks	History of type 1 diabetes; were treated with insulin within 8 weeks of the screening visit; had renal dysfunction (creatinine clearance <45 ml/min or <60 ml/min if on MET); or had a history of hypersensitivity, intolerance or a contraindication to the use of glimepiride, SU agents, MET or pioglitazone (which was included in this study as rescue therapy)
Hong et al., 2015	The eligible patients were T2DM patients who exhibited inadequate glycaemic control (glycated haemoglobin [HbA1c] > 7.0%) with metformin plus sulfonylurea (glimepiride or gliclazide) for at least 12 weeks	Patients excluded who had use insulin or GLP analogue previously, who had taken another OAD, had significant hepatic impairment or renal damage were excluded
Ji et al., 2015	Men and women ≥18 and ≤80 years of age with Type 2 diabetes who had inadequate glycaemic control [glycated haemoglobin (HbA1c) ≥7.0 and ≤10.5%] on MET alone or MET + SU, with both agents at maximum or near-maximum effective doses	Patients with a history of diabetic ketoacidosis or Type 1 diabetes; had a repeated fasting plasma glucose (FPG) ≥15mmol/l (≥270mg/dl) during the pretreatment phase; had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2; had MI or unstable angina (UA), had undergone a revascularization procedure or experienced a cerebrovascular event ≤3months before screening; had uncontrolled hypertension; or were

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Author, Year	Inclusion Criteria	Exclusion Criteria
		taking any AHA other than MET or SU ≤12weeks before screening
Liu et al., 2013	Males and females with type 2 diabetes (>20 years of age) who were taking stable doses of MET (≥1,500 mg/d) and an SU (≥half maximal dose, modified release gliclazide 60 to 120 mg daily or glimepiride 4 to 8 mg daily) for at least 10 weeks prior to the screening visit and had inadequate glycemic control (glycosylated hemoglobin [HbA1c] ≥7.0 and <11.0%) were recruited for the study	Patients were excluded if they had type 1 diabetes, insulin use within 12 weeks of the screening visit, any contraindications for the use of pioglitazone or sitagliptin, impaired renal function (serum creatinine >1.4 mg/dL), alanine aminotransferase (ALT) or aspartate aminotransferase levels (AST) >2.5 times the ULN, current or planned pregnancy, or lactation
Lukashevich et al., 2014	Age 18–80 years; body mass index (BMI) ≥22 to ≥45 kg/m^2, inadequately controlled on a stable dose of OADs for at least 12 weeks prior to the screening visit. Acceptable background therapy prior to enrollment included MET ≥1,500 mg as monotherapy [haemoglobin A1c (HbA1c) ≥8.5 and ≤11%] or dual combination of MET ≥1,500 mg with SU, TZD or glinide (HbA1c ≥7.5 and ≤11%)	Patients were excluded if they had fasting plasma glucose (FPG) ≥15.0 mmol/l; significant hepatic, renal or cardiovascular medical conditions; significant laboratory abnormalities; and pregnant or lactating females
Matthaei et al., 2015	Type 2 diabetes; age ≥ 18 years; HbA1c ≥ 7.0 – ≤ 10.5% (at randomisation); stable dose combination therapy of MET ≥ 1,500 mg/d and MTD of SU (which must be at least half the MD for ≥ 8 weeks prior to enrolment). MET could not be down titrated; SU could be down-titrated only once to mitigate hypoglycaemic events; no up-titration of MET or SU was allowed	Patients were excluded if: diagnosis of type 1 diabetes; body mass index ≥45.0 kg/m^2; serum creatinine ≥133 µmol/l (1.5 mg/dl) for men or ≥124 µmol/l (1.4 mg/dl) for women; unstable or rapidly progressing renal disease; recent cardiovascular events; congestive heart failure class IV; systolic blood pressure ≥160 mmHg; and diastolic blood pressure ≥100 mmHg at randomisation
Moses et al., 2014	Patients were ≥18 years old with type 2 diabetes, body mass index≤ 40 kg/m^2 and inadequate glycaemic control [HbA1c, 7.0–10.0% (53–86 mmol/mol)] on combination therapy with a stable MTD of MET plus a SU) daily for ≥8 weeks before screening. Women of childbearing potential were required to be using an adequate method of contraception and have a negative urine pregnancy test at visit 2 and each visit	The primary exclusion criteria were symptoms of poorly controlled diabetes; estimated creatinine clearance (CrCl) <1.0 ml/s or creatinine kinase ≥ 10 times ULN at visit 2; congestive heart failure; active liver disease and/or significant abnormal liver function; history of haemoglobinopathies; history of alcohol abuse or drug abuse ≤ 12 months before screening; use of insulin, DPP4-is, GLP-1 analogues or oral antidiabetic agents other than MET and SUs currently or within 3 months of screening; treatment with systemic glucocorticoids other than replacement therapy; treatment with cytochrome P450 3A4 inducers or potent 3A4 or 3A5 inhibitors; and

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Author, Year	Inclusion Criteria	Exclusion Criteria
	thereafter	pregnancy or breast-feeding
NCT01590771	18 Years to 79 Years Has Type 2 diabetes is currently on a stable regimen of gliclazide or glimepiride, either alone or in combination with MET for ≥ 10 weeks has a Visit 1/Screening HbA1c between 7.5% and 11.0% is a male, or a female who is highly unlikely to conceive during the study and for 14 days after the last dose of study medication	Patients who • had a history of type 1 diabetes mellitus or a history of ketoacidosis • has been treated with any antihyperglycemic therapies other than a SU (alone or with MET) within the prior 12 weeks or has ever been treated with a dipeptidyl peptidase-4 inhibitor or a glucagon-like peptide-1 mimetic or analogue has a history of intolerance or hypersensitivity, or has any contraindication to sitagliptin, gliclazide/glimepiride, or MET is on a weight loss program and not in the maintenance phase, or has started a weight loss medication or has undergone bariatric surgery within 12 months has undergone a surgical procedure within 4 weeks or has planned major surgery during the study has a medical history of active liver disease has had new or worsening signs or symptoms of coronary heart disease within the past 3 months, or has acute coronary syndrome, coronary artery intervention, or stroke or transient ischemic neurological disorder has a diagnosis of congestive heart failure with New York Heart Association Class III - IV cardiac status has a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 90 mmHg has human immunodeficiency virus (HIV) has severe peripheral vascular disease is currently being treated for hyperthyroidism or is on thyroid hormone therapy and has not been on a stable dose for at least 6 weeks • has a history of malignancy ≤ 5 years before the study, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer has a clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia) is pregnant or breast feeding, or is expecting to conceive or donate eggs during the study, including 14 days after the last dose of study medication is a user of recreational or illicit drugs or has had a recent history of drug abuse

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Author, Year	Inclusion Criteria	Exclusion Criteria
Nogueira et al., 2014	Outpatients with Type 2 Diabetes aged 57 ± 7 years (mean ± SD) inadequately controlled with MET plus glyburide	Exclusion criteria: patients with severe heart failure, respiratory failure, uncontrolled hypertension, coronary heart disease, arrhythmias, hepatic and renal dysfunctions, endocrine and gastrointestinal disorders, malignancy, alcohol abuse, use of insulin, beta blockers or calcium channel antagonists and type 1 diabetes mellitus
Owens et al., 2011	Men and women with Type 2 diabetes aged ≥18 and ≤ 80 years, with a BMI ≤ 40 kg/m^2 and HbA1c ≥ 53 mmol/mol (≥ 7.0%) and ≤ 86 mmol/mol (≤ 10.0%) despite receiving a total daily dose of ≥ 1,500 mg MET (or the MTD, if lower) and the MTD of SU. The dose and regimen of MET and the SU must have been unchanged for ≥ 10 weeks before enrolment	MI, stroke or transient ischaemic attack within 6 months before enrolment; impaired hepatic function; renal failure or renal impairment; current acute or chronic metabolic acidosis; hereditary galactose intolerance; or being unable or unwilling to avoid nursing or pregnancy. Patients treated with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months of enrolment were also excluded
Round et al., 2013	Male or female patients with age 18 to 78 years. Patients with Type 2 diabetes and HbA1c ≥ 7.5% and ≤10.5 at screening visit were included. Patients were receiving stable dose of either glimepiride or gliclazide and MET (≥1,500 mg/day) for at least 10 weeks	Patients withT1DM; history of ketoacidosis, previous treatment with DPP4 or a GLP-1 mimetic; requirement of insulin therapy within 12 weeks prior to signing informed consent, significant active cardiovascular disorder, renal and liver impairement
Schernthaner et al., 2013	Eligible subjects were men and women with18 years of age or older with type 2 diabetes using stable MET and SU therapy. Subjects at screening already using the combination of MET and SU with both agents at maximally or near-maximally effective doses (MET ≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate a higher dose]; SU at half-maximal labeled dose or more), who had A1C ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol), and who met all other enrollment criteria directly entered the 2-week single-blind placebo run-in period before randomisation	Exclusion criteria included the following: repeated fasting plasma glucose (FPG) or fasting self-monitored blood glucose measurements ≥16.7 mmol/L (300mg/dL), or both, during the pretreatment phase; history of type 1 diabetes, cardiovascular disease, or uncontrolled hypertension; treatment with either a PPARg agonist, ongoing insulin therapy, another SGLT2-i, or any other AHA (other than MET and a SU) Within 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based on restriction of MET use in the MET local label); or serum creatinine ≥124 mmol/L (men) and ≥115 mmol/L (women)
Wilding et al., 2013	Eligible patients were men and women aged 18– 80 years with Type 2 diabetes who had inadequate glycaemic control (HBA1c ≥7% to ≤10.5%) on MET plus SU, with both agents at maximally or near-maximally effective doses	Patients with a history of diabetic ketoacidosis or T1DM, repeated fasting plasma glucose (FPG)≥15.0 mmol/l during the pretreatment phase, history of ≥1 severe hypoglycaemia episode within 6 months before screening, estimated glomerular filtration rate (eGFR) < 55 ml/min/1.73 m^2 (or < 60 ml/min/1.73 m^2 based upon restriction of MET use in the local label) or serum creatinine ≥124 µmol/l for men and ≥115 µmol/l for women, uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg), or taking any antihyperglycaemic agent other than MET plus SU within

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Author, Year	Inclusion Criteria	Exclusion Criteria
		12 weeks prior to screening

A18. Table 38: Monami 2008 is cited, but this has not been included in the reference list, nor in the folder of references. Please provide the correct reference for Monami 2008.

Response:
The correct reference is Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008;81(2):184-9

The reference has been provided in pdf format attached.

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Section B: Clarification on cost-effectiveness data

Model review: Issues identified as a result of NICE review

Response:

In creating the responses to the requests for clarification, three modelling issues, described below in Table 15, were identified. Base case analyses were reassessed and a comparison of original base case and updated base case cost-effectiveness results are provided in Table 16. The difference between the two sets of results is negligible due to each of the issues being associated with both treatment and comparator therapy arms, as such univariate sensitivity and scenario analyses have not been reassessed as the findings of these analyses will still hold. However, updated ICER scatter plots and CEACs have been provided (Figure 7-Figure 16). An updated model has been provided.

Please note that the updated base case models and results have been used to perform all additional analysis requests required by NICE.

Table 15: Summary of model issues identified through NICE review

Issue	Significance
Transcription error: Cost of Met+SU/Met not applied	As this transcription error relates to both treatment and comparator therapy arms and therapy durations are equal or very similar, the impact on incremental costs is very small. Updated therapy cost inputs are detailed in response to C9.
Miscalculation of input: Cost of Met+SU not derived from latest source	As above.
Transcription error: Second line (Met+Insulin) hypoglycaemia rates incorrectly applied	As this transcription error relates to both treatment and comparator therapy arms and therapy durations are equal or very similar, the impact on incremental costs and QALYs is negligible. (QALY differences not observed at 2d.p.)

Table 16: Comparison of original and updated base case results. Originally presented result shown in brackets, in italics.

Treatment	Costs (£)	QALYs	ICER (£/QALY)
Absolute results (per patient)			
Dapagliflozin	20,910 *(20,417)*	9.62 *(9.62)*	

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Treatment	Costs (£)	QALYs	ICER (£/QALY)
DPP4-i	21,028 *(20,529)*	9.58 *(9.58)*	
Canagliflozin (100mg)	20,844 *(20,351)*	9.62 *(9.62)*	
Canagliflozin (300mg)	21,096 *(20,610)*	9.61 *(9.61)*	
Empagliflozin (10mg)	20,899 *(20,456)*	9.61 *(9.61)*	
Empagliflozin (25mg)	20,902 *(20,410)*	9.61 *(9.61)*	
Incremental results (per patient)			
Dapagliflozin versus DPP4-i	-118 *(-112)*	0.032 *(0.032)*	Dapagliflozin dominates *(as update)*
Dapagliflozin versus Canagliflozin (100mg)	66 *(66)*	-0.001 *(-0.001)*	Canagliflozin 100mg dominates *(as update)*
Dapagliflozin versus Canagliflozin (300mg)	-187 *(-192)*	0.003 *(0.003)*	Dapagliflozin dominates *(as update)*
Dapagliflozin versus Empagliflozin (10mg)	10 *(-38)*	0.005 *(0.005)*	£1,965 Dapagliflozin cost-effective (Dapagliflozin dominates)
Dapagliflozin versus Empagliflozin (25mg)	8 *(8)*	0.006 *(0.006)*	£1,354 Dapagliflozin cost-effective *(as update)*
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

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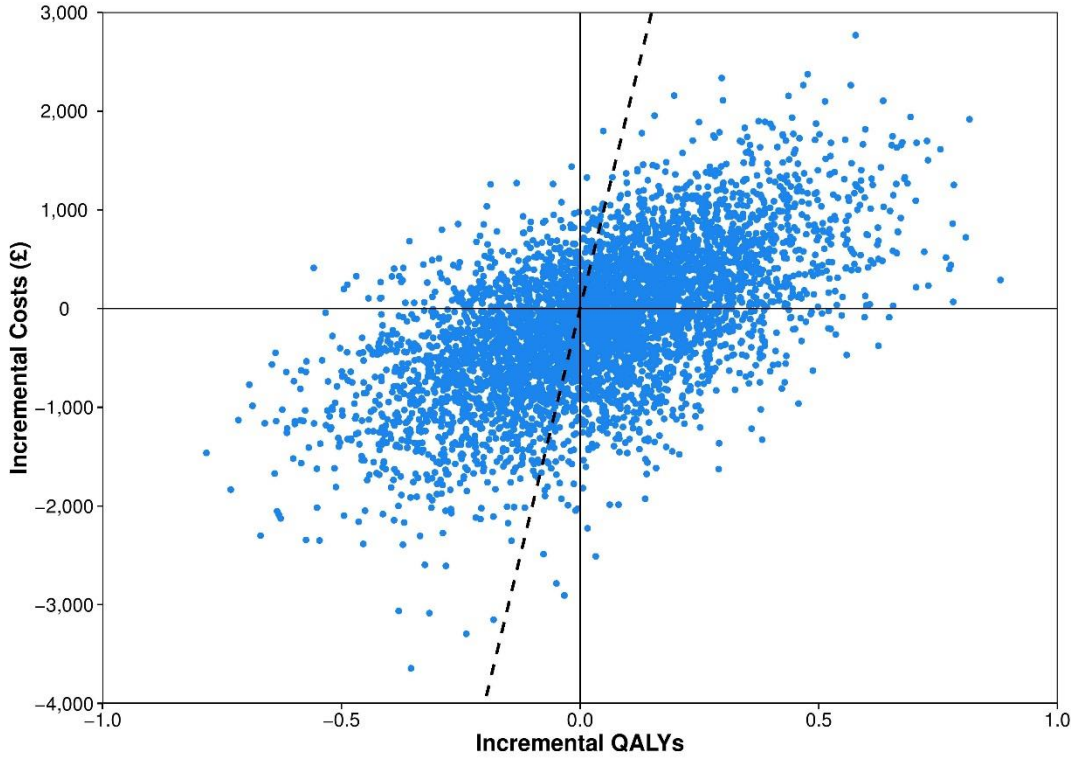

Figure 7: Scatterplot for incremental costs and QALYs (versus DPP4-i)

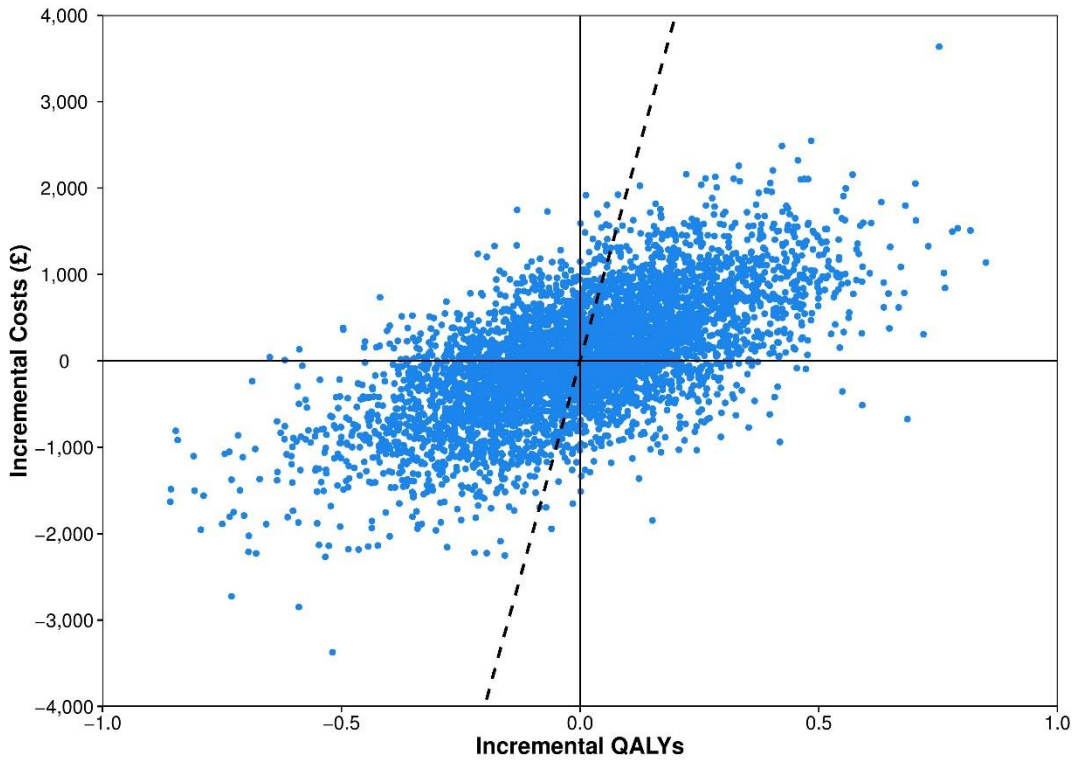

Figure 8: Scatterplot for incremental costs and QALYs (versus Canagliflozin 100mg)

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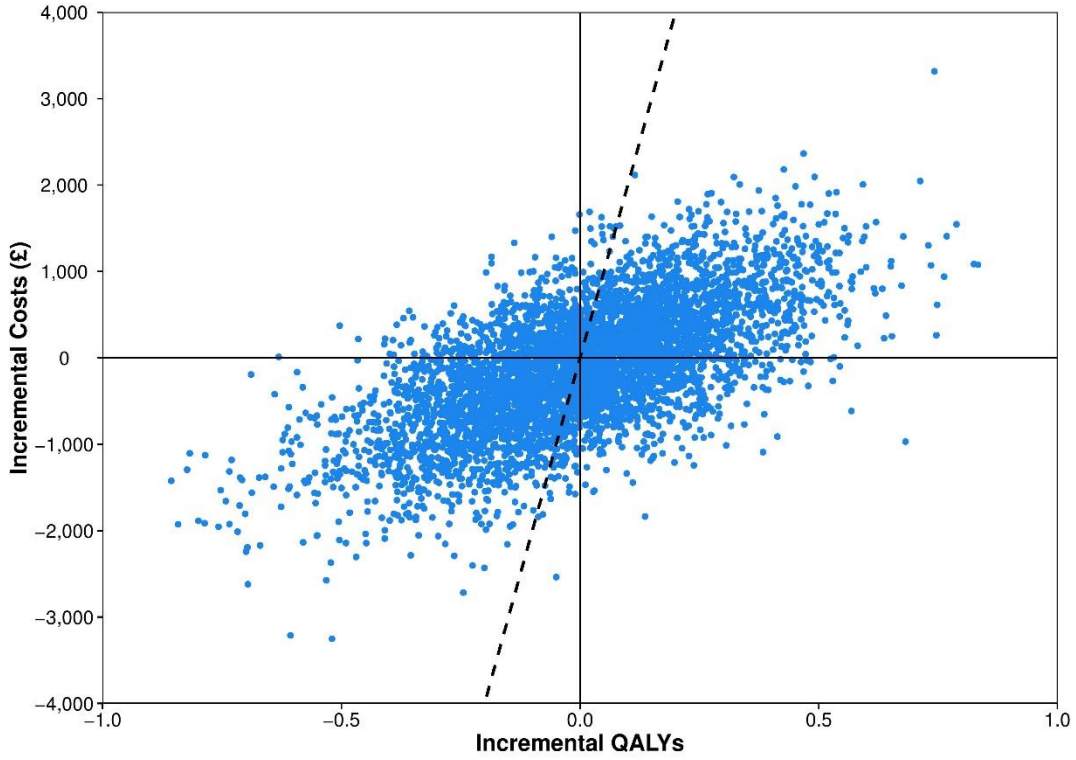

Figure 9: Scatterplot for incremental costs and QALYs (versus Canagliflozin 300mg)

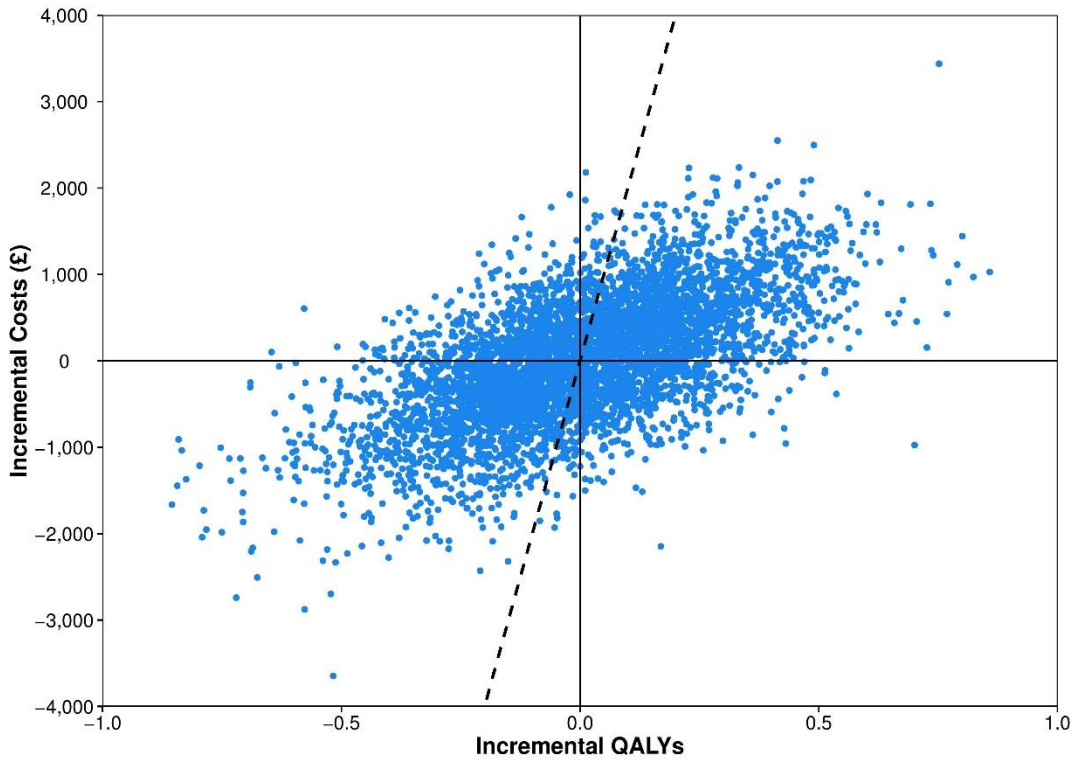

Figure 10: Scatterplot for incremental costs and QALYs (versus Empagliflozin 10mg)

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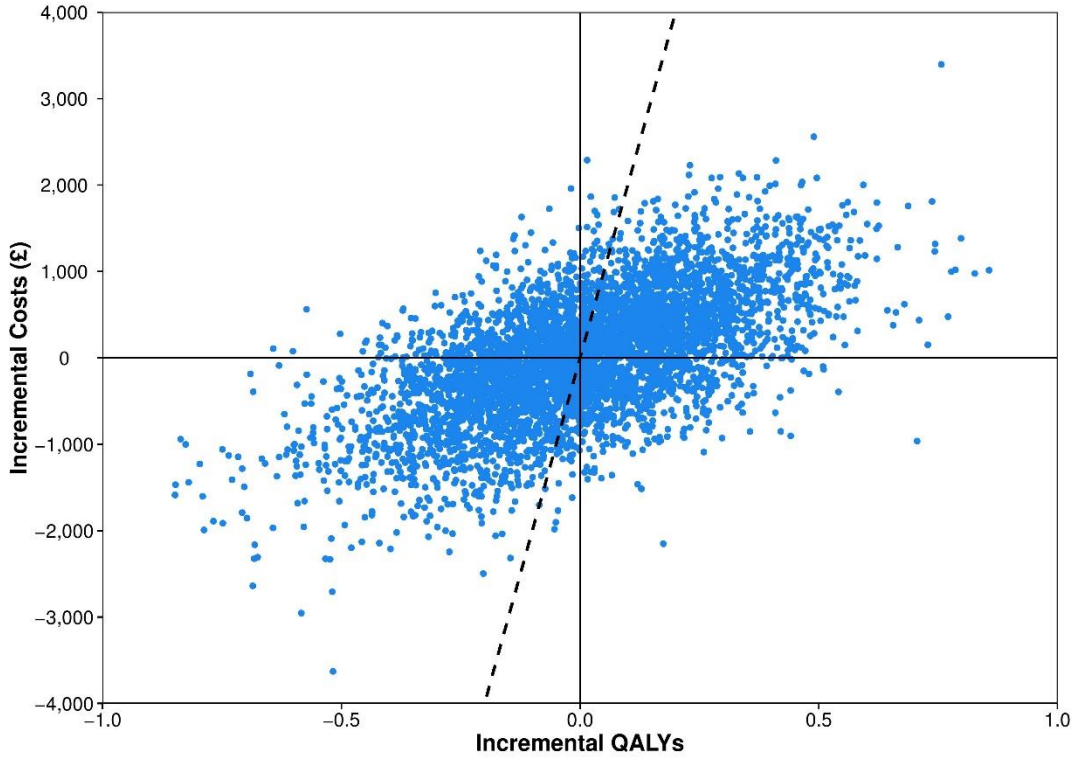

Figure 11: Scatterplot for incremental costs and QALYs (versus Empagliflozin 25mg)

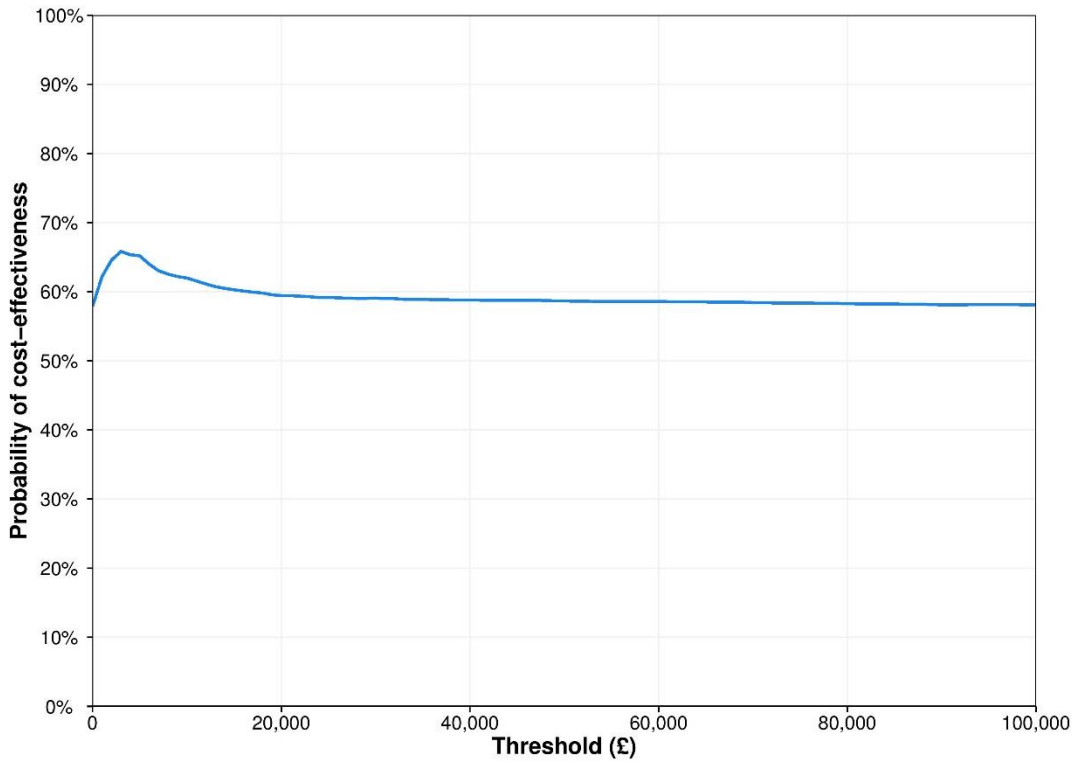

Figure 12: Cost-effectiveness acceptability curve (versus DPP4i)

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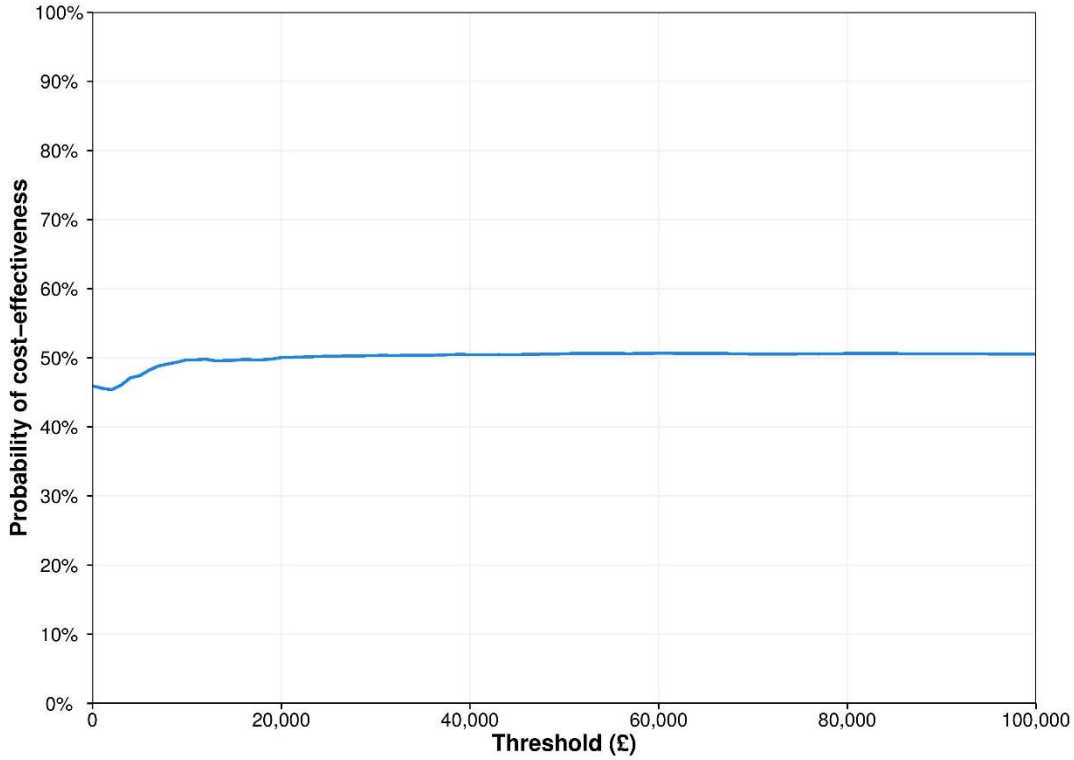

Figure 13: Cost-effectiveness acceptability curve (versus Canagliflozin 100mg)

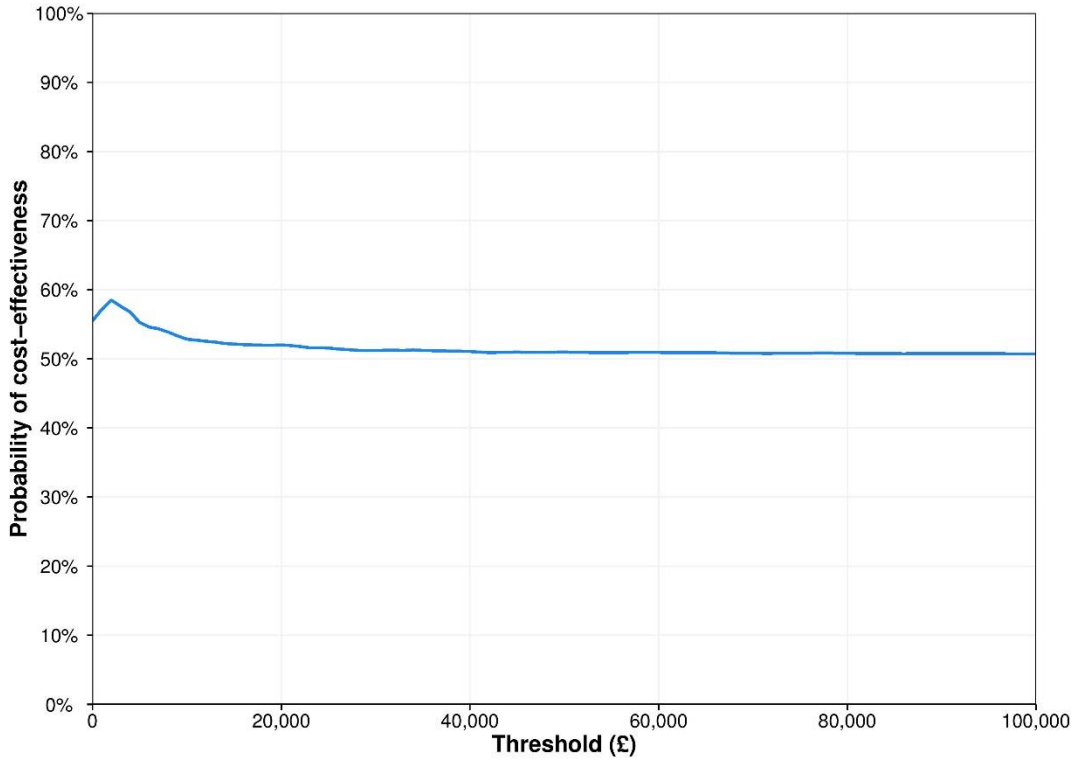

Figure 14: Cost-effectiveness acceptability curve (versus Canagliflozin 300mg)

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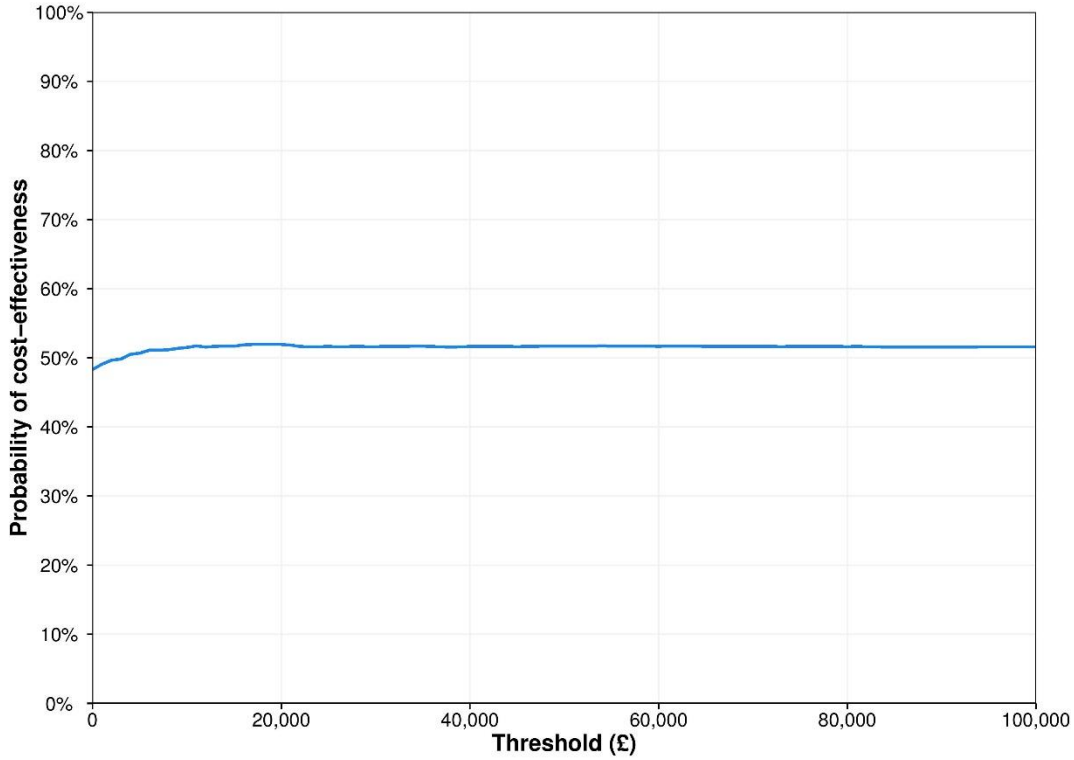

Figure 15: Cost-effectiveness acceptability curve (versus Empagliflozin 10mg)

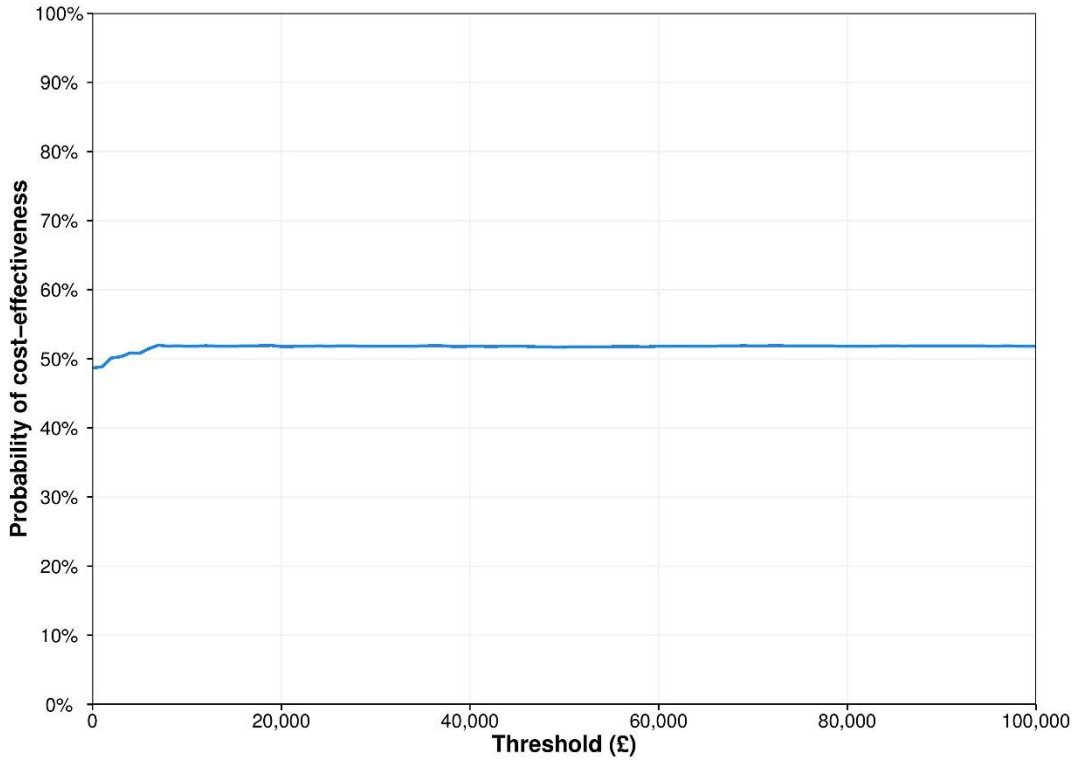

Figure 16: Cost-effectiveness acceptability curve (versus Empagliflozin 25mg)

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B1. **Priority question:** Dapagliflozin has a QALY gain compared with DPP4 inhibitors. Please describe the source of the QALY gain, including what contributions are from weight, HbA1c, SBP, lipids and hypoglycaemia events.

Response:

While it is not possible to separate the individual contributions of HbA1c and SBP due to their role as risk factors for the competing risks of long-term complications, further analysis has been undertaken to breakdown the impact of HbA1c and SBP, versus weight and hypoglycaemia on incremental QALYs, as presented in Table 17. Note that no difference in lipids was modelled and weight changes have no impact on predicted events when the UKPDS 68 event equations are utilised, as in the base case.

The predicted QALY gain associated with dapagliflozin versus DPP4 inhibitors is driven by the reduction in long-term complications as a result of an improved risk factor profile (HbA1c and SBP). As shown in Tables 48 and 49 of the submission, dapagliflozin is associated with an increase in life years and a slight decrease in vascular complications (associated QALY gain: +0.0283).

An additional QALY benefit is gained from the improved weight profile associated with dapagliflozin (+0.0041), which is very slightly offset by the impact of adverse events (UTI and GI; -0.0004) and hypoglycaemia (-0.0001).

Table 17: Breakdown of predicted incremental QALYs associated with Met+SU+dapagliflozin compared to MET+SU+DPP4-i in the base case analysis

Treatment	Incremental QALYs	Incremental QALY breakdown			
		Adverse events	Hypoglycaemia	BMI	Long-term complications
Incremental results (per patient)					
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	+0.032	-0.0004	-0.0001	+0.0041	+0.0283

QALYs, quality-adjusted life years

B2. **Priority question:** Table 38 of the submission gives figures for “Intensified insulin”. Please explain the company’s interpretation/definition of “intensified insulin”, and the source of the figures given for intensified insulin (particularly for hypoglycaemia). It is noted that in the cited reference (Waugh 2010) there is a figure of 1.11% for reduction in HbA1c (Table 38 of the HTA report), however this result is for glargine. Intensified insulin therapy usually refers to a basal bolus regimen.

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Response:

For the purpose of this analysis, intensified insulin is assumed to be a 50% increase in dose over the initial insulin dose used when starting insulin treatment (NICE TA288 2013). Model inputs (treatment effects) applied for intensified insulin were populated based on Waugh, et al (2010). Details of the utilised model input values are as follows:

HbA1c: The network meta-analysis reported in Waugh et al. concluded that there was no difference between insulin glargine and intensified NPH insulin with respect the HbA1c effect (Waugh, et al (2010); Chapter 4, figure 2); the HbA1c reduction of 1.11% reported for insulin glargine (Waugh, et al (2010); Table 38) was thus applied in the modelled intensified insulin arm. This approach is aligned with previous NICE submissions for dapagliflozin (TA288).

Weight: Waugh et al. state that a meta-analysis of weight change was not possible due to a large number of missing standard deviations. Therefore, the weight change from the PREDICTIVE-BMI trial (+1.6 kg) was utilised. This trial was chosen as it was the only relevant trial reported in the study undertaken in a non-chinese and non-treatment naive population.

Hypoglycaemia:

Both the number of symptomatic hypoglycaemia events and the proportion of severe events were sourced from Waugh et al. The number of symptomatic events was approximated by taking the total number of patients observing one or more symptomatic event across all studies and dividing by the total number of patients (498/809 = 0.616 [Waugh, et al (2010); Chapter 4, Figure 8]).The proportion of severe events was derived by taking the total number of severe events across all studies used in the hypoglycaemia network meta-analysis and dividing this by the total number of hypoglycaemic events (33/1,479 = 0.022 [Waugh, et al (2010); Chapter 4, Figure 8]).

An additional analysis was conducted to demonstrate the limited impact any uncertainty in these model inputs has on modelled results. Annual rates of 4.08 symptomatic and 0.1 severe hypoglycaemic events were applied to both Met+Insulin and Met+Intensified Insulin regimens, based on rates of hypoglycaemia reported by the UK hypoglycaemia study group (see reference below). Table 18 shows negligible differences in incremental results of the base case and sensitivity analysis.

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UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007 Jun;50(6):1140-7. Epub 2007 Apr 6.

Table 18: Summary of incremental results of sensitivity analysis conducted with alternate insulin hypoglycaemia rates5

Treatment	Δ Costs (£)	Δ QALYs	ICER(£/QALY)
Base case			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-118	0.0319	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	66	-0.0009	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-187	0.0026	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	10	0.0053	£1,965 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.0058	£1,354 Dapagliflozin cost-effective
Sensitivity			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-118	0.0319	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	64	-0.0009	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-27	-0.0003	£98,247 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	10	0.0053	£1,950 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.0058	£1,357 Dapagliflozin cost-effective
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

B3. Please outline how the baseline QoL value of 0.87 has been calculated and why this is preferred over the 0.85 baseline mean of study 5. Please also provide the VBA code for the age adjusted utility value in the absence of complications.

Response: The baseline utility of 0.87 was calculated utilising the following equation, which was derived from Health Survey for England data (2003) collected in patients with no major complications: Baseline utility = 1.2066 - 0.0184 *Age + 0.0004*Age2 - 0.0000*Age3 (coefficients rounded to 4 d.p.). Within the model, this value is derived on the "Advanced Inputs" worksheet and read into VBA when the relevant setting is activated from the "Model settings" menu (as in the base case). This method was applied to ensure consistency across analyses.

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The impact of using the alternative suggested baseline utility value has a negligible impact on predicted total and incremental QALYs and has no material impact on cost-effectiveness results, as shown in Table 19.

Table 19: Summary incremental results of sensitivity analysis conducted with baseline utility value 0.85

Scenario	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-118	0.032	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	66	-0.001	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-187	0.003	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	10	0.005	£1,965 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.006	£1,354 Dapagliflozin cost-effective
Sensitivity analysis			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-118	0.031	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	66	-0.001	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-187	0.003	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	10	0.005	£1,962 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.006	£1,355 Dapagliflozin cost-effective
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

B4. Appendix 22 outlines the code for the UKPDS 82 equations. Please:

a. provide the corollary for the event equations for the UKPDS 68 for both complications and deaths, and any other equations qualifying these equations, together with their sources.

b. provide a detailed explanation of how deaths are modelled when UKPDS 68 is selected for the model, the degree to which this corresponds with equations 8, 9 and 10 of UKPDS 68, and how this is qualified when the life tables check box is selected within the model.

c. outline if equation 14 of the UKPDS 68 has been applied, and if so how.

Response:

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a. Appendix 22 has been replicated for the UKPDS 68 equations. Though not utilised in the submitted analysis, life tables may be used to model death related to non-diabetes, non-event mortality when the UKPDS 68 event equations are utilised (see part b); as such the procedure used to evaluate life tables has also been included in this appendix.

b. When using the UKPDS 68 event equations, if the life tables option is not activated then mortality is modelled using UKPDS 68 equations 8 (event-related), 9 (diabetes-related) and 10 (other) (as published). If the life tables option is activated when using the UKPDS 68 event equations, event-related and diabetes-related mortality is modelled using UKPDS 68 equations 8 and 9; this probability is subtracted from all-cause death described by life-tables to model other deaths (avoiding potential double counting). This approach to modelling mortality was developed in accordance with a previous ERG as part of the NICE appraisal of dapagliflozin in combination therapy for the treating of type 2 diabetes (2013).

c. UKPDS 68 equation 14 (smoking status) has not been implemented. Contemporary trends in smoking behaviour are likely to have changed significantly, among the general population and diabetics, since the UKPDS study was conducted (1977-1997) (Figure 17). Smoking status at baseline is assumed to remain unchanged over the course of the simulation and used as a risk factor for MI, stroke and other death within the UKPDS 68 event equations (also, MI, stroke and death in UKPDS 82). The impact of this structural assumption is unlikely to significantly impact modelled results as demonstrated by the sensitivity analysis results shown in Table 20, in which alternative percentages of smokers were tested in the comparison of dapagliflozin versus DPP4 inhibitors.

Figure 17: Proportion of population who smoke cigarettes, by sex, Great Britain 1974-2013 (Source: Opinions and Lifestyle Survey, General Lifestyle Survey, General Household Survey - Office for National Statistics)

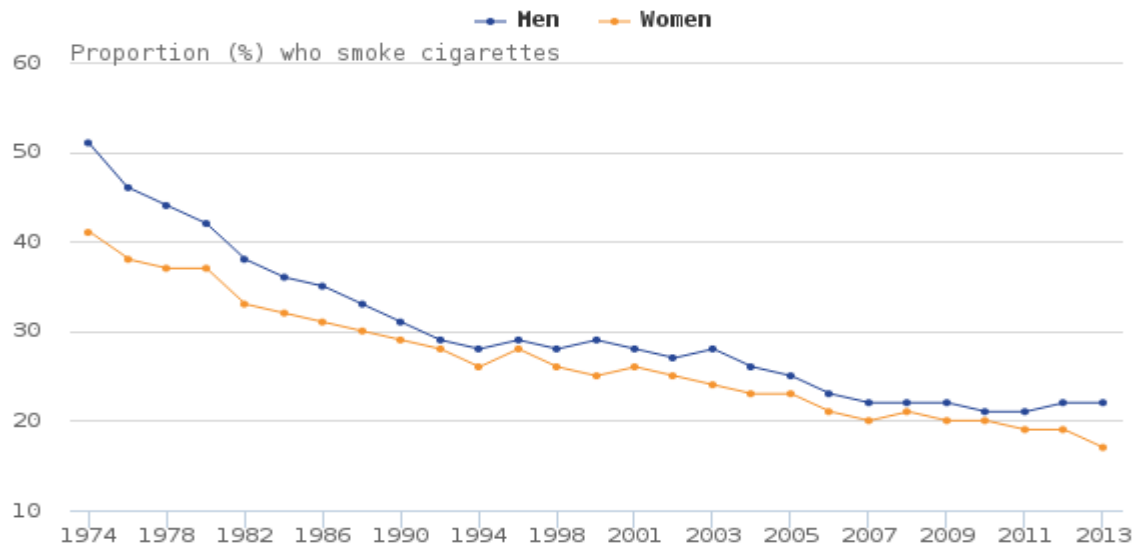

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Table 20: Summary results of sensitivity analysis testing alternative smoking inputs for the comparison of Met+SU+dapagliflozin compared to MET+SU+DPP4-i

Scenario	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case (19% smoker)	-118	0.032	Dapagliflozin dominates
Sensitivity: 0% smoker	-120	0.032	Dapagliflozin dominates
Sensitivity: 100% smoker	-109	0.034	Dapagliflozin dominates
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

B5. **Priority question:** Within the model it appears that in some instances, patients do not immediately switch treatments when HbA1c rises above the set threshold, but instead continue treatment for six months (or more) before changing therapy. For example, in the model, in the Biannual Risk Factor Input worksheet, in cells AM5:AM6, the switch to 2nd line therapy appears to be delayed by one cycle, suggesting that those in the DPP4-inhibitor arm remain on the more expensive triple therapy for too long. Cells AR6:AR8 suggest that there is no parallel delay in the dapagliflozin arm. Is this an error, or does the model assume that treatment switches occur at year ends (which would obviate the need for a six month cycle)?

Response:

There is no error in the model but as suggested the model only allows switches in therapies to occur at the end of each year. All therapies are subject to the same structural assumption within the model. This approach is common within T2DM models, with most models operating over annual cycles.

B6. From the data in visual basic, it appears that the evolution of HbA1c, when applying the UKPDS 68 equation, is deterministic. Please state whether the modelled evolutions of HbA1c, SBP and TC:HDL ratio within the PSA are deterministic or probabilistic in terms of the UKPDS 68 parameters.

Response: The evolution of risk factors (HbA1c, SBP and TC:HDL) is modelled deterministically (i.e. the parameters of the UKPDS equations are not sampled).

B7. **Priority question:** UKPDS 68 equations 11, 12 and 13 clearly differentiate between values at diagnosis and values lagged by one year; e.g. HBA1C_BASE and LHBA1C. However, in the model, the clinical risk factors that appear when clicking on the Select Patient Profile button of the Simulation worksheet do not appear to make this distinction. Please outline what the HbA1c, SBP, TC and HDL values are at diagnosis and what the values are at baseline and where these values can be found within the model.

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Response: HbA1c, SBP, TC and HDL values at diagnosis are not required model inputs, since this data is rarely available. Whenever the UKPDS equations call for risk factor values at diagnosis, the baseline value (prior to the application of any treatment effects, as specified in the Patient Profile) are implemented as a proxy. This approach was developed in accordance with a previous ERG as part of the NICE appraisal of dapagliflozin in combination therapy for the treating of type 2 diabetes (2013).

B8. **Priority question:** When using the UKPDS 82 modelling, please:

a. provide more detail about the assumptions used for the evolution of HbA1c, SBP, TC:HDL ratio, smoking status, BMI, eGFR, haemoglobin, albuminuria, WBC and heart rate.

b. clarify whether secondary events are simulated during a UKPDS 82 based analysis.

c. outline how to run the model to replicate the scenario analysis of the UKPDS 82 equations.

Response:

a. Modelling the evolution of HbA1c, SBP, TC:HDL, smoking status and BMI follows identical methodology when using either set of event equations. Since there is not yet sufficient published evidence characterising the natural evolution of eGFR, haemoglobin, albuminuria, WBC and heart rate, these risk factors are assumed to remain constant under natural history (i.e. in the absence of treatment effects).

b. If the UKPDS 82 event equations are utilised then secondary MI (equation 5), stroke (equation 6) and amputation (equation 12) are modelled.

c. To replicate the scenario analysis, the "UKPDS 82" option should be selected in the "Equation selection" drop-down menu at the top-left of the "Simulation" worksheet. Table 21 presents the results of this analysis.

Table 21: Summary results of sensitivity analysis testing the use of UKPDS 82 event equations for the comparison of Met+SU+dapagliflozin compared to MET+SU+DPP4-i

Scenario	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case (UKPDS 68)	-118	0.032	Dapagliflozin dominates
Sensitivity: UKPDS 82	64	0.018	£3,532 Dapagliflozin cost-effective
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

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B9. For the disutility associated with hypoglycaemia, both the NICE diabetes clinical guideline (NG28) and the Assessment Group report for SGLT2-inhibitor monotherapy for diabetes (TA390) note that non-severe hypoglycaemia event rates need to be converted to 3-monthly rates (due to the recall period in Currie et al before the 1.773 HFS coefficient can be applied). Please confirm if this assumption has been used in the current modelling. It also appears that the model does not include the Insulin use 2.668 coefficient of Currie et al, despite patients intensifying to insulin at different time points as determined by a treatments' initial HbA1c effect. Please confirm if this is the case, and if so, what would be the probable impact of including the 2.668 coefficient?

Response:

The model does apply methodology in line with this assumption, accounting for the 3-month recall period in the underlying utility study.

We chose to implement only the marginal effects of hypoglycaemia from the Currie, et al (2006) equation, principally due to the fact that the Cardiff Model captures age and treatment-related changes in utility as part of the natural progression of patients through the model. Specifically, the insulin coefficient from the fear of hypoglycaemia equation has not been implemented within the model, nor has age or the other covariates included in the EQ-5D equation (BMI, CHD, CVD, Diabetic foot and ESRD) to avoid potential double counting the impact of these variables elsewhere in the model. It should be noted that it is not customary within diabetes modelling to apply an insulin-disutility (related to fear of hypoglycaemia, fear of injections, fear of weight gain etc.) in addition to the associated incidence of adverse events and hypoglycaemia; furthermore, to do so would be inconsistent with the NICE diabetes guideline (NG28) and previous technology assessments.

Since treatment escalation occurs at the same time for all simulated treatments, with the exception of canagliflozin (300 mg), the impact on modelled results is unlikely to be significant. The impact of insulin on the hypoglycaemia fear score (HFS) can be approximated within the model by applying a disutility via a dummy adverse event within the appropriate therapy profile, using the following: Insulin HFS change * HFS utility change = 2.668 * -0.008 = -0.021344. When this additional disutility of insulin is applied to insulin therapies within the comparison of dapagliflozin against canagliflozin (300 mg) the results change as shown in Table 22. Under the assumption of the base case and scenario analysis incremental QALYs are small, indicating that the two therapies lead to similar predicted outcomes; however, it should be noted that this comparison does not reflect the use of canagliflozin in clinical practice. The starting dose for all patients on canagliflozin is 100mg and this is increased to 300 mg as required.

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Table 22: Summary results of sensitivity analysis testing additional disutility applied to insulin therapies for the comparison of Met+SU+dapagliflozin compared to MET+SU+canagliflozin (300mg)

Scenario	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case	-187	0.003	Dapagliflozin dominates
Sensitivity: additional insulin disutility	-187	-0.015	£12,396 Dapagliflozin cost-effective
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

B10. The control arm does not have the £47 one off costs of renal functioning and creatinine clearance monitoring. Please confirm if this assumption was also used within the base case modelling. Please also confirm if the costs in cells B110:B119 are additional to those of cells B8:B40; i.e. would a patient with blindness maintenance have an annual cost of £714+£512 applied?

Response: The base case analysis includes an additional one-off cost of renal function monitoring/testing (£47) applied to dapagliflozin; conservatively, this cost was not applied in the control arm.

Since all SGLT-2 inhibitors would be subject to such requirements, the exclusion of this cost in the control arm biases against dapagliflozin in comparisons against other treatments in the same class: canagliflozin and empagliflozin. Table 23 presents the results of a sensitivity analysis in which the additional cost of renal monitoring/testing was applied to all SGLT-2 inhibitors. The cost-effectiveness conclusions of the base case remain unchanged or improve; in the comparisons of dapagliflozin versus empagliflozin, dapagliflozin changes from highly cost-effective in the base case to the dominant therapy in the sensitivity analysis.

Table 23: Summary results of sensitivity analysis in which the one-off cost of renal function monitoring/testing was applied to all SGLT-2 inhibitors

Treatment	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-118	0.0319	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	66	-0.0009	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-187	0.0026	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	10	0.0053	£1,965 Dapagliflozin cost-effective

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MET + SU + Dapagliflozin versus Empagliflozin (25mg)	8	0.0058	£1,354 Dapagliflozin cost-effective
Sensitivity			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	As base case	As base case	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	19	-0.001	Canagliflozin 100mg dominates
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-234	0.003	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	-37	0.005	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	-39	0.006	Dapagliflozin dominates
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

The complication costs in cells B8:B40 of the "Cost Profiles" worksheet are applied (to patients experiencing complications) in addition to the costs contained in cells B110:B119 of the same sheet.

B11. **Priority question:** In the probabilistic sensitivity analyses, what were the central estimates of the costs and QALYs, and what is the variance reduction? Please also clarify whether figure 33 presents the likelihood of dapagliflozin being more cost effective than canagliflozin 300mg or the likelihood of canagliflozin 300mg being more cost effective than dapagliflozin.

Response: Table 24 summarises the point estimates of the PSA results.

Table 24: Point estimates of incremental cost and QALYs produced from PSA

Treatment	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Incremental results (per patient)			
MET + SU + Dapagliflozin versus MET + SU + DPP4-i	-140	0.0387	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Canagliflozin (100mg)	58	0.0035	£16,612 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Canagliflozin (300mg)	-104	0.0019	Dapagliflozin dominates
MET + SU + Dapagliflozin versus Empagliflozin (10mg)	13	0.0046	£2,754 Dapagliflozin cost-effective
MET + SU + Dapagliflozin versus Empagliflozin (25mg)	11	0.0054	£1,978 Dapagliflozin cost-effective
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio			

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Within the Cardiff Model, variance reduction relates to the application of antithetic variates within the PSA. The technique of antithetic variates aims to provide reductions in stochastic uncertainty, through the introduction of negatively correlated pairs of simulation replicates (Glasserman, P. (2004) Monte Carlo Methods in Financial Engineering. Los Angeles (CA): Springer Science.). Consequently, the precision of modelled outputs may be improved and the number of simulation runs (and hence runtime) to produce stable point estimates may be reduced. The following publications discuss the application of antithetic variates within the Cardiff Model:

- McEwan P, Bergenheim K, Yuan Y, Tetlow AP, Gordon JP. Assessing the relationship between computational speed and precision: a case study comparing an interpreted versus compiled programming language using a stochastic simulation model in diabetes care. Pharmacoeconomics 2010; 28(8):665-74

- Bennett H, Tetlow AP, McEwan P. Variance reduction through antithetic variates as a means of developing complex VBA models with reasonable computation times. Value in Health 2013; 16(7):A585-6

Figure 33 of the submission document presents the probability of dapagliflozin being more cost-effective than canagliflozin.

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Section C: Textual clarifications and additional points

C1. On page 119, the company submission states "For the purposes of this analysis, a total of 5,000 simulations, each containing 5,000 patients, were undertaken". However, it is unclear how this relates to the results of the base case, the PSA results and the model inputs in the Simulation worksheet:

a. Does the Simulation worksheet number of runs correspond to the number of monte carlo trials each patient is run through, or to the number of PSA iterations when second order sampling is being explored?

b. When running the model with the Mean Value Analysis selected with a cohort size of 5,000 and a number of runs of 5,000, how many monte carlo trials is each of the 5,000 patients subject to; i.e. how many times is each of the 5,000 patients run through the model?

c. When running the model with the Probabilistic Sensitivity Analyses selected with a cohort size of 5,000 and a number of runs of 5,000, how many PSA iterations are each of the 5,000 patients subject to; i.e. how many sets of parameter values are sampled with the model being run once for each of these parameter sets, and for each model PSA iteration and parameter set, how many monte carlo trials is each of the 5,000 patients subject to?

d. Do the results of table 48 correspond to a Mean Value Analysis or a Probabilistic Sensitivity Analyses?

e. Do the results of table 51 correspond to a Mean Value Analysis or a Probabilistic Sensitivity Analyses?

Response: The cohort size represents the number of times a patient is simulated within a single simulation run (i.e. cohort size of 5,000 represents the replication of 5,000 patients that are identical at baseline). The number of runs represents how many cohorts are simulated. Regardless of the analysis mode (mean values or PSA), cohorts of 5,000 identical patients were simulated in each of 5,000 runs. In the mean values analysis the same model inputs were used in each run; in PSA a new set of sampled model inputs were utilised in each run.

a. Please see above explanation.

b. If mean values analysis is conducted, a total of 5,000x5,000 Monte Carlo simulations will be conducted (with each patient identical at baseline).

c. If PSA is conducted, a total of 5,000 sets of sampled parameter values are tested; within each PSA iteration (run), 5,000 identical patients are simulated (Monte Carlo simulations).

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d. Table 48 of the submission document corresponds to results of mean values analysis.

e. Table 51 of the submission document corresponds to results of mean values analysis.

C2. Please describe what effect the “Number of years at or below target” variable has upon the model.

Response: The modelled scenario is not impacted by the therapy targets defined in the "Model settings" or the number of years (x) defined on the Results worksheet. These additional results track the proportion of patients whose risk factors (HbA1c, SBP and weight) lie below specified thresholds, over the first x years. This functionality is purely informative, with no impact on the modelled pathway and has no relevance to the current evaluation.

C3. Please clarify if the scenario analysis of no AE disutility values applies only to UTIs and GTIs, or also to hypoglycaemic events.

Response: The scenario analysis of no AE disutility values applies to UTI and GI events only; disutility associated with hypoglycaemia is modelled in this scenario.

C4. Please clarify if the disutility for BMI is applied only when a patient’s BMI is above 25kg/m^2 or is applied more generally to weight gains and losses relative to the patient’s baseline BMI.

Response: The model follows the latter approach, applying utility consequences to changes in BMI. It should be noted that modelled BMI is always above 25 kg/m2.

C5. Please expand table 37 to provide the baseline characteristics for the UKPDS 82 modelling. The UKPDS 82 specific modifiable risk factors and the proportions with a clinical history are the same for the base case and the THIN scenario analysis. What are the sources of these estimates?

Response:

Table 25 presents an extension to table 37 of the submission document. The patient profile applied in the base case analysis and UKPDS 82 scenario analysis was identical; however, the UKPDS 82-specific risk factors (LDL, eGFR, haemoglobin, albuminuria, WBC, and heart rate) had no impact on the base case analysis.

Additional baseline characteristics required for the application of the UKPDS 82 equations were populated based on values reported in the UKPDS 82 study, since this data was not available from Matthaei 2015b or NICE clinical guideline NG28.

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All clinical event history data were obtained from NG28, since this data was not available from Matthaei 2015b. In the development of NG28, the NICE Internal Clinical Guidelines team analysed THIN data for patient groups defined by duration of diabetes; the second intensification group was selected based on durations of diabetes 6.5-10.5 years. The mean duration of diabetes of Matthaei 2015b falls comfortably within this range.

Table 25: Summary of baseline variables applied in the economic model under base case and scenario analyses

Input parameter	Add on to MET+SU Dapa RCT (SE) (Matthaei 2015b)	Alternative population THIN data second intensification	Additional inputs required in UKPDS 82 scenario analysis
Demographics			
Current Age (yrs)	61.00 (0.64)	65.4	As base case
Proportion female	0.51 (0.03)	0.44	As base case
Duration diabetes (yrs)	9.45 (0.43)	8.5	As base case
Height (m)	1.68 (0.00)*	1.68	As base case
Proportion AC	0.0270 (0.0008)*	0.0270	As base case
Proportion Indian	0.0270 (0.0008)*	0.0270	As base case
Proportion smokers	0.1900 (0.0019)*	0.1900*	As base case
Modifiable risk factors			
HbA1c (%)	8.15 (0.06)	7.9	As base case
Total Cholesterol (mg/dL)	211.97 (0.21)*	211.97	As base case
HDL Cholesterol (mg/dL)	46.72 (0.06)*	46.72	As base case
SBP (mmHg)	135.40 (0.09)	143.2	As base case
Weight (kg)	89.35 (1.15)	86.7	As base case
LDL Cholesterol (mg/dL)	NA	NA	93.85
eGFR (ml/min/1.73m^2)	NA	NA	77.5
Haemoglobin (g/dL)	NA	NA	14.5
Albuminuria (mg/L)	NA	NA	47
White blood cell count (x106/ml)	NA	NA	6.8
Heart rate (BPM)	NA	NA	72
Clinical event history			
AF	0.0063 (0.0004)*	0.0063	As base case
PVD	0.0047 (0.0003)*	0.0047	As base case
IHD	0.0970 (0.0014)*	0.0970	As base case
MI	0.0250 (0.0008)*	0.0250	As base case

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CHF	0.0230 (0.0007)*	0.0230	As base case
Stroke	0.0180 (0.0006)*	0.0180	As base case
Amputation	0.0040 (0.0003)*	0.0040	As base case
Blindness	0.0220 (0.0007)*	0.0220	As base case
ESRD	0.0100 (0.0005)*	0.0100	As base case
Abbreviations: AC, Afro-Caribbean; AF, atrial fibrilation; CHF, congestive heart failure; DPP4, dipeptidyl peptidase 4 inhibitor; ESRD, end-stage renal disease; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IHD, ischaemic heart disease; MET, metformin; n/a, not available; MI, myocardial infarction; NMA, network meta-analysis; PVD, peripheral vascular disease; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea;			
*Values based on THIN data reported in NG28			

C6. When the baseline characteristics are sampled, are they sampled independently or is there an underlying variance-covariance structure?

Response: Since variance-covariance data is rarely available, baseline characteristics are sampled independently within the model.

C7. Are the discontinuation rates only applied during the 1st cycle of treatment? What is assumed to happen to those who discontinue?

Response: The probability of discontinuation is evaluated in the first cycle of treatment only. If patients discontinue therapy they commence the next line of therapy (e.g. patients discontinuing Met+SU+Dapa receive Insulin+Met therapy). Discontinuation from third line is not modelled.

C8. Please clarify if the adverse event rates of table 38 are annual, six monthly or something else. Please also clarify if the electronic model treats these and the rates of hypoglycaemic events as being annual, six monthly or something else.

Response: The rates reported in Table 38 are annual. Model inputs are specified as annual values and transformed dynamically for application over the model's 6-month cycles.

C9. Please provide the spreadsheet estimating daily insulin costs of £0.0055 per kg/day and £0.0082 per kg/day.

Response: In line with the updates highlighted in the Model review section, updated therapy costs are provided in Table 26-Table 28.

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Table 26: Derivation of tablet-based therapy costs

Therapy	Price per pack	Tablets per pack	Price per tablet Φ	Dose per tablet	Daily dose	Annual cost (£)
Dapagliflozin	£36.59	28	£1.31	10 mg	10 mg	£476.98
DPP4-is						
Sitagliptin	£33.26	28	£1.19	100 mg	100 mg	£433.57
Saxagliptin	£31.60	28	£1.13	5 mg	5 mg	£411.93
Vildagliptin	£33.35	56	£0.60	50 mg	100 mg	£434.74
Linagliptin	£33.26	28	£1.19	5 mg	5 mg	£433.57
Alogliptin	£26.60	28	£0.95	25 mg	25 mg	£346.75
Weighted average of DPP4-is*	-	-	-	-	-	£428.62
SGLT2s						
Canagliflozin	£39.20	30	£1.31	100/300 mg	100/300 mg	£476.93
Empagliflozin	£36.59	28	£1.31	10/25 mg	10/25 mg	£476.98
Other						
SU (Gliclazide)	£0.85	28	£0.03	80 mg	160 mg	£22.16
MET	£1.30	56	£0.02	850 mg	1700mg	£16.95

MET, metformin; SU, sulfonylurea.
*Weighted cost based on prescription estimates for UK with 71% sitagliptin, 10% saxagliptin, 12% linagliptin 3% vildagliptin and 3% alogliptin (due to rounding, the remaining 1% was equally distributed across all regimens) (AstraZeneca 2013b)

Table 27: Derivation of insulin-based therapy costs

Insulin therapy	Price per pack	Size of pack	Price per IU	Estimated daily dose	Daily dose per kg^	Cost per kg per day (£)
Insulin (Insuman basel) – add-on to MET	£17.50	5 x 3ml	£0.0117	40 IU	0.46	£0.00538

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Intensified insulin (Insuman basel) – add-on to MET	£17.50	5 x 3ml	£0.0117	60 IU	0.69	£0.00807

MET, metformin.
^Assuming average body weight of 86.7kg

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Table 28: Therapy costs applied in model

Therapy	Non-insulin annual cost (£)	Insulin cost per kg per day (£)
Dapagliflozin + MET + SU	£516.08	-
DPP4i + MET + SU	£467.73	-
Canagliflozin 100/300mg + MET + SU	£516.04	-
Empagliflozin 10/25mg + MET + SU	£516.08	-
Insulin + MET	£16.95	£0.00538
Intensified Insulin + MET	£16.95	£0.00807
MET, metformin; SU, sulfonylurea.		

C10. Is there any cost consideration of self-monitoring of blood glucose for those intensifying to insulin?

Response: No cost of self-monitoring of blood glucose has been incorporated. Since escalation to insulin therapy occurs at the same (or similar) times across the modelled arms, the impact of including such a cost would be negligible on incremental results.

C11. Within the T2 events of the model what does TTG stand for, how is it calculated and why does it fall to zero between year 9 and year 10?

Response: TTG stands for treat to goal; zero values indicate that no patients meet a specified HbA1c criteria. The results displayed in this row serve a similar purpose to those described in C2, but do not directly correlate. This summary output is not a supported feature of the model and is not relevant to the current evaluation; furthermore, it is note related to, or used for any aspect of the cost-effectiveness calculations.

C12. Please provide the technical report for the model.

Response: The technical report for the Cardiff model has been provided in an appendix.

UKPDS 68 coded equations

Ishaemic heart disease

Cumulative probability

```
Private Function equationIHD(time As Double) As Double

    Dim beta As Double

    beta = -5.31 + 0.031 * ageTransform - 0.471 * sex + 0.125 * hba1c + 0.098 * sbp + 1.498 *
    logTcHdlRatio

    equationIHD = Exp(beta) * time ^ 1.15

End Function
```

Risk

```
    ihdRisk = 1 – Exp(equationIHD (startTime),  equationIHD(endTime))
```

Myocardial Infarction

Cumulative probability

```
Private Function equationMI(time As Double) As Double

    Dim beta As Double

    beta = -4.977 + 0.055 * ageTransform - 0.826 * sex - 1.312 * ac + 0.346 * smoke + 0.118 *
    hba1c + 0.101 * sbp + 1.19 * logTcHdlRatio + 0.914 * ihd + 1.558 * chf

    equationMI = Exp(beta) * time ^ 1.257

End Function
```

Risk

```
    miRisk = 1 – Exp(equationMI (startTime),  equationMI (endTime))
```

Congestive Heart Failure

Cumulative probability

```
Private Function equationCHF(time As Double) As Double

    Dim beta As Double

    beta = -8.018 + 0.093 * ageTransform + 0.066 * bmi + 0.157 * hba1c + 0.114 * sbp

    equationCHF = Exp(beta) * time ^ 1.711

End Function
```

Risk

```
    chfRisk = 1 – Exp (equationCHF (startTime),  equationCHF (endTime))
```

Stroke

Cumulative probability

```
Private Function equationSTROKE(time As Double) As Double

    Dim beta As Double

    beta = -7.163 + 0.085 * ageTransform - 0.516 * sex + 0.355 * smoke + 0.128 * hba1c + 0.276
    * sbp + 0.113 * tcHdlRatio + 1.428 * af + 1.742 * chf

    equationSTROKE = Exp(beta) * time ^ 1.497

End Function
```

Risk

```
    strokeRisk = 1 – Exp (equationSTROKE (startTime),  equationSTROKE (endTime))
```

Amputation

```
Private Function equationAMP(time As Double) As Double

    Dim beta As Double

    beta = -8.718 + 0.435 * hba1c + 0.228 * sbp + 2.436 * pvd + 1.812 * blind

    equationAMP = Exp(beta) * time ^ 1.451

End Function
```

Risk

```
    ampRisk = 1 – Exp (equationAMP (startTime),  equationAMP(endTime))
```

Blind

Cumulative probability

```
Private Function equationBLIND(time As Double) As Double

    Dim beta As Double

    beta = -6.464 + 0.069 * ageTransform + 0.221 * hba1c

    equationBLIND = Exp(beta) * time ^ 1.154

End Function
```

Risk

```
    blindRisk = 1 – Exp (equationBLIND (startTime),  equationBLIND(endTime))
```

End-stage renal disease

Cumulative probability

```
Private Function equationRENAL(time As Double) As Double
    Dim beta As Double
    beta = -10.016 + 0.404 * sbp + 2.082 * blind
    equationRENAL = Exp(beta) * time ^ 1.865
End Function
```

Risk

```
    blindRisk = 1 – Exp (equationRENAL (startTime),  equationRENAL(endTime))
```

Event Mortality

Fatal probability

```
Private Function equationFatal() As Double
    Dim beta As Double
    Dim logAgeEvent As Double
    logAgeEvent = log(age_event) - log(52.59)
    beta = -3.251 + 2.772 * logAgeEvent + 0.114 * hba1c + 2.64 * mi + 1.048 * stroke
    equationFatal = Exp(beta) / (1 + Exp(beta))
End Function
```

Risk

```
    eventFatalRisk = equationFatal()
```

Diabetes Related Mortality

Cumulative probability

```
Private Function diabetesRelatedMortality(time As Double) As Double
    Dim beta As Double
    Dim logAgeEvent As Double
    logAgeEvent = log(age_event) - log(52.59)
    beta = -5.124 + 4.731 * logAgeEvent + 0.109 * tcHdlRatio + 1.119 * miPost + 3.939 * miEvent
    + 2.807 * strokeEvent + 1.585 * renal + 1.032 * amp
    diabetesRelatedMortality = Exp(beta) / 0.003 * (Exp(0.003 * time) - 1)
```

End Function

Risk

diabetesRelatedFatalityRisk = 1 – Exp (diabetesRelatedMortality (startTime),

diabetesRelatedMortality (endTime))

<u>All Cause Mortality (Life Tables not used)</u>

Cumulative probability

Private Function allCauseDeath(time As Double) As Double

Dim beta As Double

beta = -6.373 + 0.081 * ageTransform * sex + 0.104 * ageTransform * (1 - sex) +
0.307 * smoke

allCauseDeath = Exp(beta) / 0.154 * (Exp(0.154 * time) - 1)

End Function

Risk

allCauseMortality = 1 – Exp (allCauseDeath (startTime), allCauseDeath (endTime))

<u>Other Cause Mortality (Life Tables used)</u>

Cumulative probability

Private Function otherCauseDeath() As Double

otherCauseDeath = sex * lifeTables(2, ageYears) + (1 - sex) * lifeTables(1, ageYears)

End Function

Risk

allCauseMortality = otherCauseDeath * (1 - probDiabetesMortality)

7

TECHNICAL REPORT
The Cardiff Diabetes Model

Prepared for

AstraZeneca

This technical report has been prepared for AstraZeneca by Health Economics & Outcomes Research (HEOR) Ltd, in collaboration with the Swansea Centre for Health Economics (SCHE) at Swansea University.

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Abbreviations

ACM	All-cause mortality
AE	Adverse event
BMI	Body mass index
CEAC	Cost effectiveness acceptability curve
CHF	Congestive heart failure
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
dll	Dynamic link library
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQoL-5 Dimensions
HbA1c	(Glycated) haemoglobin A1c
HCU	Health care utilisation
HDL-C	High density lipoprotein cholesterol
HRQoL	Health-related quality of life
HRs	Hazard ratios
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
LDL-C	Low Density Lipoprotein cholesterol
MI	Myocardial infarction
NA	Not applicable
NR	Not reported
NICE	National Institute for Health and Care Excellence
OAD	Oral anti-diabetic agent
PSSRU	Personal Social Services Research Unit
PSA	Probabilistic sensitivity analysis
QALM	Quality adjusted life month
QALY	Quality-adjusted life-year
QoL	Quality of life
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
VBA	Visual Basic for Applications
WBC	White blood cell

1 Introduction

1.1 Background

Type 2 diabetes mellitus (T2DM) is a chronic condition associated with substantial excess morbidity and mortality. The current and expected future healthcare expenditure associated with managing T2DM is substantial. Simulation models are vital tools to support decision making in this area.

The Cardiff Diabetes Model is an economic model designed to evaluate the cost-effectiveness of comparator therapies in diabetes. The original Cardiff Diabetes Model has been used as the basis of a number of previous models including those developed for the economic evaluation of Forxiga (dapaglifloxin) in collaboration with AstraZeneca and Bristol-Myers Squibb, and Onglyza (saxagliptin) before that.

Previously constructed models were developed utilising equations from the United Kingdom Prospective Diabetes Study (UKPDS)[1] and have been internally validated against the UKPDS 68 study[2], externally validated as part of the Mount Hood Challenges and endured the scrutiny associated with peer-reviewed publications[3-6] and health technology assessments.

The model has been designed to determine the cost-effectiveness of a particular 'treatment' arm compared to a 'control' arm, with each arm comprised of up to three lines of therapy. The model provides estimates of the long-term economic and health impact of managing T2DM patients. Cost-effectiveness is assessed in terms of the cost per quality adjusted life year (QALY) gained (i.e. how much it costs for one year of life at full health).

This report outlines the design, structure and input parameters used when modelling treatment of a T2DM population.

1.2 Objectives

This version of the Cardiff Diabetes Model was further developed to:

- Provide users with a new interface
- Incorporate the UKPDS 82 events equations[7]
- Output patient level model outputs

2 Model Overview

2.1 Implementation

The Cardiff Diabetes Model is a patient level fixed-time increment, Monte Carlo micro simulation model. It has been designed to run within a Microsoft Excel front-end that provides data input for dynamic link libraries (dlls) that perform the computational component of the simulations. The simulation engine is written in C++ and compiled into a dll to minimise computation time.

2.2 Model structure and simulation process

The model was designed to simulate the disease progression of a cohort of subjects (typically up to 10,000) over a maximum of 40 years. The logical flow of the model is depicted in Figure 1. The model utilizes published UKPDS68 [2] and UKPDS82 [7] risk equations to estimate the risk of clinical endpoints associated with T2DM.

In the initial run (control arm) of the model, a patient cohort is generated based upon the mean demographic, clinical and risk factor profiles defined by the user. Modifiable risk factor profiles are adjusted to reflect any treatment effect specified for weight, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) and/or HbA1c for the control group. Each simulated subject of the generated cohort is then progressed through the model in 6-monthly time increments. At the beginning of each time period (cycle) modifiable risk factors, including; weight, TC, HDL-C, SBP, HbA1c, low-density lipoprotein cholesterol (LDL-C), heart rate, haemoglobin, albuminuria, white blood cell (WBC) count and estimated glomerular filtration rate (eGFR) are progressed in line with estimations of their natural history. Each risk factor influences the likelihood of clinical events occurring and thus alters the probability of events over an individuals simulated time horizon.

Once the trajectories of risk factors have been updated, checks are made for specific fatal or non-fatal events. Predicted clinical events (and their related risk equations) include the incidence of micro- and macro-vascular events [2, 7], hypoglycaemia, all-cause mortality[2, 7], and adverse events. The sequence of these checks is randomised (see section 2.3 for further detail). If a fatal event occurs, all costs, life years and quality adjusted life years (QALYs) are accumulated and the simulation ends for that subject.

The model then selects the next subject to simulate and the process begins again. Assuming a subject does not die in a specific year then following the ‘check for events’ stage a simulated subjects’ disease state is updated, any appropriate decrement in health utility is applied together with any costs associated with treatment, complications and/or maintenance of therapy. The simulation clock is then advanced and the process repeated until the time horizon is reached, at which point the simulation ends for that subject and the process starts again with the next simulated subject.

The second run (treatment arm) of the model utilises exactly the same patient cohort data (i.e. baseline demographics and modifiable risk factors) as the initial run, but applies the treatment

specific effects for the treatment group to the relevant variables (weight, TC, HDL-C, SBP, and/or HbA1c). Additionally, applied therapy costs will differ depending on the user defined unit costs supplied. After applying any differential effects to the patient data the model is then re-initialised and run through in exactly the same manner as for the initial run.

Once all individuals have been simulated the process ends and all summary statistics are collected for that particular run of the model.

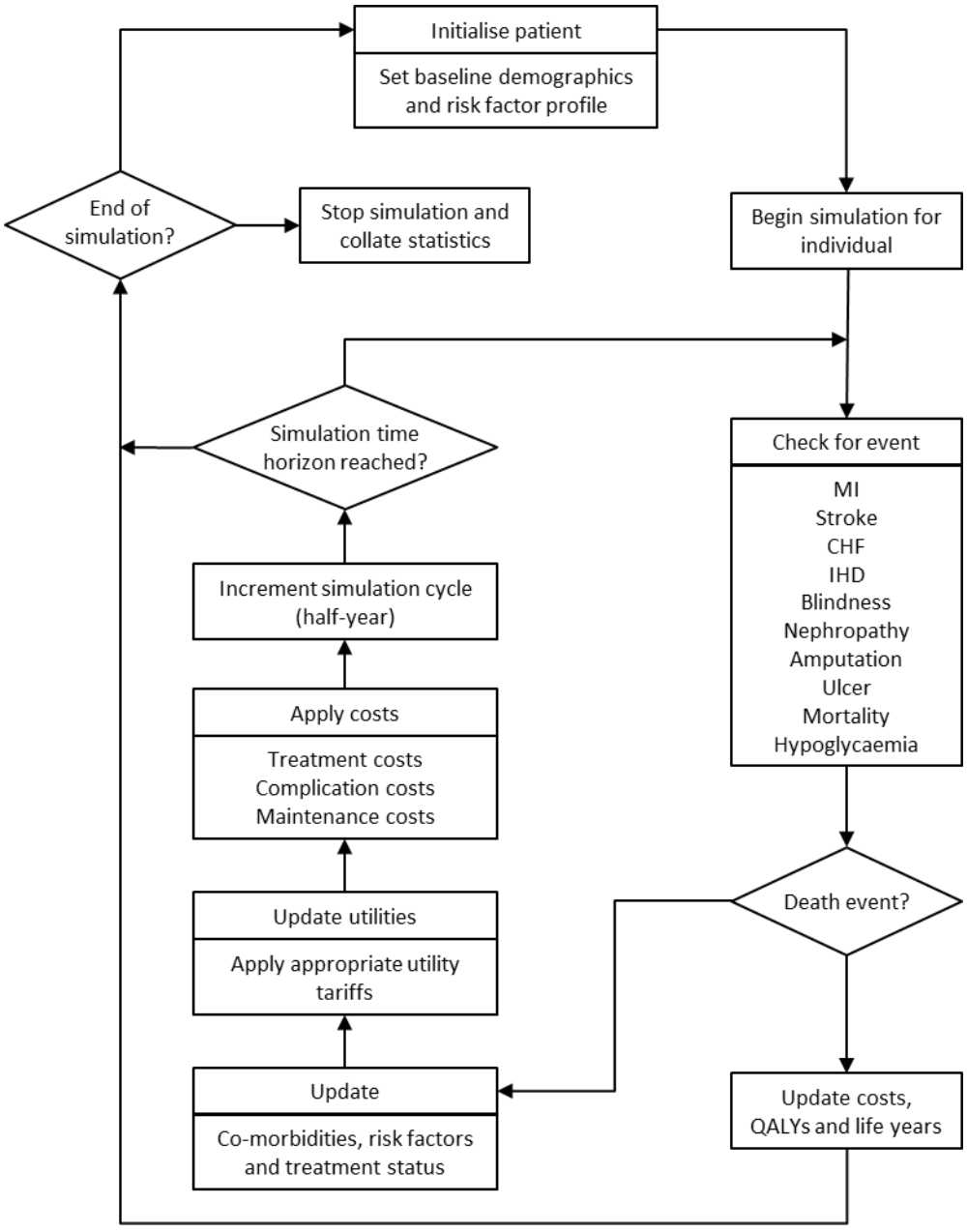

Figure 1: Flow diagram of patient simulation process in the Cardiff Diabetes Model

2.3. Monte Carlo simulation and random numbers

The Cardiff Diabetes Model is a patient level fixed-time increment, Monte Carlo micro simulation model. Monte Carlo simulation models utilise pseudo random numbers in the sampling of values

assigned to random variables. Among a cohort of identical individuals, with an identical probability of an event occurring, a number of individuals will be modelled as experiencing this event, while the remaining do not. Random numbers (a sampled value, uniformly distributed over [0,1]) are used to determine the likelihood of an event occurring for the individual currently being simulated. Over many simulated replications the proportion of modelled individuals that experience the event will converge to the defined probability.

2.3.1 Random number seed

Despite the variability that exists within the model, in either mode it is possible to exactly replicate the results obtained due to the implementation of a random number seed. The random seed controls which sequence of randomly-generated numbers is applied in each simulation, so that while the model contains variability, this variability is fixed. The ability to replicate results exactly should prove to be a useful function since it allows the verification of results produced in previously conducted analyses and allows the user to set up a base case and examine the effects of changes to the input parameters.

Two random number generators are employed within the model. The first generates random numbers utilised in the simulation of outcomes, e.g. whether a modelled patient experiences a stroke in a particular cycle. The second generates random numbers utilised in the sampling of input parameters when running a probabilistic sensitivity analysis (PSA). The number streams are reset for each therapy arm (control or treatment) such that the same sequence of randomly generated numbers are utilised in the sampling of parameters and the evaluation of event occurrence.

2.3.2 Variance reduction through antithetic variates

One disadvantage of Monte Carlo simulations is that they provide imprecise statistical estimates. The error associated with such estimates (Monte Carlo error or first order uncertainty) is reduced with increased cohort size (replications of simulated individuals). A number of variance-reduction techniques have been developed,[8] including common random numbers, antithetic variates, control variates and importance sampling, as an alternative to increasing the cohort size and/or number of simulation replications. The technique of antithetic variates aims to provide reductions in stochastic uncertainty, through the introduction of negatively correlated pairs of simulation replicates.[9] Based on the rational that if a random variable U is distributed uniformly over [0,1], so too is its reflection (1-U); two simulation paths may be generated in which a large value in one variable is balanced by a small value in the other, thereby reducing variance. The model incorporates the option to apply antithetic variates via the “PSA” sheet.

2.3.3 Randomisation of event order

In order to prevent any potential bias relating to the prediction of clinical events, at the beginning of each time period (cycle), randomized checks are made for the occurrence of clinical events. The order in which the model checks for the occurrence of a particular event, is randomly generated each cycle using random numbers as described above.

2.4 Modes of analysis

The model is capable of running in two key modes; deterministic (mean values) and probabilistic sensitivity analysis (PSA), which are described briefly in Section 2.4.1 and Section 2.4.2 respectively. A third mode is available to run user-defined patient level data inputs, described in section 2.3.5. Underlying each of these modes is a Monte Carlo simulation that simulates the progress of each patient within a cohort over a lifetime, described in Section 2.3 (as depicted in Figure 1).

2.4.1 Mean values analysis

The deterministic analysis is the core analysis of the model, which calculates the cost-effectiveness outputs using mean values as inputs for each of the model parameters. Each modelled patient will be initiated with the cohort's mean characteristics at baseline, receive the mean treatment effect and be subject to the mean costs and utility implications of treatment and events.

Note that a degree of variability exists in the modelling of some parameters, such as gender, and the incidence of events will vary between identical patients. As such predicted outcomes will vary from one modelled cohort to the next; however these values will tend towards the mean as the number of runs increases.

2.4.2 Probabilistic sensitivity analysis

In the PSA, the parameter values used in the deterministic analysis are varied simultaneously over a reasonable and meaningful range around the mean. Such analyses are used to estimate the overall uncertainty that exists in the model as a consequence of the uncertainty associated with model inputs. The PSA allows the user to see the combined impact of the variability of each of the input parameters. Note that which variables are to be varied in the PSA can be individually selected.

Parameter distribution types

Each parameter included in the PSA is sampled independently. The limitation of this approach is that any relationship between parameters, for instance correlation between baseline characteristics, is not accounted for. The variation of each parameter depends upon the distribution type assigned to describe that variation. Three distribution types are used in the PSA: Normal, Beta and Gamma, Figure 2.

Normal distributions are typically applied to model inputs that describe baseline patient characteristics such as age or height, and treatment effects such as change in SBP. Values sampled from a normal distribution are symmetrically distributed around the mean in a bell shape. Gamma distributions are applied to cost inputs, whose sampled values are restricted to be positive. Beta distributions restrict sampled values to lie between zero and one and are thus applied to model inputs describing health related utilities.

Sampling from each distribution requires specification of the mean and standard error (SE). Since the aim of the PSA is to model parameter uncertainty the SE is an appropriate measure of

variation. If between-patient variation was of interest, the functionality of the PSA may be employed with inputs that instead represent standard deviations (SD) to conduct such analyses. Sampling from the Normal distributions also require the specification of reasonable minimum and maximum values on the "PSA" worksheet. Only parameters included on this worksheet may be sampled as part of the PSA; their inclusion in the analysis is controlled by a series of indicator variables where values 0/1 relate to the use of mean values/sampled deviates.

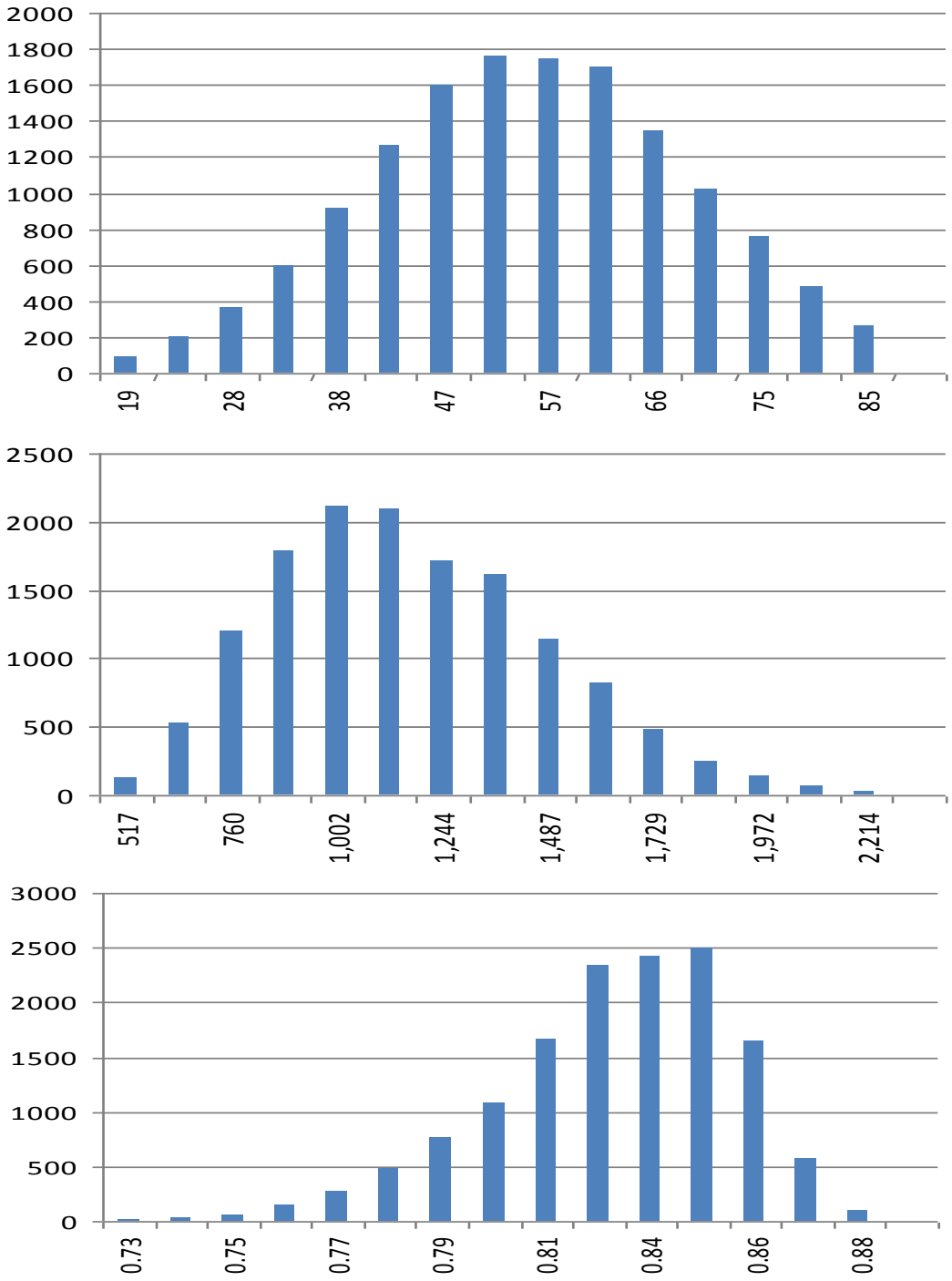

Figure 2: Example profiles drawn from the normal, gamma and beta distributions.
Top: Age drawn from a normal distribution with mean = 60 and SD = 15 with minimum age = 20 and maximum age = 90; Middle: Cost drawn from a Gamma distribution with mean = £1000; Bottom: utility values sampled from a beta distribution mean = 0.85

2.4.3 User-supplied patient level data

Though not intended for regular use, the model includes the functionality to run user-supplied patient level data through the model when the UKPDS 68 equations are selected (see Section 4.1). The user may define baseline characteristics, clinical history, end of treatment risk factor values and number of hypoglycaemic episodes individually for each patient. This data is inputted and loaded to the model from worksheets named “User Data Treatment” and “User Data Control” in which each row represents an individual patient to be simulated. When utilising the user-supplied data option the model simulates patients in the order in which they appear on the user data sheet. If the cohort size defined on the “Simulation” worksheet is larger than the number of patient rows the defined cohort will be simulated multiple times.

By defining baseline characteristics and treatment effects at an individual patient level, assumptions regarding choice of appropriate sampling distributions are avoided and correlations between patient variables can be accurately represented.

Note: Patient level data has not been pre-loaded in this version of the model.

2.5 Univariate sensitivity analysis

Univariate sensitivity analysis is of significant importance when evaluating the influence of input parameters upon results and promotes an understanding of the drivers of cost-effectiveness. The introduction of form controls to the user interface (as described in Section 3) enables users to edit and save multiple profiles that may be used to easily perform multiple sets of sensitivity analyses that relate to alternative treatment profiles, patient characteristics or other alternative scenarios.

The model also enables users to perform a series of sensitivity analyses in a succinct fashion via the “Tornado” worksheet. Users may select from the following parameters to be included in the analysis: age, gender, BMI, Afro-Caribbean, smoking status, total cholesterol, HDL cholesterol, SBP, HbA1c, complication history, adverse event rates and event-related utility and cost. Absolute minimum and maximum values may be defined for age, gender, BMI, ethnicity and smoking parameters. In contrast, a percentage change is defined for all other parameters. For example, defining a 20% change in HbA1c, when a baseline value of 8% has been defined, leads to the testing of alternative values 6.4% and 9.6% as part of the sensitivity analysis.

Once selected the model performs multiple simulation scenarios and provides results relating to each choice of sensitivity analysis, thus allowing users to investigate multiple scenarios in a relatively straightforward fashion. Once the sensitivity simulation begins users should not interrupt the process as the alternate values being processed may be stored within the model.

Key cost-effectiveness results for each simulation are output to the “TornadoResults” worksheet. Total costs and quality-adjusted life years (QALYs) are presented for each arm under the minimum and maximum parameter values tested as part of the analysis. The range of resultant incremental cost-effectiveness ratios (ICER) is presented via a tornado plot. The lower and upper bounds on the ICER relate to the absolute value of the ICER, rather than how cost-effective the treatment arm is relative to the control arm.

3 Model Interface

The model's interface separates the model inputs from the model engine with the following aims:

- improve ease of use for both inexperienced and experienced users
- improve ease of model update and quality control
- improve ease of analysis replication

The interface is linked to a data repository which allows users to store multiple model input profiles describing:

1) patient baseline characteristics
2) treatments
3) costs
4) utilities

Combinations of model input profiles (1-4) may be stored as a single simulation profile as described in the accompanying user guide.

Users' primary interaction with the model is controlled via a single excel worksheet ("Simulation"), from which a series of menus (userforms) can be launched. Each menu allows the modification, creation and removal of input profiles in addition to selection for use in the current analysis. Following the selection of all required inputs and any additional model settings incorporated in the 'Simulation' worksheet, data is passed to the model engine for use in the simulation, Figure 3.

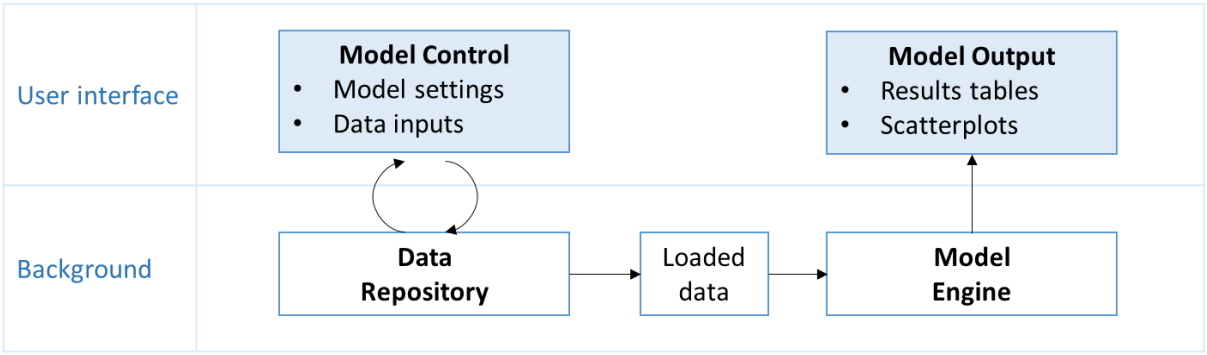

Figure 3: Flow diagram of interaction between the model user interface and engine in the Cardiff Diabetes Model

Data workbook

The data workbook is a stand-alone excel workbook that acts as a storage unit for the model input profile listed above. All data from the workbook may be loaded into the model, overwriting any data currently contained within the model. In order to load the data from the data workbook users must ensure that the data workbook is located in the same folder as the model. It is intended that data in the data workbook be modified and loaded into a particular model on a single occasion, however small adaptations may be made within the model itself utilising edit and save functionality within the model's user forms.

Userforms

The userforms utilised to handle model inputs present numbers in the format such that decimals are represented by a dot (period). This is true irrespective of the current Microsoft/Excel regional settings. It is necessary for users to input all numeric values in this format even if numbers are input in another format within the spreadsheet cells. For example, when entering the number one thousand and fifty and a half into a userform it must be entered as "1050.5". If the value is entered as "1050,5" the model will fail to recognise this value as a number when loaded and errors will occur.

4 Risk Equations

4.1 Diabetes-related events

Risk equations

The occurrence of a number of diabetes-related clinical events, including macrovascular and microvascular complications, is modelled over the simulated horizon according to risk estimations which depend on patient risk factors such as age, HbA1c and clinical history. Two sets of risk equations, derived from the United Kingdom Prospective Diabetes Study (UKPDS), are available to model the risk of diabetes-related events: UKPDS 68 equations[2] and UKPDS 82 equations.[7] Selection of either UKPDS 68 or UKPDS 82 risk equations may be made from the "Simulation" worksheet.

The UKPDS 68 equations are comprised of a series of seven Weibull proportional hazards models derived from a cohort of 5,102 diabetic subjects, aged 25 – 65 years in the UK.[2] These risk equations enable the prediction of macrovascular events: myocardial infarction (MI), stroke, ischaemic heart disease (IHD) and congestive heart failure (CHF), microvascular events: amputation, end-stage renal disease (ESRD) and blindness. The UKPDS 68 equations have been widely used in diabetes modelling and extensively validated. The model predicts only the first event in any single category of diabetes-related complications, and does not allow series of events to be modelled directly. However, this limitation should not be overstated, as: (i) such multiple events in the UKPDS data were relatively infrequent; (ii) subsequent fatal events in specific categories of diabetes-related complications are included in the diabetes-related mortality equation.

The UKPDS 82 equations[7] were developed later, based on a longer term follow up of the same study population. The UKPDS 82 risk equations were published for the same seven original events as well as an addition four clinical endpoints: second myocardial infarction (MI), second stroke, second amputation and ulcer. The UKPDS 82 equations also use a wider range of predictive risk factors, such as LDL-C and eGFR to predict the likelihood of a clinical event occurring. Due to their recent publication (2013) the UKPDS 82 equations are yet to be widely implemented, tested and

validated, and as such their accuracy in predicting the incidence of clinical events is yet to be determined. Due to this limitation the model utilises the UKPDS 68 equations as the default setting.

Risk factors

Table 1 details the patient characteristics that influence the likelihood of clinical events and Table 2 details which factors influence each individual equation. Where equations call for a risk factor value at diagnosis, the baseline value (prior to any treatment effect) is implemented as a proxy. HbA1c features in each of the UKPDS 68 equations with the exception of blindness. Updated UKPDS 82 equations predicting the incidence of CHF and IHD do not include HbA1c as a predictive risk factor.

BMI features in the UKPDS 68 CHF equation, which in turn affects MI and stroke. However, it should be noted that the risk factor is defined as BMI at diabetes diagnosis and as such the BMI value at baseline is used as a proxy within the UKPDS 68 equation for predicting CHF. The 'BMI at diagnosis' value is therefore the same for both control and treatment arms and thus any treatment effect on weight will have no direct influence on the prediction of CV risk when UKPDS 68 equations are used.

The updated UKPDS 82 equations for CHF, ESRD and ulcer also feature BMI as a predictive risk factor. In contrast to UKPDS 68 equations, the BMI risk factor included in the UKPDS 82 equations is updated over time. As such, treatment effects related to weight change may have an impact on future predicted events when utilising UKPDS 82 equations for CHF, ESRD and ulcer.

Table 1: Summary of patient characteristics

Patient characteristic	Description	Modifiable /Static*	Units
Demographics			
Age	The age of the patient	Modifiable	Years
Age at diagnosis	The age of the patient upon T2DM diagnosis	Static	Years
T2DM duration	The duration since T2DM diagnosis	Modifiable	Years
Gender	Male or Female	Static	1=Female, 0=Male
Height	The height of a subject	Static	Meters
Ethnicity	Certain risk equations utilize information on ethnicity, specifically those of Indian or Afro-Caribbean (AC) origin	Static	1=Indian or AC, 0=Otherwise
Smoking status	Whether a patient smokes or not	Static	1=Current smoker, 0=non-smoker
Clinical risk factors			
HbA1c	Glycated haemoglobin A1c	Modifiable	%
TC	Total cholesterol	Modifiable	mmol/l
HDL-C	High-density lipoprotein cholesterol	Modifiable	mmol/l
SBP	Systolic blood pressure	Modifiable	mmHg
BMI	Body mass index	Modifiable	kg/m^2
BMI at diagnosis	Body mass index upon T2DM diagnosis	Static	kg/m^2
eGFR	Estimated glomerular filtration rate	Static	$ml/min/1.73m^2$
Haemoglobin	Haemoglobin levels	Static	g/dL
Albuminuria	Presence of micro-albuminuria defined as albuminuria ≥ 50mg/l	Static	mg/l

WBC	White blood cell count	Static	Per 10^6ml

T2DM, type 2 diabetes mellitus
**Static risk factors remain constant throughout the modelled time horizon and modifiable risk factors may incur treatment effects and/or time-dependent progression*

Table 2: Events predicted using UKPDS 68 and 82 event equations and their predictive risk factors

Study	Event	Predictive risk factors
UKPDS 68 [2]	Ischaemic heart disease (IHD)	Age at diagnosis, gender, HbA1c, TC/HDL-C, SBP
	Myocardial infarction (MI)	Age at diagnosis, ethnicity, gender, HbA1c, TC/HD-C, smoking status, SBP, history of CHF, history of IHD
	Congestive heart failure (CHF)	Age at diagnosis, BMI at diagnosis, HbA1c, TC/HDL-C, SBP
	Stroke	Age at diagnosis, gender, history of AF, HbA1c, TC/HDL-C, smoking status, SBP, history of CHF
	Amputation	HbA1c, SBP, history of PVD, history of blindness
	Blindness	Age at diagnosis, HbA1c
	Renal	SBP, history of blindness
UKPDS 82 [7]	CHF	Age at diagnosis, gender, ethnicity, history of AF, BMI, eGFR, haemoglobin, HbA1c, HDL-C, heart rate, LDL-C, albuminuria, history of PVD, history of amputation, history of ulcer
	IHD	Age at diagnosis, gender, eGFR, HDL-C, LDL-C, history of PVD, SBP, history of amputation, history of CHF
	1st MI - male	Age at diagnosis, ethnicity, HbA1c, HDL-C, LDL-C, albuminuria, history of PVD, smoking status, SBP, WBC, history of amputation, history of CHF, history of IHD, history of stroke
	1st MI - female	Afro-Caribbean, age at diagnosis, female, eGFR, HbA1c, LDL-C, micro/macro albuminuria, PVD, Smoker, SBP, TC, white blood cells, history, IHD history
	2nd MI	LDL-C, micro/macro albuminuria
	1st stroke	Age at diagnosis, gender, history of AF, HbA1c, LDL-C, albuminuria, smoking status, SBP, WBC, history of amputation, history of IHD
	2nd stroke	Age at diagnosis, albuminuria, smoking status
	Blindness	Age at diagnosis, HbA1c, heart rate, SBP, WBC, history of CHF, history of IHD
	Ulcer	Age at diagnosis, ethnicity, gender, BMI, history of PVD
	1st Amputation	Age at diagnosis, gender, history of AF, HbA1c, HDL-C, heart rate, albuminuria, history of PVD, SBP, WBC, history of stroke, history of ulcer
	2nd Amputation	HbA1c
	Renal	Age at diagnosis, gender, history of AF, BMI, eGFR, haemoglobin, LDL-C, albuminuria, SBP, WBC, history of amputation, history of blindness

AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; IHD, ischaemic heart disease; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; PVD, peripheral vascular disease; WBC white blood cell.

4.2 Natural progression of predictive risk factors

The likelihood of clinical events occurring is influenced by risk factors including HbA1c, SBP, TC, HDL-C, LDL-C, eGFR, haemoglobin, heart rate, albuminuria, WBC and weight. Risk factors are modelled in a dynamic fashion and thus the likelihood of an event occurring also changes over the modelled time horizon. Risk factors may be subject to change as a result of a new therapy (as described in Section 6), after which the natural progression of each risk factor is altered.

4.2.1 Natural progression of HbA1c

The model allows users to select from five different methodologies to model the natural progression of HbA1c. Each method is summarised below. A report detailing the development of the latter three approaches is included in Appendix 1. Please note, it is recommended that the approach of choice is assessed for suitability, with respect to the clinical plausibility of its generated trajectory, before any cost-effectiveness analysis is performed.

Non-linear (UKPDS)

A common approach taken to modelling the natural progression of HbA1c in type 2 diabetes models is the implementation of an equation published from the UKPDS 68 study.[2] Due to the characteristics of the UKPDS population (newly diagnosed), this method may be best suited to describe the evolution of HbA1c in early lines of therapy.

The implementation of these equations utilises the base value defined as HbA1c prior to first line of treatment (cohort mean) and the lagged value as the HbA1c value from the previous year.

Linear (User defined)

A user-defined linear increase in HbA1c % may be specified.

Non-linear (2015 clinical data)

The published UKPDS HbA1c progression equation was refitted to data identified by a literature review (Appendix 1) of studies reporting estimates of HbA1c progression. The UKPDS equation takes the form:

$$h(t) = \begin{cases} h_0 \quad if \quad t = 0 \\ h_1 \quad \text{if} \quad t = 1 \\ a + b \times \ln(t) + c \times h(t-1) + d \times h_0 \quad if \quad t \geq 2 \end{cases}$$

where the HbA1c level at time t is denoted by $h(t)$ and $a, b, c \; and \; d$ are constants which specify the profile.

In order to produce a justifiable fit to the dataset available, it was necessary to transform the equation to a more suitable form, resulting in the following equation:

$$h(t) = \begin{cases} h_0 \quad \text{if} \quad t = 0 \\ h_1 + (h_0 - h_1) \times \ln(t)/\ln(24.833) \; + 0.51168 \times (h(t-1) - h_0) \quad \text{if} \quad t \geq 1 \end{cases}$$

where the HbA1c level at time t is denoted by $h(t)$.

The complete analysis informing the equation may be found in Appendix 1 (referred to as "Modification of the UKPDS model").

Linear (2015 clinical data)

Based on the data identified in the same review literature review, a multivariate linear regression was performed using the explanatory variables identified in the review. The fitted regression model for HbA1c was defined by the following equation:

$$HbA1c = 4.523925 + (0.621904 \times Baseline\ HbA1c) + (0.036403 \times Duration) - (0.038890 \times Age\ at\ baseline) - (0.485704 \times Insulin)$$

When considering the implementation of this regression equation within a simulation model, the relevance of the included covariates is limited to the dependence of future HbA1c on duration of diabetes (the only dynamic covariate). This is because, in the simulation context, the specification of baseline HbA1c and associated treatment effects fully determine the level of HbA1c from which progression is to be modelled. The utility of this regression equation therefore lies in the provision of an evidence-based value for the coefficient associated with time in a linear model of HbA1c progression. As such, the implemented HbA1c profile within the simulation model is of the form:

$$HbA1c = (Baseline\ HbA1c - Treatment\ effect) + (0.036403 \times (Time\ from\ baseline\text{-}1))$$

The complete analysis informing the equation may be found in Appendix 1 (referred to as "Statistical regression model").

Parametric

Based on the data identified in the same literature review, a parametric model for HbA1c profiles was designed to incorporate the observation that, in a large number of studies in which data was available at multiple time points, HbA1c tended to decrease from the baseline level following the commencement of treatment, until it reaches some minimum level, after which it increases toward some upper limiting value. This observed behaviour is not universal and a second class of profile was accounted for, in which the HbA1c level decreases monotonically from its baseline towards some lower limiting value.

The following parametric equation was developed:

$$h(t) = h_\tau + \left(\sqrt{h_\infty - h_\tau} - \left(\sqrt{h_\infty - h_\tau} + \sqrt{h_0 - h_\tau}\right)e^{-\frac{r}{2}\times t}\right)^2$$

where the HbA1c level at time t is denoted by $h(t)$, the time at which the minimum is reached, if it is reached, is denoted by τ, and the baseline, minimum and limiting values are denoted by h_0, h_τ and h_∞ respectively.

The HbA1c drop rate r is fixed to account for treatment effects by forcing the profile at time $t = 1$ to be a given number h_1:

$$r = 2 \times \ln\left(\left|\sqrt{h_\infty - h_\tau} - \sqrt{h_0 - h_\tau}\right|\right) - 2 \times \ln\left(\left|\sqrt{h_\infty - h_\tau} - \sqrt{h_1 - h_\tau}\right|\right).$$

In order to use this model, it was necessary to estimate the maximum HbA1c level which will be reached by the profile. The maximum level reported across the studies considered was taken: $h_\infty = 9.3\%$.

The minimum value attained would usually be assumed to be h_1 but we have observed that there is often a degree of overshoot to the treatment effect such that the HbA1c level continues to decrease for a short while after time $t = 1$. In the applicable data sets, we have found the mean overshoot to be $h_\tau \,/\, h_1 = 0.980982$, which is the last parameter required to describe this model.

The complete analysis informing the equation may be found in Appendix 1 (referred to as "Parametric model").

4.2.2 Natural progression of SBP, total and HDL cholesterol

The natural progression of SBP is modelled following any treatment effect via the implementation of the published UKPDS 68 equation for SBP. Modelling the natural progression of cholesterol is similarly undertaken using the UKPDS 68 equation for the ratio of TC:HDL; HDL is assumed to remain constant and TC derived from the predicted ration of TC:HDL.

The implementation of these equations utilises the base value defined as the value prior to the first line of treatment (cohort mean) and the lagged value as the value from the previous year.

4.2.3 Natural progression of weight

The natural progression of weight is modelled linearly according to a user specified annual weight gain.

4.2.4 Natural progression of other risk factors

New equations have not been published describing the natural progression of diabetes-related risk factors to complement the publication of the UKPDS 82 event equations. As such, the most appropriate way to model the progression of newly included risk factors, such as eGFR or LDL-C, is as yet unclear. Therefore a model assumption is that the natural progression of these risk factors is held constant, i.e. there is no change in parameter values over time.

4.3 Mortality

4.3.1 Diabetes-related mortality and event mortality

Mortality related to diabetes and its associated complications is predicted according to either the UKPDS 68 or UKPDS 82 equations, in accordance with the selection made by the user. Two equations, defined in the UKPDS 68 study are used to model both event fatality (influenced by age

at event occurrence and HbA1c), and diabetes-related mortality (influenced by age, cholesterol and event history). Four equations are employed as defined in the UKPDS 82 study to model mortality. These include: (1) mortality in years with no prior history or occurrence of clinical events, (2) mortality in the first year of a clinical event occurring, (3) mortality in years where there is prior clinical event history but no occurrence of clinical events in that year and (4) mortality in subsequent years.

4.3.2 All-cause mortality

When the UKPDS 68 equations are selected, all-cause mortality may be modelled using the UKPDS 68 'other death' equation. Alternatively, all-cause mortality may be modelled using gender specific life tables for the United Kingdom.[10] These life tables show the annual probability of death at each age in male and female subjects. For each simulated individual the appropriate gender-specific probabilities will be utilised. Since mortality relating to cardiovascular events and diabetes have already been accounted for in the above risk equations, the all-cause mortality does not include mortality from these events (i.e. cardiovascular and diabetes-related mortality are subtracted from the all-cause mortality).

UKPDS 68 equations must be the chosen set of risk equations and life tables turned on via the option on the 'Life tables' worksheet in order to apply mortality related to life tables in the simulation. Once life tables are turned on the UKPDS 68 'other death' equation is no longer utilised. As a patient progresses through the model their risk of all-cause mortality based on life tables, is updated at the beginning of each cycle based on the patients age (rounded down to the nearest integer) and gender (explicitly defined as either male or female).

When the UKPDS 82 risk equations are selected, mortality is modelled entirely through the four death equations described above. Life tables will not be utilised when the UKPDS 82 equation is selected, regardless of whether the life tables option is selected.

4.3.3 BMI-related risk multiplier

The BMI-related risk multiplier can only be implemented when the UKPDS 68 risk equations have been selected. The impact of a BMI-related risk multiplier on the risk of mortality (both cardiovascular and all-cause) may be modelled as described in Section 4.4.

4.4 Risk multipliers

A number of risk multipliers have been incorporated in the model to allow the risk of events, including mortality, to be altered to reflect instances where a specific therapy, patient characteristic or population is associated with increased (or decreased) risk. When no such relationship exists, or is to be modelled, risk multipliers should be set to 1; representing a null effect. The risk multipliers described below are only applied when the UKPDS 68 equations are selected.

Increased BMI is associated with an increased risk of mortality. If selected from the risk multipliers menu located on the 'Simulation' worksheet, risk multipliers of 1.63 and 1.33 are applied to cardiovascular and all-cause mortality, respectively.[11]

Therapy specific risk multipliers may be applied to the prediction of CHF, MI and/or cardiovascular mortality risks. These values may be set in the "Advanced" tab of any treatment profile. For example, Sulphonylureas (SU) have been linked to an increase in MI (HR: 1.11) and CV death (HR: 1.27) compared to other oral anti-diabetic agents (OADs).[12]

Additional options are available in the risk multipliers menu, to facilitate the application of a general cardiovascular risk multiplier, or a BMI risk multiplier to primary events and to enable the modelling of secondary events with/without an associated risk multiplier to adjust risks predicted using the UKPDS 68 equations for initial events.

5 Baseline Patient Characteristics

The cohort is initialised with a set of baseline demographics and risk factors as defined by the user. Table 3 shows an example patient profile; comprising baseline demographics, risk factor values and clinical history, derived from UKPDS 33 and UKPDS 82 studies.[1, 7] Individuals of both genders are modelled within the same cohort; each individual is assigned a gender (male/female) such that over many simulated individuals the proportion of female patients reflects the user defined input.

Note: Many of these risk factor variables are likely to change from baseline as the simulation progresses, either due to treatment effects or natural progression.

Model inputs may be viewed and modified in the patient menu. The definition of both means and standard errors (SE's) are required for each variable when running the PSA. The objective of the model is to estimate the mean clinical and economic outputs associated with a particular cohort thus the choice of SE's as a measure of variation (as opposed to standard deviations (SD's)) has been made. It should be noted that those variables included in the PSA are sampled independently. A limitation of the model is that it does not account for the correlation between these patient characteristics when simulating a PSA. However, users have the option to input individual patient-level data in to the model, thus inherently incorporating correlated data and removing any potential biases created through uncorrelated sampling. Similarly, analysing patient-level data naturally provides an insight in to the variation amongst a particular population.

Table 3: Illustrative patient profile: baseline demographics, risk factors and clinical history mean values

Input parameter	Value	Source
Baseline demographics		
Current age (years)	53.3	UKPDS 33[1]
Proportion female	0.39	UKPDS 33[1]
Duration diabetes (years)	0.00	UKPDS 33[1]
Height (m)	1.68	UKPDS 33[1]
Proportion Afro-Caribbean	0.08	UKPDS 33[1]
Proportion Indian	0.05	UKPDS 33[1]
Proportion smokers	0.31	UKPDS 33[1]
Modifiable risk factors		
HbA1c (%)	7.08	UKPDS 33[1]
TC (mmol/L)	5.4	UKPDS 33[1]
HDL-C (mmol/L)	1.07	UKPDS 33[1]
LDL-C (mmol/L)	3.5	UKPDS 82[7]
SBP (mmHg)	135	UKPDS 33[1]
Weight (kg)	77.5	UKPDS 33[1]
eGFR (ml/min/1.73m^2)	77.5	UKPDS 82[7]
Haemoglobin (g/dL)	145	UKPDS 82[7]
Albuminuria (mg/L)	47	UKPDS 82[7]
White blood cell count (x10^6/ml)	6.8	UKPDS 82[7]
Heart rate (BPM)	72.0	UKPDS 82[7]
Percentage with clinical history^		
MI	0.0%	Assumed
CHF	0.0%	Assumed
Stroke	0.0%	Assumed
AMP	0.0%	Assumed
Blind	0.0%	Assumed
ESRD	0.0%	Assumed

AMP, amputation; CHF, congestive heart failure; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol
^ assumed no clinical history

6 Treatments - Including Clinical Data

All therapy-specific model inputs are defined in a series of therapy profile menus.

6.1 Effectiveness data

Modelled outcomes are driven by treatment induced changes applied to key variables in the analysis (i.e. those which impact upon the risk equations). Treatment effects vary by therapy arm, which will lead to differences in modifiable risk factors and crucially differential rates of clinical events. Due to the high cost and quality of life impact associated with these clinical events significant differences in the differential rates of clinical events should lead to substantial differences in the overall costs and QALYs obtained in each therapy arm.

Key treatment effects are applied in the first year of treatment. An example or four treatments is shown in Table 4. The primary efficacy benefit of diabetes therapies is a reduction in HbA1c. In addition to HbA1c benefit, therapies may also have an effect on risk factors such as weight, SBP, TC and HDL-C.

Table 4: Illustrative treatment profiles: risk factor treatment effects, hypoglycaemia, adverse events and discontinuation

Treatment input parameter	MET [13]	MET+SU [14]	MET+ SGLT-2 inhibitor [14]	Insulin [15]
HbA1c (%)	-1.06	-0.52	-0.52	-1.11‡
Weight (kg)	0	+1.44	-3.22	+1.9^
TC (mmol/L)	-0.59	-0.03	+0.07	0.00*
HDL-C (mmol/L)	0.00	-0.002	+0.07	0.00*
SBP	0.00*	0.8	-4.3	0.00*
Number of symptomatic hypoglycaemia episodes	0.02	0.408	0.035	0.616
Proportion with severe hypoglycaemia	0.001	0.00735	0.000	0.022
Probability of UTI & GI	0.00	0.09	0.23	0.00
Probability of discontinuation	0.00	0.059	0.091	0.00

GI, gastrointestinal; MET, metformin; HDL-C, high density lipoprotein cholesterol; SGLT-2, sodium-glucose linked transporter 2; SBP, systolic blood pressure; SU, sulphonylurea; TC, total cholesterol; UTI, urinary tract infection.
** assumed value*
‡ Glycaemic control shown to be equivalent with NPH and long-acting insulin analogues
^ Weight change from Montanana et al. [16] - chosen as most recent study reporting weight effect included in the NICE HTA report

6.2 Hypoglycaemia, adverse events and discontinuation

Adverse events and hypoglycaemic events are modelled according to therapy-specific incidence rates. Hypoglycaemia is separated into the annual numbers of symptomatic and nocturnal hypoglycaemic events and the proportion of patients that experience severe hypoglycaemia. Table 4 includes illustrative annual rates of hypoglycaemia, adverse events and discontinuations associated with each of the four example treatments.

The model allows users to customise the modelling of adverse events. There are five adverse event placeholders available (numbered 1 to 5) in each therapy arm. For each adverse event the user should enter the probability of that event occurring, the cost associated with the occurrence of that adverse event and the disutility associated with that adverse event. While it is good practice to assign the same adverse events to each placeholder across all therapies where possible, this approach allows any five adverse events to be modelled for each therapy.

The model incorporates additional functionality for the first adverse event, where it is possible to restrict the occurrence of that event to a specific number of cycles. For example restricting the incidence of an adverse event to the first six months (1 cycle) of treatment may be appropriate for adverse events that are only likely to occur at therapy initiation. Note that for the same specified annual probability, half as many predicted events would be expected when events are restricted to the first cycle compared to a restriction to the first two cycles. If no such restriction is required, this model input should be set to zero.

Cost and utility decrements may be applied to hypoglycaemic events, adverse events and therapy discontinuation, as described in Sections 7 and Section 8.

6.3 Continued risk factor progression following treatment effect

A number of model inputs may be used to define the way in which risk factors progress following the initial modelled treatment effect.

6.3.1 Weight progression

Four user-defined model inputs drive the treatment effect and progression of weight: weight change, years of maintained weight effect, years to loss of weight effect and natural progression of weight. These inputs are briefly described in Table 5 and illustrated in Figure 4, following graph of two hypothetical therapy arms.

In the illustrative control arm, an increase in weight of 1.00 kg occurs in the first 12 months. This effect is maintained for the first year only. The weight effect is not lost and from this point onwards the subject's weight increases in accordance with the natural progression of weight (0.1 kg per year).

In the illustrative treatment arm, a reduction in weight of 3.22 kg occurs in the first 12 months. This effect is maintained for 2 years (i.e. stays at reduced value of 84.80 kg) before beginning to rise. Weight rises for 1 year, as the weight effect is lost. Note that weight rises by more than the original

reduction of 3.22 kg; it is assumed that weight would be regained until it is back in line with natural weight progression (i.e. the value that weight would be if no weight effect had occurred). Thereafter, the subject's weight increases in accordance with the natural weight progression.

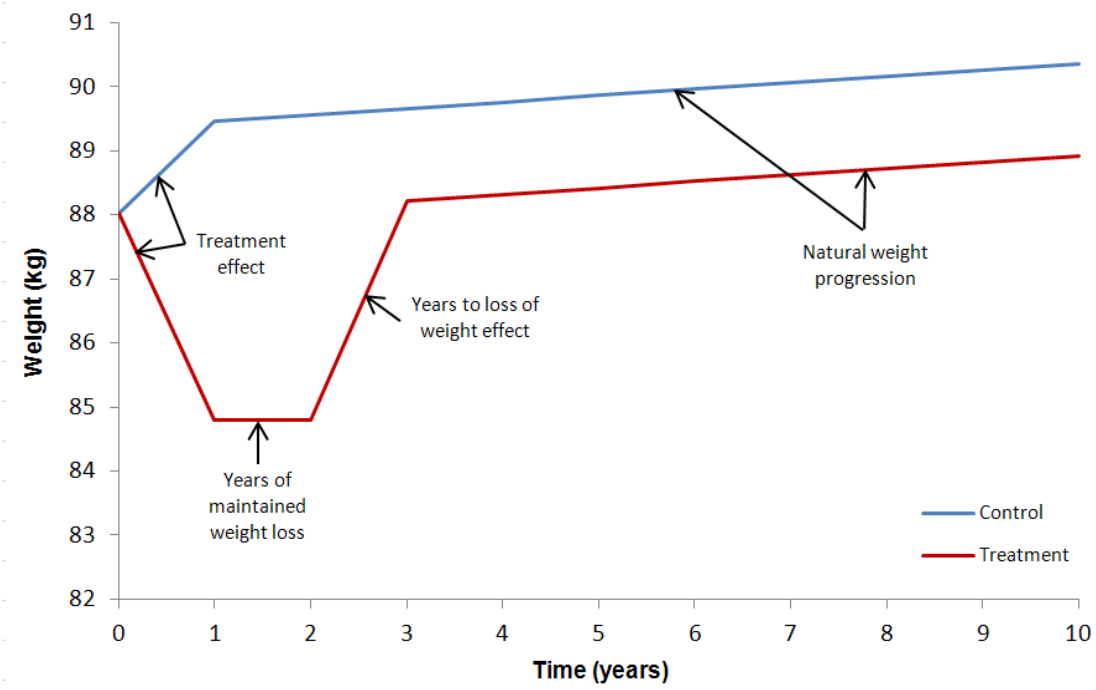

Figure 4: Illustration of model inputs employed to model dynamic weight profiles

Table 5: Effects driving the changes in weight observed in HbA1c

Effect	Description	Comparator	Treatment
Weight change (kg)	The magnitude and direction of the weight change applied.	+1.00	-3.22
Years of maintained weight effect	Period over which weight remains at its new value i.e. how long the effect lasts. Minimum value = 1. In this case, weight is reduced to 84.80 kg in the treatment arm (year 1) and maintained for a further year (year 2).	1	2
Years to loss of weight effect	Period over which weight effect is lost before it is back in line with natural weight progression. If set to zero, natural progression begins from the end of maintained weight loss.	0	1
Natural progression (kg/year)	How the risk factor would behave in the absence of an intervention. In this instance, weight can be seen to increase by 0.1 kg per year.	0.1	0.1

6.3.2 HbA1c progression

The key effects driving the progression of HbA1c are annotated in the graph, Figure 5, of two hypothetical therapy arms below and briefly described in Table 6. Five variables define treatment

effect with respect to HbA1c; the change in HbA1c, how much of the effect is applied over the first year, how long the effect lasts before HbA1c begins to rise in line with natural progression, the coefficient relating to the rate at which HbA1c increases and the glucose drift. The first three inputs are commonly modified across treatments and are provided as baseline modifiable inputs.

The final two settings (slope coefficient and glucose drift) are only applicable when utilising the original UKPDS equation to model the natural progression of HbA1c; they provide additional flexibility for advanced users and are located under the 'Advanced' tab in the treatment effects forms.

The alternative methods of modelling the natural progression are described in Section 4.2.1.

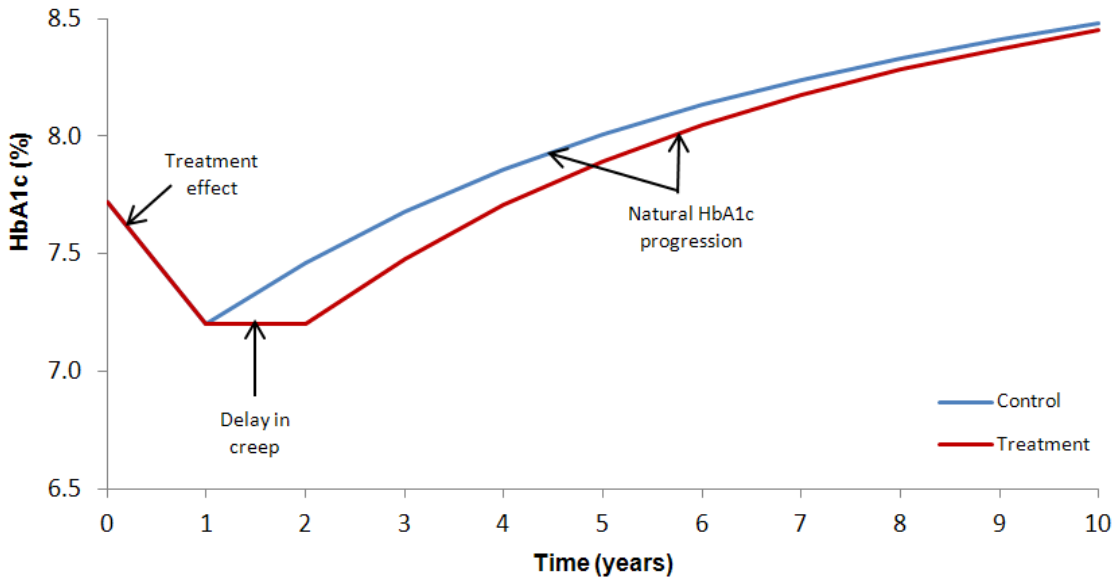

Figure 5: Illustration of dynamic risk factor profile using percentage HbA1c as an example

Table 6: Effects driving the changes in HbA1c

Effect	Description	Comparator	Treatment
HbA1c change	The magnitude and direction of the change applied to HbA1c.	-0.52	-0.52
Months benefit in year 1	How much of the HbA1c effect is applied in year 1.	12	12
Delay in creep (years)	The period following treatment before HbA1c progresses naturally	0	2
Slope coefficient	The coefficient used to derive the annual increase in HbA1c.	0.759	0.759
Glucose drift	The annual additional increase in HbA1c.	0	0

HbA1c, haemoglobin A1c

6.3.3 SBP, total and HDL cholesterol progression

The remaining treatment effects applied to blood pressure and cholesterol are simply applied over the first year. Natural progression is assumed to resume following this treatment effect as described in Section 4.2.

6.4 Therapy pathways and escalation thresholds

Each therapy arm (i.e. 'treatment' and 'control') is comprised of up to three therapy lines, reflecting the progressive nature of T2DM and the stepwise approach taken to its management. Typically, there is a reduction in HbA1c associated with the commencement of therapy but this effect wears off and HbA1c begins to rise again.

Each therapy line is selected from the 'Simulation' worksheet. The model incorporates two methods of modelling therapy escalation; escalation may be triggered when a specified HbA1c threshold is reached or the timing of escalation may be associated with a particular duration of therapy. Selection of either option and specification of its associated model inputs may be made on the 'Simulation' worksheet. By default, HbA1c thresholds are employed as the method of therapy escalation.

Simulated subjects will receive a particular therapy until either their HbA1c crosses the specified threshold (escalation threshold) or the specified therapy duration has been reached, at which point they cease receiving that therapy and move onto the next therapy. HbA1c levels are checked at the end of each year (not each cycle) to determine when switches are made in therapy lines, and therapy durations must be specified in whole years.

Figure 6 illustrates an example HbA1c profile with a switching threshold of 8.00%. The graph shows an initial reduction in HbA1c (between year 0 and 1) associated with the commencement of therapy (i.e. the treatment effect). However, this treatment effect is not maintained and from year 1 onwards HbA1c begins to rise again. Note that the slope of the curve is not linear as HbA1c rises at a quicker rate immediately following the reduction, in line with the time paths reported in the UKPDS 68 study.[2] HbA1c continues to rise until the specified HbA1c switching threshold of 8.00% is reached, at which point HbA1c decreases again following the commencement of a new therapy. The process then begins again with HbA1c rising until the next HbA1c switching threshold is reached (not shown on graph).

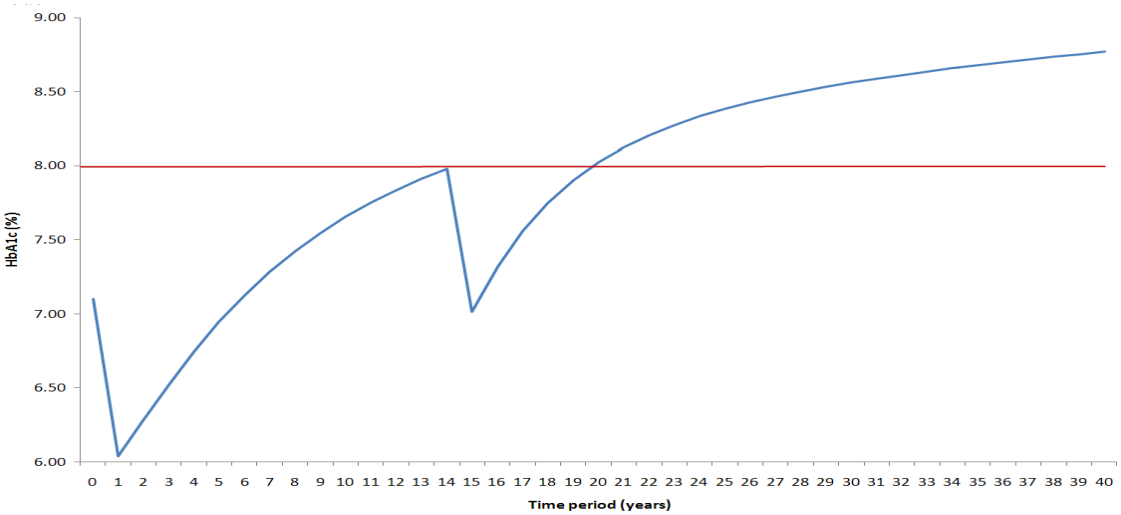

Figure 6: Example HbA1c profile with HbA1c switching threshold set to 8.00%

If therapy discontinuation occurs in the first or second line, patients commence the next selected therapy line. Therapy discontinuation is not modelled from third line. If the aim of simulation is to compare less than three lines of therapy, a rescue therapy, such as insulin, should be selected in later therapy lines (for discontinuing patients) and a very high HbA1c threshold set to prevent routine therapy escalation beyond the therapy lines subject to evaluation.

7 Costs

The model considers the full costs of treatment in both the treatment and comparator arm. This includes the costs of drug acquisition as well as appropriate inpatient, outpatient and primary care management costs (associated with maintenance and events). Costs of therapy, hypoglycaemia and adverse events are specified in the therapy profile menus, while costs of diabetes-related complications and costs associated with BMI are defined in the costs menu.

Note: Some of the costs are presented as annual costs, while the model operates on half-yearly cycles. This is an artefact of a previous incarnation of the model (AZ UKPDS 68), which did operate on annual cycles. The costs presented here are adjusted to half-yearly values in the model code.

Discounting of costs may be applied in order to present future costs at their present value. By default a discount rate of 3.5% is applied as recommended by the National Institute for Health and Clinical Effectiveness (NICE).

7.1 Therapy costs

Therapy costs are defined in the therapy profile menus. Model inputs are required describing annual therapy costs. While the annual costs of oral anti-diabetic agents (OADs) are constant, the cost of insulin is calculated for each cycle, accounting for changes in weight over a patient's lifetime.

7.2 Diabetes-related event costs

The incidence of diabetes-related events (microvascular and macrovascular) is associated with additional healthcare costs. These costs are split into fatal or non-fatal costs and are initially applied within the cycle in which the event occurs.

If the UKPDS 68 equations are selected, mortality is checked immediately after an event occurs thus fatalities are directly associated with a particular event and the appropriate cost is applied as such; in contrast, the functional form of the UKPDS 82 mortality equations means that event mortality is not checked immediately subsequent to an event but during the cycle, similarly to all-cause mortality, therefore it assumed that a fatality in a year in which an event occurs is as a result of the last event that occurred. The fatal event cost is then applied as appropriate (in place of the non-fatal event cost). Maintenance costs for those subjects surviving are applied in all subsequent years until either the end of the simulated time horizon or the subject dies. Figure 7 shows the UK event costs as an example of costs that may be applied in the model.

With the exception of ESRD, all event costs were sourced from the United Kingdom Prospective Diabetes Study 65 (UKPDS 65)[17] and inflated to 2012/13 prices using the Hospital & Community Health Services (HCHS) index (inflation factor ~1.603), published by the PSSRU.[18] The ESRD cost is based on the cost of dialysis (annual weighted mean cost for peritoneal and haemodialysis) from Baboolal *et al.*[19]and the 2013 distribution of prevalent diabetic dialysis patients as estimated by the Renal Registry[20], and is inflated using the HCHS index (inflation factor ~1.112).[18] An appropriate cost of ulcer is yet to be determined.

In this example, the initial fatal or non-fatal costs associated with second MIs and strokes are assumed to be equal to that of the first event. No maintenance costs are applied since maintenance costs associated with the first event continue to be modelled. Further research is required to identify the most appropriate cost inputs to apply to these events.

Table 7: Microvascular and macrovascular event costs

Event	Costs			Reference
	Fatal	Non-fatal	Maintenance	
Ischaemic heart disease	-	£3,139.40	£790.06	UKPDS 65 [17]
Myocardial infarction	£1,846.14	£6,522.38	£743.58	UKPDS 65 [17]
Congestive heart failure	-	£3,559.26	£1,011.21	UKPDS 65 [17]
Stroke	£5,421.43	£3,793.24	£399.03	UKPDS 65 [17]
Amputation	-	£13,555.97	£480.76	UKPDS 65 [17]
Blindness	-	£1,397.42	£450.32	UKPDS 65 [17]
ESRD	-	£34,738.88	£34,738.88	Baboolal *et al.*[19] Renal registry [20]
2nd Myocardial Infarction	£1,580.98	£5,585.60	-	Assumption
2nd Stroke	£4,642.77	£3,248.43	-	Assumption
Ulcer	-	TBD	TBD	TBD

ESRD, end-stage renal disease; TBD, to be determined.

7.3 Hypoglycaemia, adverse events and discontinuation costs

UK costs associated with hypoglycaemic events are shown in Table 6. Costs are presented for severe events only, as it is assumed that symptomatic and nocturnal events do not require healthcare resources. The cost of a severe event is based on a published population-based study of health service resource use in the treatment of hypoglycaemia [21]; the cost was inflated to 2012/13 prices using the Hospital & Community Health Services (HCHS) index assuming the source cost was reporting in 2002/3 prices (inflation factor ~1.353).[18]

Costs associated with adverse events may be applied in the year of their predicted occurrence. Suggested UK costs that may be applied to urinary tract infection (UTI), gastrointestinal (GI) and other adverse events are presented in Table 8. The cost of UTI and GI was obtained from a published study into the cost-effectiveness of management strategies for UTIs.[22] For the purposes of the model, the cost of the midstream urine analysis was chosen because it was the most expensive strategy - a conservative approach when the treatment arm is associated with more UTI/GI events than the comparator. The 2005/6 cost reported in the study was inflated to 2012/13 prices using the Hospital & Community Health Services (HCHS) index (inflation factor ~1.200). All other adverse events are assumed to incur the cost of a GP consultation as presented in the 2013 PSSRU unit cost of Health and Social Care; £45 per event.[23]

The model allows a cost to be applied to discontinuers, in the year of their discontinuation of therapy, the default cost is set to £0.

Table 8: Hypoglycaemic event and adverse event costs

Event	Cost	Reference
Symptomatic events	£0.00	Assumption
Nocturnal events	£0.00	Assumption
Severe events	£120.40	Cost of accident and emergency (A&E) attendance from Leese *et al.*[21]
GI or UTI events	£44.52	Turner *et al.*[22]
Other adverse events	£36	GP consultation – PSSRU.[23]

A&E, accident and emergency; GI, Gastrointestinal; UTI, urinary tract infection

7.4 BMI-related costs

The model applies an annual cost related to the simulated subject's body mass index (BMI), stratified by gender, as shown in Table 9. Due to the absence of more recent data, the BMI related costs were obtained from a published study into the influence of BMI on prescribing costs in a UK healthcare setting. Costs were obtained from a 2001 Counterweight audit of medical records[24] and inflated to 2012/13 prices using the Hospital & Community Health Services (HCHS) index assuming the source cost was reporting in 2001/2 prices (inflation factor ~1.400).[18]

The data clearly shows a positive relationship between BMI and costs. Thus, there will be cost savings associated with those patients that experience a weight reduction. For example, if a male subject's weight was reduced such that their BMI falls from 36 to 35 then there would be a cost saving of £11.77. Note that due to the manner in which the original analysis was performed (a piecewise regression was undertaken), BMI related costs increase in pronounced steps at certain points. In particular, there is a large increase in cost (£43.48 in males and £51.97 in females) between a BMI level of 29 and 30. This is a result of patients moving into a new subdivision of BMI, which is associated with higher risk and higher costs.

7.5 Indirect costs

The model allows the user to incorporate costs not directly associated with healthcare by applying indirect costs (it allows the user to model the analysis from a societal perspective). A typical application of indirect costs is in the inclusion of costs relating to employment whereby a reduction in employment is usually observed as a result of illness.

For each diabetes-related event, the model allows the user to define a cost incurred during the first year following the event and a cost incurred during all subsequent years. An annual indirect cost associated with diabetes can also be applied.

Indirect costs are not applied in the base case. If applied, indirect costs are only applied below a specified age threshold which can be specified by the user.

Table 9: Annual BMI-related costs, stratified by gender

BMI	Annual costs	
	Male	Female
20	£70.99	£87.63
21	£77.25	£92.88
22	£84.03	£98.42
23	£91.35	£104.29
24	£99.29	£110.47
25	£107.86	£117.03
26	£110.56	£113.58
27	£113.29	£110.22
28	£116.03	£106.95
29	£118.82	£103.75
30	£162.30	£155.72
31	£171.54	£161.64
32	£181.23	£167.78
33	£191.41	£174.12
34	£202.10	£180.68
35	£213.30	£187.47
36	£225.08	£194.49
37	£237.41	£201.74
38	£250.35	£209.24
39	£263.90	£217.00
≥40*	£278.12	£225.02

BMI, body mass index

**Those patients with a BMI above 40 are estimated to incur the same cost as a patient with a BMI of 40kg/m^2*

7.6 Other costs

Though not intended for regular use, the model has the facility to employ additional annual costs that are not otherwise modelled as part of the simulation. Up to five annual costs may be defined for application to patients in the treatment and control arms. Note that if defined, the year 5+ cost is applied in year 5 and all subsequent modelled years.

8 Health-related Utility

Quality of life is modelled in terms of quality-adjusted life years (QALYs). Decrements in utility (disutilities) associated with hypoglycaemia, adverse events and discontinuation are specified in the therapy profile menus, while the impact of diabetes-related complications and BMI are defined in the utilities menu. Model inputs are presented as annual values but are adjusted within the model to reflect the shorter cycle length of 6 months.

Discounting of QALYs may be applied in order to present future benefits at their present value. By default a discount rate of 3.5% is applied to benefits as recommended by the National Institute for Health and Clinical Effectiveness (NICE).

8.1 Age-dependent baseline utility

The relationship between age and baseline utility (a measure of quality of life) was modelled using mean EQ-5D by age group in subjects with no major complications, obtained from the Health Survey for England 2003.[25]

The polynomial in Figure 7 shows the inverse relationship estimated between age and utility, in which utility decreases as age increases. Furthermore, the rate at which utility decreases can be seen to vary at different stages of life. Between the ages of 30 and 60, the curve is relatively shallow showing a slow rate of decline, whilst in the later stages of life the rate of decrease is high.

At the beginning of the simulation, all patients are assigned a baseline utility value dependent on baseline age in accordance with this relationship.

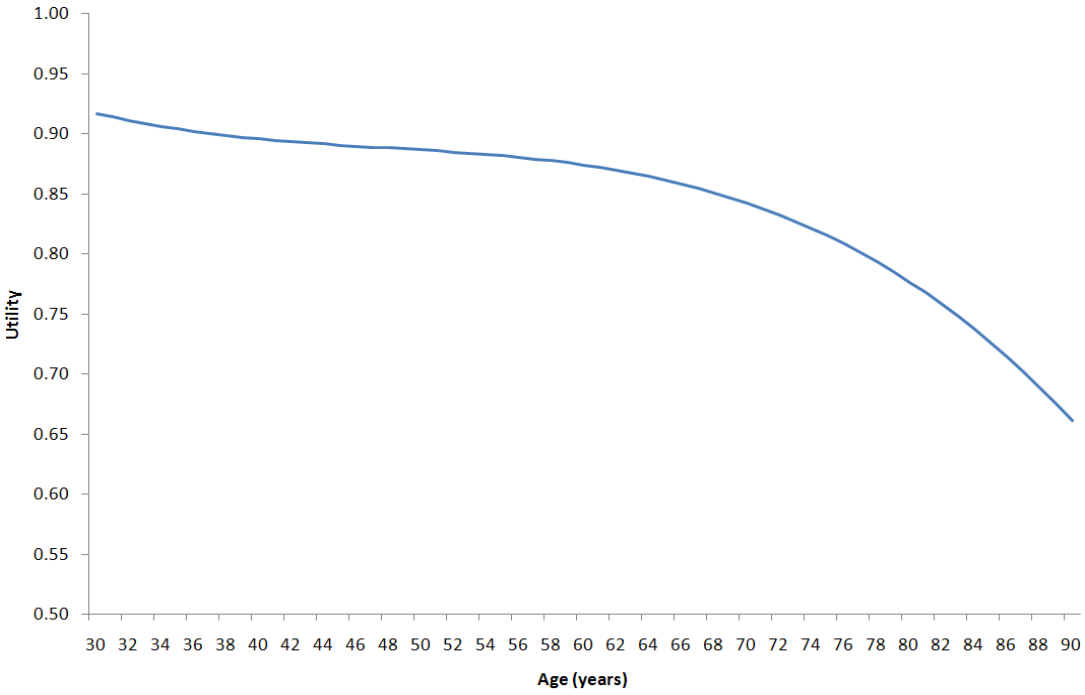

Figure 7: Age-dependent baseline utility function

8.2 Event-related utility decrements

The occurrence of diabetes-related events is associated with reductions in quality of life, which may be applied through utility decrements as shown in Table 10. The majority of the decrements were sourced from the United Kingdom Prospective Diabetes Study 62 (UKPDS 62),[26] with the exception of ESRD and blindness, which were sourced from a published study by Currie *et al.* [27] Subsequent events, by default, incur the same utility decrement as in the initial event, although the model allows for alternative values for subsequent events to be applied.

The model handles utility decrements for multiple events by applying the individual decrements additively.

The utility decrements associated with the newly modelled UKPDS 82 events are yet to be determined. Care must be taken in identifying appropriate model inputs, since decrements are applied additively and decrements have previously been applied in all years subsequent to initial events.

Table 10: Utility decrements associated with events in the model

Event	Utility decrement	
	In year of event	Subsequent years
Ischemic heart disease	0.090	0.090
Myocardial infarction	0.055	0.055
Congestive heart failure	0.108	0.108
Stroke	0.164	0.164
Blind	0.074	0.074
ESRD	0.263	0.263
Amputation	0.280	0.280
2nd myocardial infarction	TBD	TBD
2nd stroke	TBD	TBD
2nd amputation	TBD	TBD
Ulcer	TBD	TBD

ESRD, end stage renal disease; TBD, to be determined

8.3 Hypoglycaemia fear score and related utility

Utility associated with hypoglycaemia events is handled somewhat differently. Published equations characterising the relationship between the fear of hypoglycaemia and health-related utility were hard coded into the model.[28]

The multivariate regression models employed were developed using pooled data from two postal surveys conducted in Cardiff, UK (n=1,305 responses), in which the fear of hypoglycaemia was characterised using the fear of hypoglycaemia survey (FHS [eight question worry sub-scale only]) and health-related utility using the EQ-5D index.

The analysis revealed the FHS value to be the best estimate of the EQ-5D, while the number of hypoglycaemic events was found to be an important predictor of the FHS value. A two-stage approach was therefore adopted to predict EQ-5D; the relationship between frequency of hypoglycaemic events and FHS value was estimated, before estimating the EQ-5D using the predicted FHS value. Validation exercises proved the predictive power of the equations to be strong, with actual and predicted FHS score and EQ-5D values closely matched across all hypoglycaemia frequency and severity categories and across quartiles of the FHS.

8.4 Adverse event and discontinuation utility decrements

The model allows utility decrements to be applied to the incidence of adverse events, in the year in which the event occurs. In the base case, only UTI and GI events are considered and these are associated with a utility decrement of 0.00283 per event. This was obtained from a published study into UTIs in ambulatory women.[29] For the purposes of the model, the utility decrement associated with the "culture and wait" strategy was adopted because it had the largest decrement - a conservative approach when the treatment arm is associated with a greater number of UTI/GI events than the comparator. The utility reported in the study was shown in quality adjusted life months (QALMs) and so were divided by 12 to convert them to QALYs.

The model allows utility decrements to be applied to discontinuers. The decrement is applied in the year in which the discontinuation occurs.

8.5 BMI-related utility

The effect of changes in BMI on quality of life is detailed in Table 11.[30] A unit increase in BMI has a larger (negative) effect on quality of life, than the (positive) effect of a unit decrease in BMI.

Table 11: Change in utility associated with changes in BMI

Event	Change in utility
BMI – 1 unit increase	-0.0472
BMI – 1 unit decrease	+0.0171

BMI, body mass index

9 Model Outputs

9.1 Results summary

The key simulation outputs are summarised on the 'Results' or 'Results (UKPDS 82)' worksheets, according to the equation selection made for each analysis. These results have been averaged over all simulation runs, whether running a mean values analysis or PSA.

For each therapy arm (treatment and control), the mean numbers of predicted diabetes-related events and deaths are presented for the total cohort over the simulated horizon, together with the difference between the two arms. The total numbers of hypoglycaemic events are also presented. The total costs incurred in each arm are broken down by event, hypoglycaemia, adverse events, treatment, BMI and indirect costs.

Total discounted costs, QALYs and life years accumulated over the simulated horizon are reported per cohort and per patient for each arm, together with the difference between the two arms. The main outcome of the analysis is the cost per QALY gained, referred to as the incremental cost effectiveness ratio (ICER). The ICER is calculated as the incremental cost (cost in treatment arm

minus costs in comparator arm) divided by the incremental QALYs (QALYs in treatment arm minus QALYs in comparator arm).

Similar results are presented over a 5 year horizon for the interested user, in complimentary worksheets: 'Results (5 YR)' and 'Results (UKPDS 82) (5 YR)'.

In addition to the standard cost-effectiveness result (ICER), further outputs may be viewed as described in the following sections, which provide a more in-depth analysis of cost-effectiveness and related outcomes.

9.2 ICER scatter

The ICER scatterplot shows the cost effectiveness pairs estimated in each individual run of the model, in terms of the incremental costs (y axis) and incremental utility (x axis).

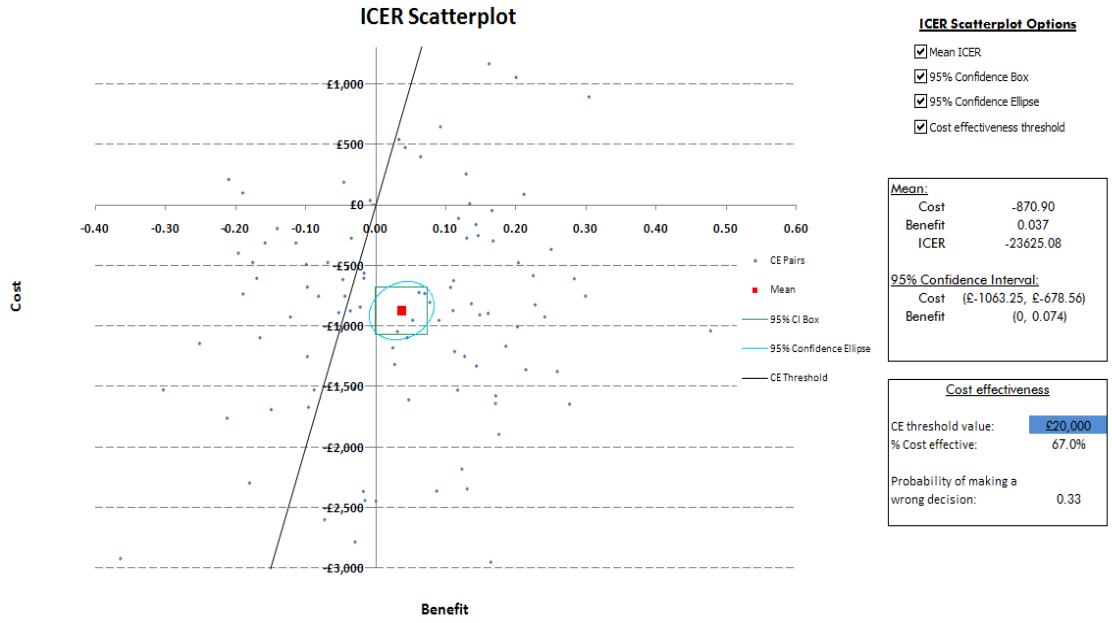

Figure 8: ICER scatterplot

The 95% confidence intervals on cost and benefit are calculated according the equations below[31]:

Cost: $\left(\Delta\bar{C} - z_{\frac{\alpha}{2}}\sigma_{\Delta\bar{C}},\ \Delta\bar{C} + z_{\frac{\alpha}{2}}\sigma_{\Delta\bar{C}}\right)$ Benefit: $\left(\Delta\bar{E} - z_{\frac{\alpha}{2}}\sigma_{\Delta\bar{E}},\ \Delta\bar{E} + z_{\frac{\alpha}{2}}\sigma_{\Delta\bar{E}}\right)$

Where:

$\Delta\bar{C}$ is the mean cost difference between treatment and comparator

$\Delta\bar{E}$ is the mean effect (benefit) difference between treatment and comparator

$\sigma^2_{\Delta\bar{C}}$ is the sample variance of the cost difference between treatment and comparator

$\sigma^2_{\Delta\bar{E}}$ is the sample variance of the effect difference between treatment and comparator

$z_{\frac{\alpha}{2}}$ is the critical value from the standard normal distribution.

For a 95% confidence interval the significance level, α=0.05 and $z_{\frac{\alpha}{2}}$ = 1.96

Confidence box plot: The confidence box plot is constructed using the upper and lower 95% confidence limits on the mean cost and mean benefit. The probability that the true cost and true benefit fall within the area covered by combining the two confidence intervals is $(1-\alpha)^2$ and thus this probability is in fact 90%.[31]

The construction of a confidence ellipse has the advantage over the confidence box of accounting for covariance between costs and benefits.[31] The following equations can be used to construct a 95% confidence ellipse:

Take the covariance matrix of costs and effects:

$$C_{\Delta\bar{E}\Delta\bar{C}} = \begin{bmatrix} \sigma^2_{\Delta\bar{E}} & \sigma_{\Delta\bar{E}\Delta\bar{C}} \\ \sigma_{\Delta\bar{E}\Delta\bar{C}} & \sigma^2_{\Delta\bar{C}} \end{bmatrix}$$

Where $\sigma_{\Delta\bar{E}\Delta\bar{C}}$ is the covariance of the cost and effect differences between treatment and comparator.

The angle of rotation (ϑ) is calculated by solving the following equation to give two bearings π/2 radians apart (ϑ_1 and ϑ_2):

$$\theta = \frac{1}{2}.\arctan\left(\frac{-2\sigma_{\Delta\bar{E}\Delta\bar{C}}}{\sigma^2_{\Delta\bar{E}} - \sigma^2_{\Delta\bar{C}}}\right)$$

For another coordinate system [u,v]:

$$u = \sin(\theta).\cos(\theta).\Delta\bar{E} \text{ and } v = -\cos(\theta).\sin(\theta).\Delta\bar{C}$$

With variances:

$$\sigma^2_u = \sigma^2_{\Delta\bar{E}}.sin^2(\theta) + 2\sigma_{\Delta\bar{E}\Delta\bar{C}}.\sin(\theta)\cos(\theta) + \sigma^2_{\Delta\bar{C}}.cos^2(\theta)$$

$$\sigma^2_v = \sigma^2_{\Delta\bar{E}}.cos^2(\theta) + 2\sigma_{\Delta\bar{E}\Delta\bar{C}}.\sin(\theta)\cos(\theta) + \sigma^2_{\Delta\bar{C}}.sin^2(\theta)$$

Substitute ϑ into the equation for σ^2_u to find the lengths of the major (a) and minor (b) axes of the ellipse:

$$a = \sigma_u(\theta_2) \text{ and } b = \sigma_u(\theta_1)$$

To plot the 95% confidence region scale these lengths by a factor of 2.447:

$$a_{95\%} = 2.447.\sigma_u(\theta_1) \text{ and } b_{95\%} = 2.447.\sigma_u(\theta_2)$$

95% confidence ellipse plot: For the axes lengths ($a_{95\%}$ and $b_{95\%}$) and angle of rotation (ϑ) in radians calculated above, coordinates of the confidence ellipse (x_t and y_t) are calculated using the equation below:

$$x_t = \Delta\bar{E} + a_{95\%}.\cos(t).\cos(\theta) - b_{95\%}.\sin(t).\sin(\theta)$$

$$y_t = \Delta\bar{C} + a_{95\%}.\cos(t).\sin(\theta) - b_{95\%}.\sin(t).\cos(\theta)$$

Where:

$$t = i.\frac{\pi}{180} \text{ for } i = 1 \text{ to } 360$$

9.3 Cost-effectiveness acceptability curve (CEAC)

Each iteration (cohort of patients simulated) of the PSA produces an estimate of the total costs and effects accumulated in the treatment and comparator arms; this process is performed n times providing n cost/effect pairs and consequently n estimates of the ICER.

The cost-effectiveness acceptability curve (CEAC) derived from this process represents the proportion of simulation replications whose ICER estimate lies on the acceptable side of the relevant ceiling ratio.

In the UK, typical ceiling values employed are £20,000 and £30,000 per QALY gained. The range of cost-effectiveness thresholds (or ceiling ratios) of interest may be changed on the 'CEAC Parameters' worksheet.

9.4 Net monetary benefit

A further outcome that the user may want to view is the net monetary benefit (NMB) which can be found on the 'NMB' worksheet (Figure 9). The net monetary benefit is essentially a re-working of the ICER equation (a monetary value is assigned to the incremental benefit achieved and this is subtracted from the incremental cost of achieving the benefit.

A positive net monetary benefit implies that the cost of a new therapy is less than the value of the additional benefit achieved. A negative net monetary benefit implies that an intervention should be rejected, as its costs are higher than the value of the benefit achieved.

The NMB graph on the "NMB" worksheet is shown in Figure 9 below.

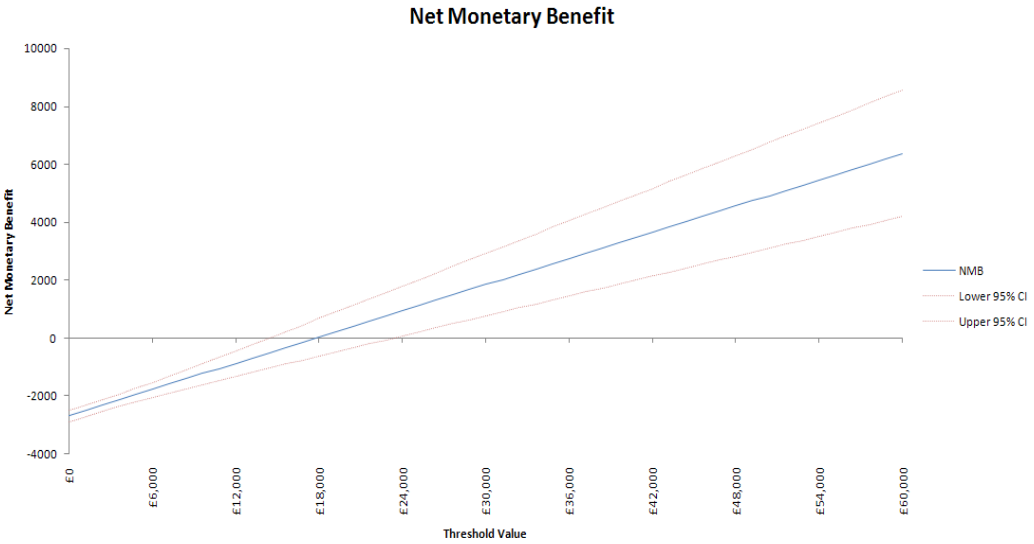

Figure 9: Net monetary benefit graph

Net monetary benefit (NMB) is calculated using a rearrangement of the cost-effectiveness decision rule as shown below:

$$NMB = \lambda.\Delta\bar{E} - \Delta\bar{C}$$

Where λ is the cost-effectiveness threshold.

The 95% confidence interval on the NMB is calculated as per the below equations:

Confidence interval:

$$(NMB - z_{\frac{\alpha}{2}}\sigma_{NMB},\ NMB + z_{\frac{\alpha}{2}}\sigma_{NMB})$$

Where:

$$\sigma^2_{NMB} = \lambda^2.\sigma^2_{\Delta\bar{E}} + \sigma^2_{\Delta\bar{C}} - 2\lambda.\sigma_{\Delta\bar{E}\Delta\bar{C}}$$

9.5 Patient level model output

Outputting the simulated outcomes at a patient level offers the potential to analyse the relationship between individual patient profiles and predicted cost-effectiveness. By identifying individual patients in whom treatment is most cost-effective or cost saving for example, differences between these patient groups can be analysed.

To enable such analyses new functionality has been incorporated in the model, to save patient level outputs estimated as part of the PSA to external CSV files. This is achieved by selecting the 'Generate patient level output' option on the 'PSA' worksheet. The PSA is then run as normal. On completion of the simulation two CSV files will be saved in the same folder in which the Cardiff Diabetes Model is currently saved.

These files, one for the control arm and one for treatment, are named according to the following convention: "Arm_Risk equation selection_date&time". For example, running an evaluation at 10.30am on the 15th of April 2014, using the UKPDS 68 equations would produce two CSV files named "Control_UKPDS_68_201404151030" and "Treatment_UKPDS_68_201404151030".

Each file contains baseline demographics, risk factors values and clinical history for each simulated patient, followed by the predicted incidence of diabetes-related complications (where 0/1 represents no event/event incidence) and total discounted costs, QALYs and life years accumulated. Each line corresponds to an individual simulated patient. Thus, if a cohort of 100 patients is simulated over 1,000 replications, each file will contain 100,000 patient rows. Each patient row in the treatment arm corresponds to the same patient row in the control arm, thus total costs and QALYs in corresponding rows may be compared to produce incremental cost-effectiveness pairs and scatterplots plotted accordingly.

9.6 Other results outputs

There are a number of intermediary worksheets that feed into the results summary sheet or present outputs for more advanced evaluation of the simulation process/output. It is not anticipated that these sheets would be viewed by the majority of users.

Risk factor trajectories

Information regarded simulated risk factor trajectories are shown in the 'HbA1c Profile', 'Risk factors' and 'Biannual risk factors' worksheets. These sheets present risk factor values at baseline and at each modelled cycle/year. Note that the "Data used in model" columns presented account for changes in therapy lines for a patient who does not discontinue therapy.

T2 events sheets

The T2 events sheets ('T2 events', 'T2 events (5 yr'), 'T2 events (UKPDS 82)', 'T2 events (UKPDS 82) (5 yr)') present the number of events predicted each year and the total costs, QALYs and life years accumulated each year. Note that the number of life years accumulated over year 1 may not equal the size of the cohort. This is because simulating patients over 6 monthly cycles allows mortality events to occur mid-year, and thus not all patients will accumulate a full life year.

Additionally, the total number of patients receiving each line of therapy is presented at the start of each year. The total presented is the sum of the three lines of therapy and may be interpreted as the number of patients alive at the start of each year.

Therapy targets

Users may specify treatment targets relating to the attainment of specific clinical thresholds for HbA1c, SBP and weight. Each target threshold is specified in the 'Simulation' worksheet and results defining the average number of years spent below the target are presented in the 'Results (5 YR)' and 'Results (UKPDS 82) (5 YR)' worksheets, for years 1 to 5.

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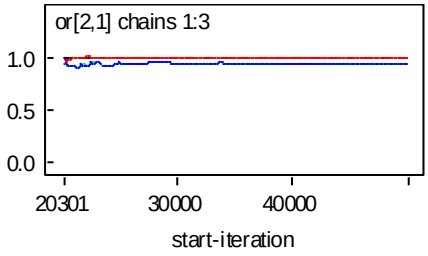
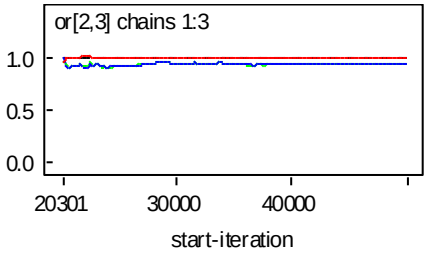
Appendix 1

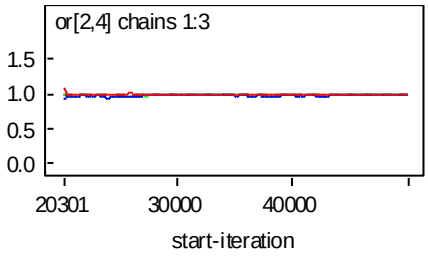
HbA1c Progression Report.docx

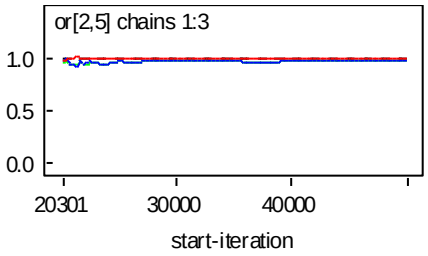
Any hypoglycemia FEM

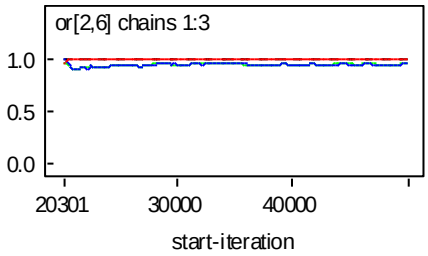
BGR Plots for model convergence:

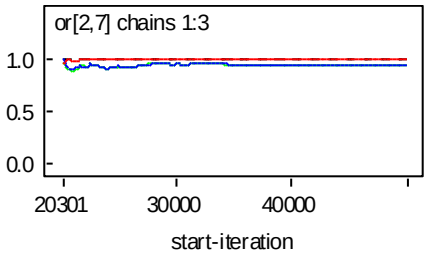


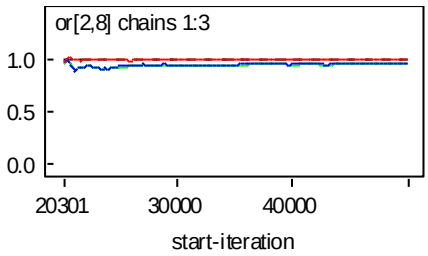




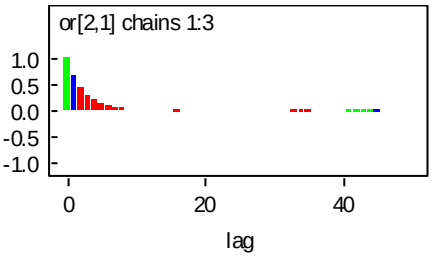


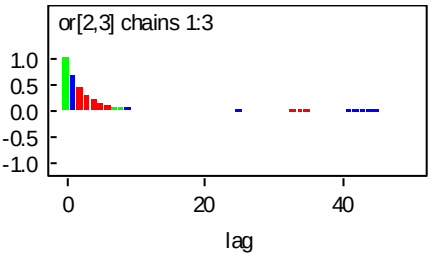


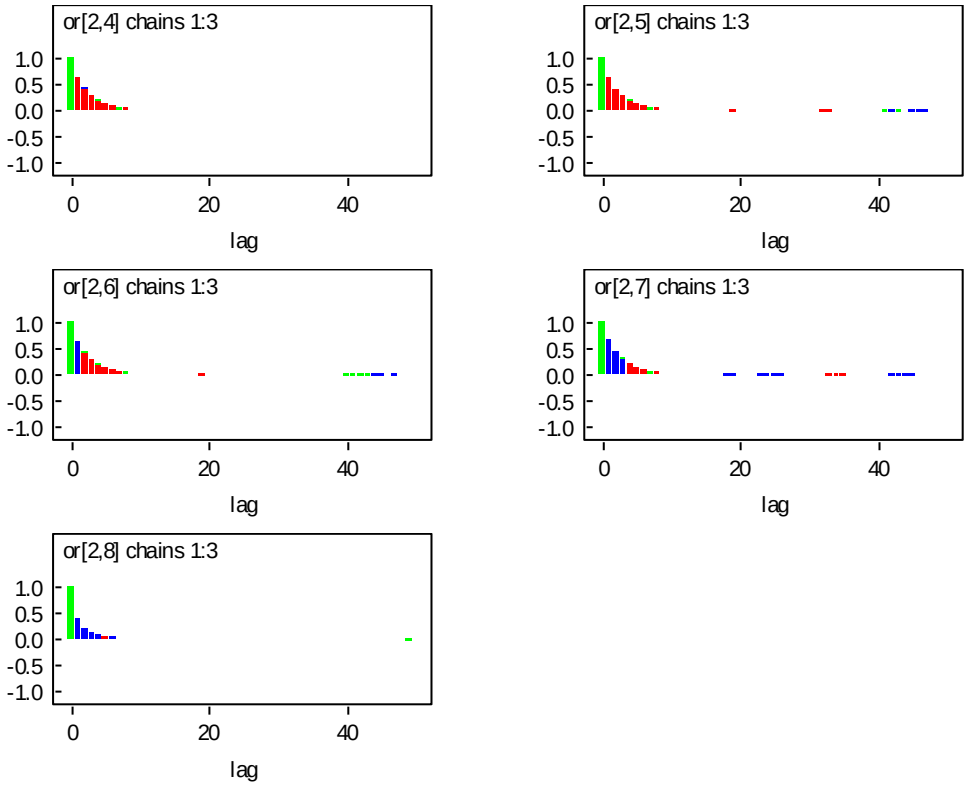




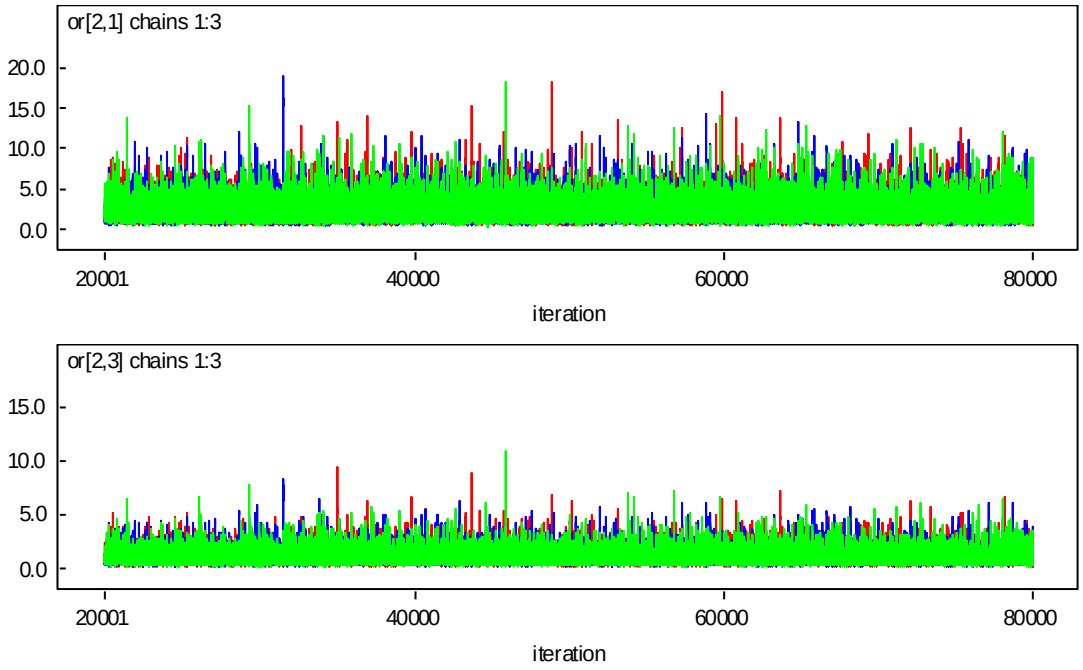
Autocorrelation plots:

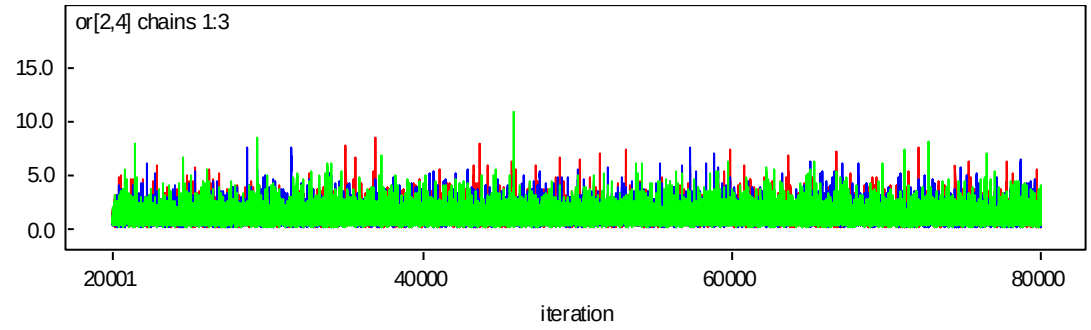






Time series Plots:

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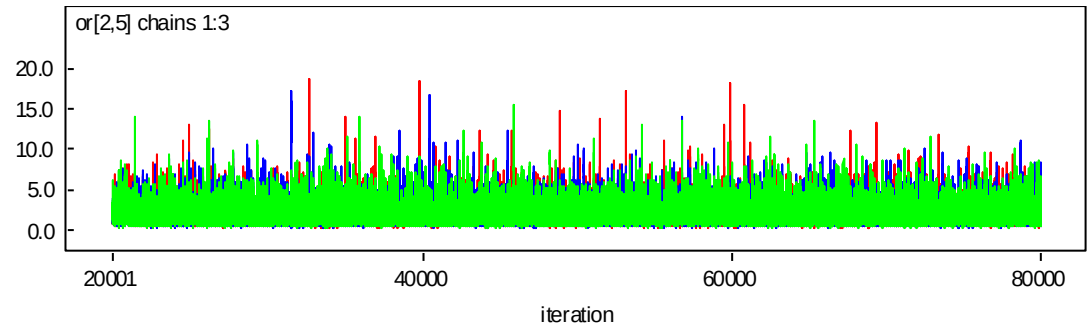
10.0
5.0
0.0
20001
40000
60000
80000
iteration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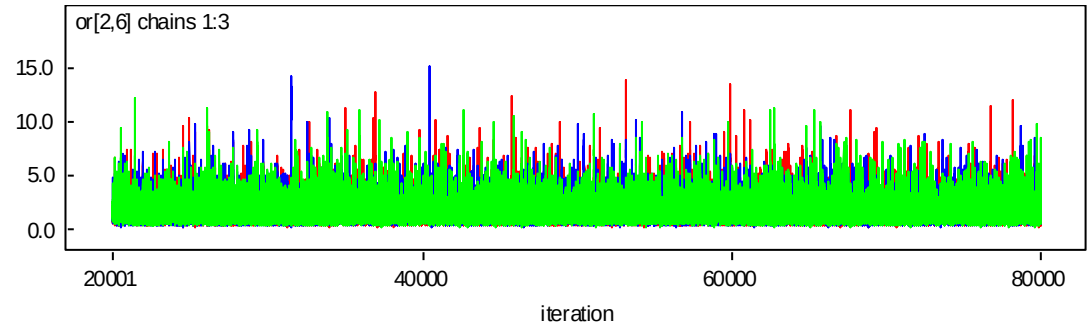
iteration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40000
60000
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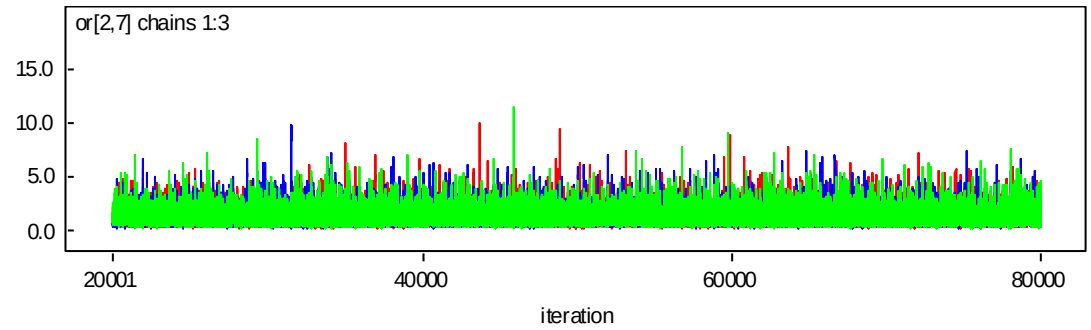
iteration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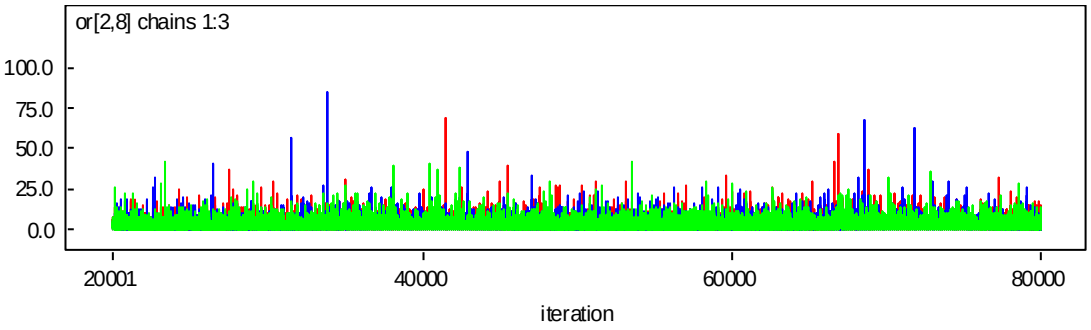
40000
60000
80000
iteration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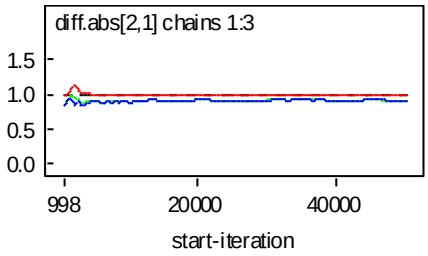
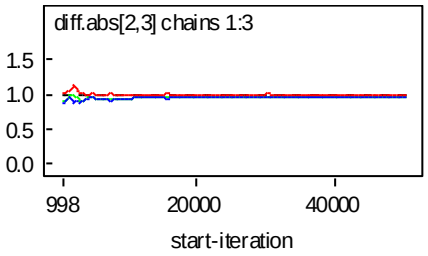
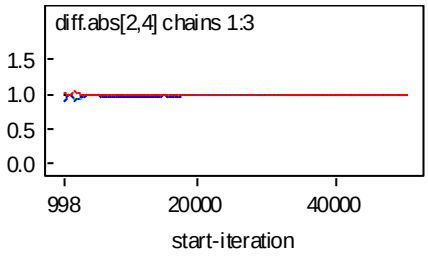
50.0
25.0
0.0
20001
40000
60000
80000
iteration

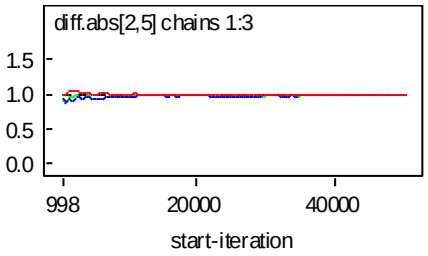
HbA1c CFB REM

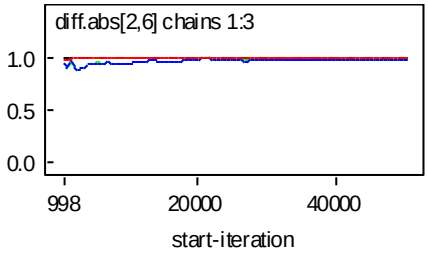
BGR Plots for model convergence:

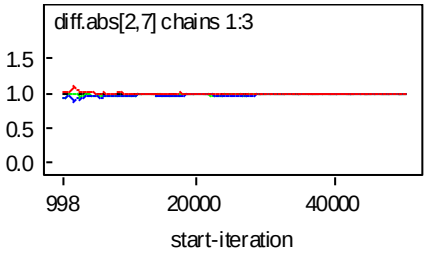


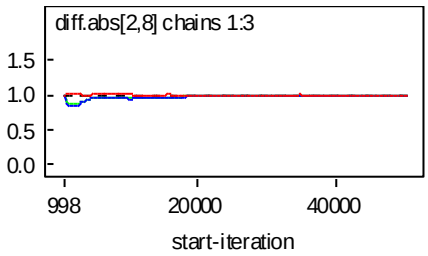




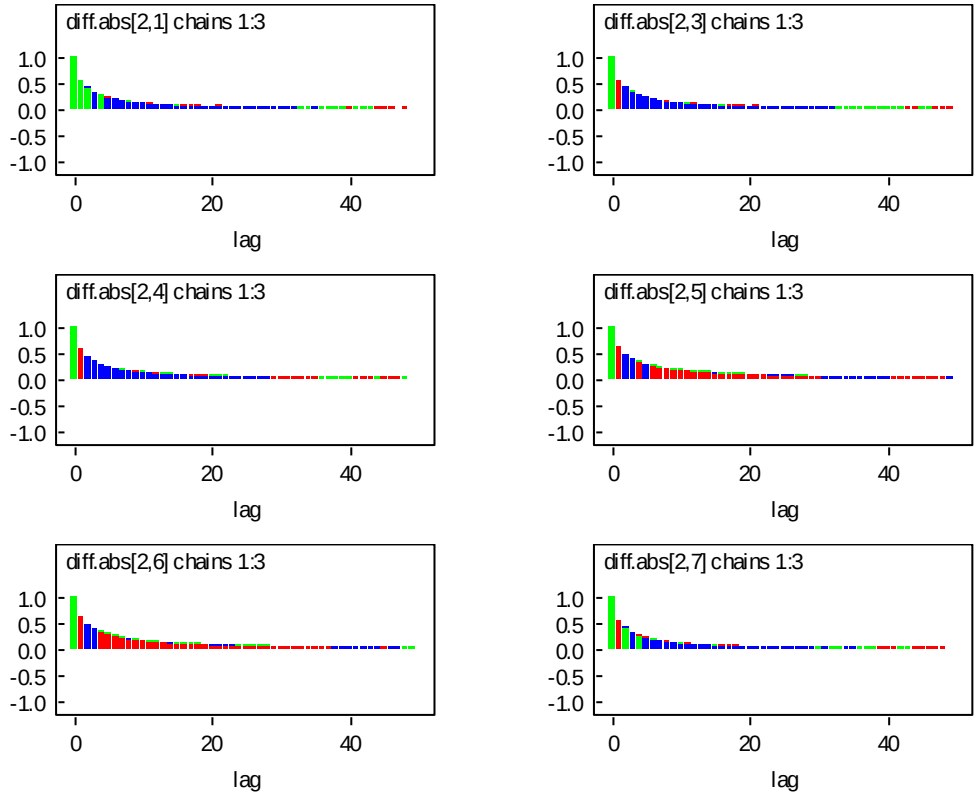




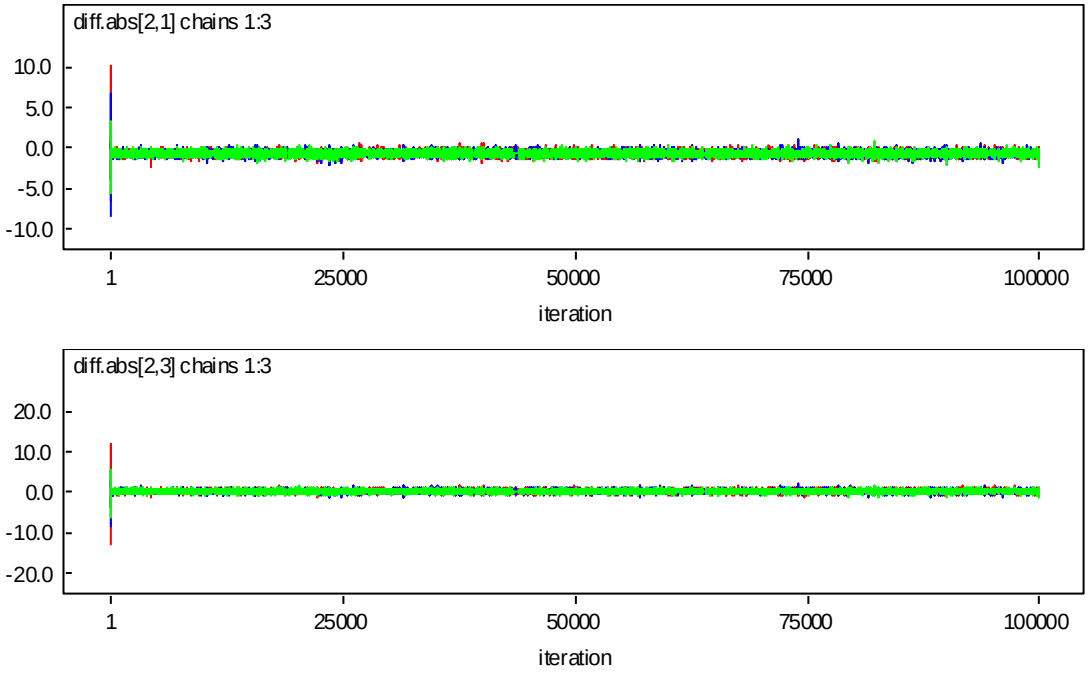


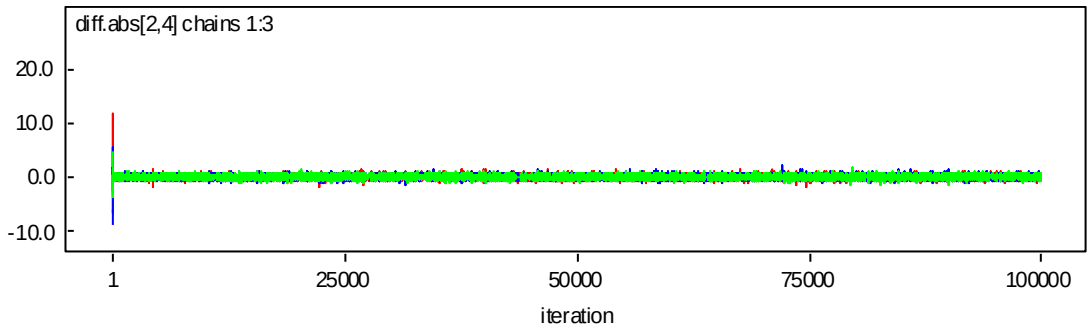


Autocorrelation plots:



Time series Plots:

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1
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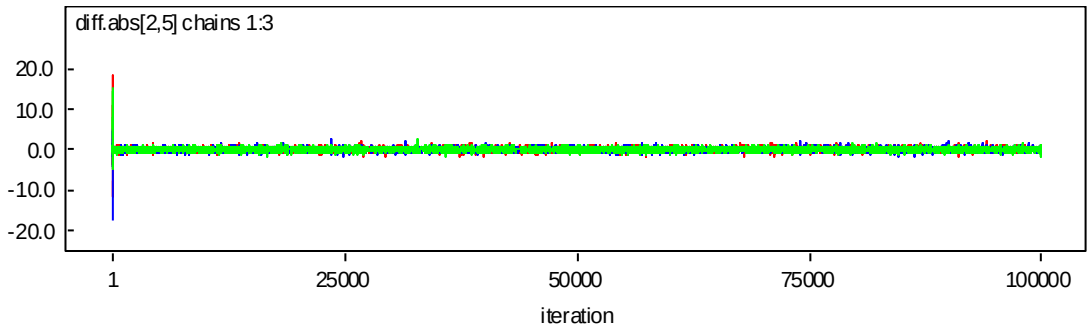
50000
75000
100000
iteration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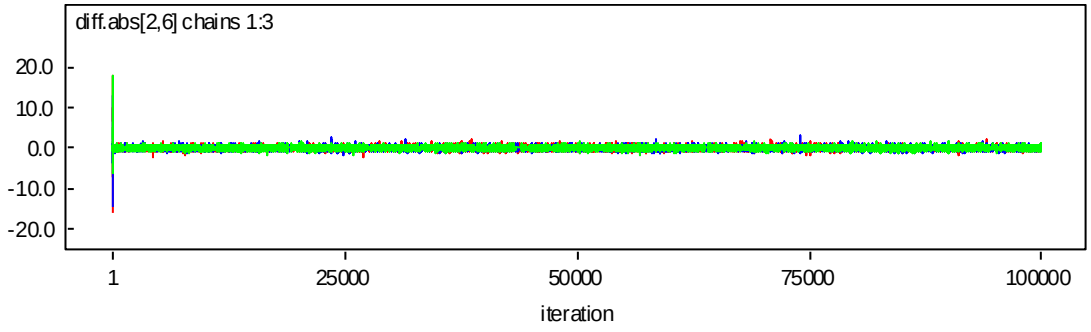
0.0
-10.0
-20.0
1
25000
50000
75000
100000
iteration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0.0
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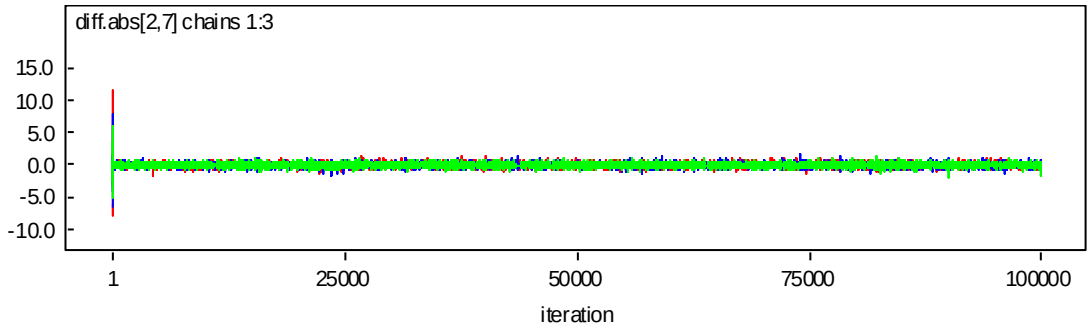
50000
75000
100000
iteration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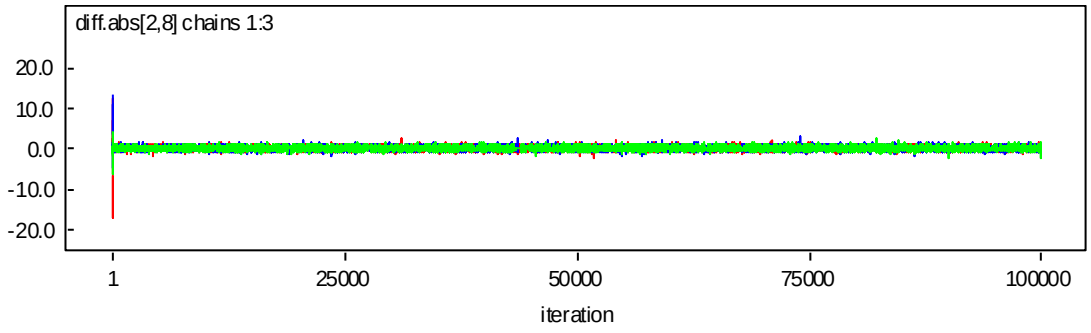
1
25000
50000
75000
100000
iteration


diff.abs[2,8] chains 1:3
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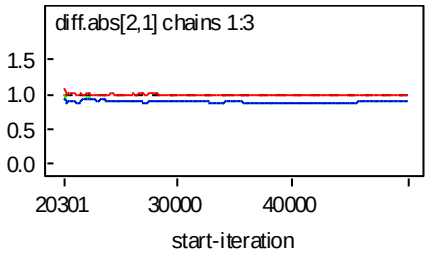
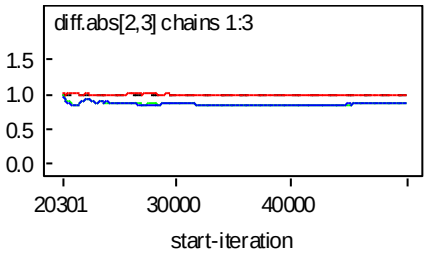
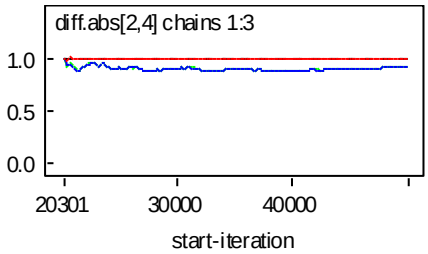
-20.0
1
25000
50000
75000
100000
iteration

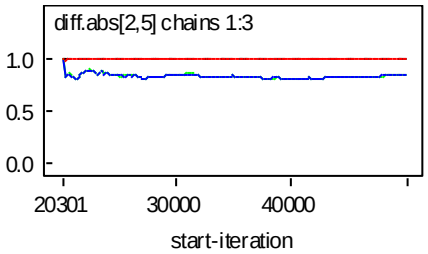
SBP CFB REM

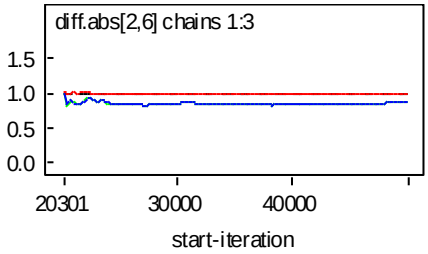
BGR Plots for model convergence:

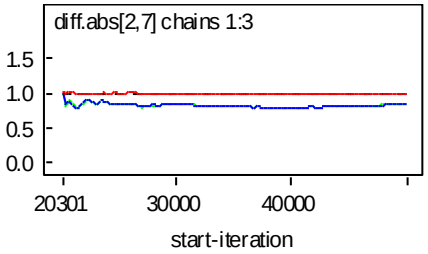


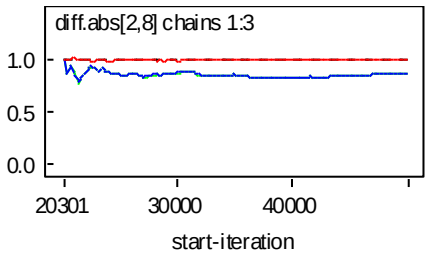


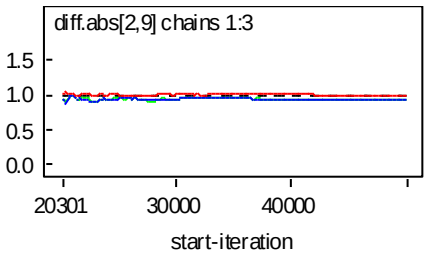




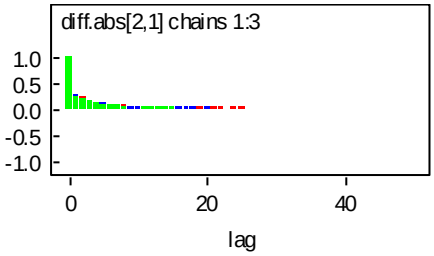


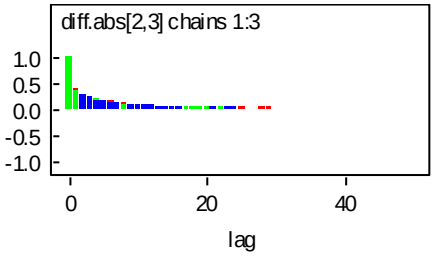


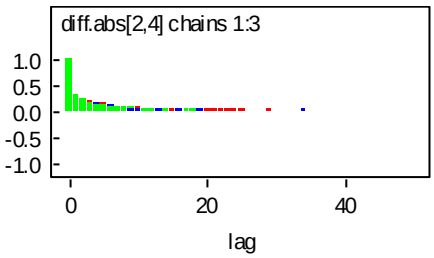


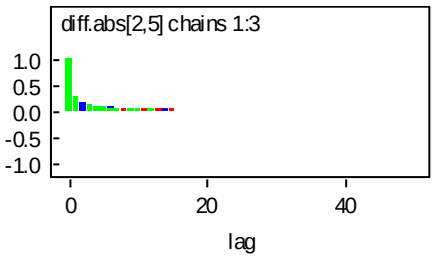


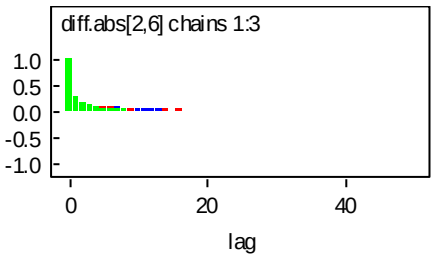
Autocorrelation plots:

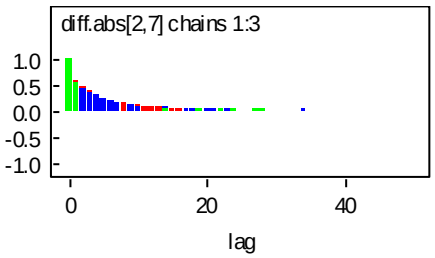


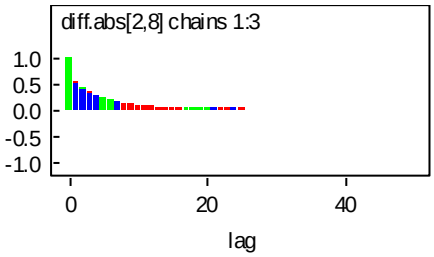


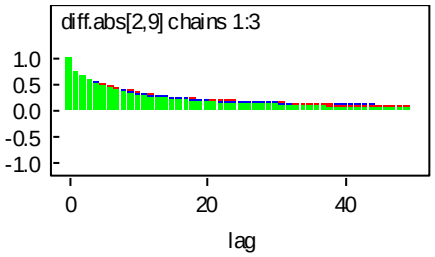




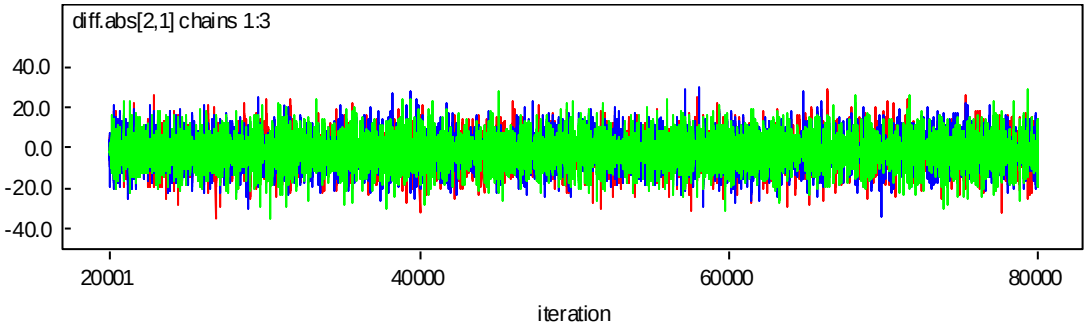


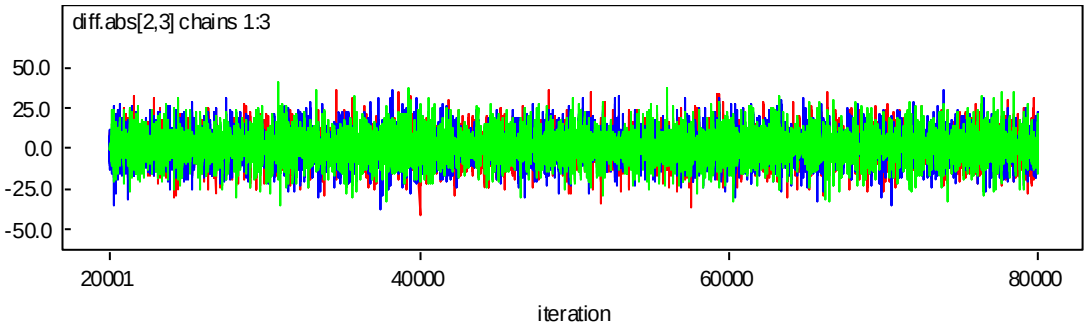


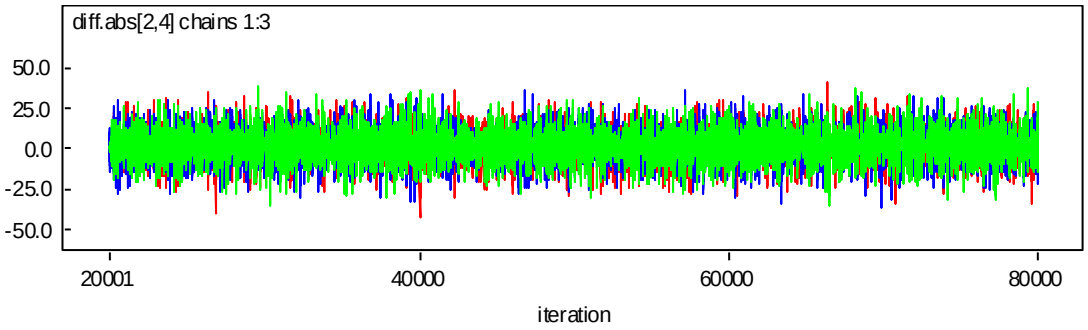


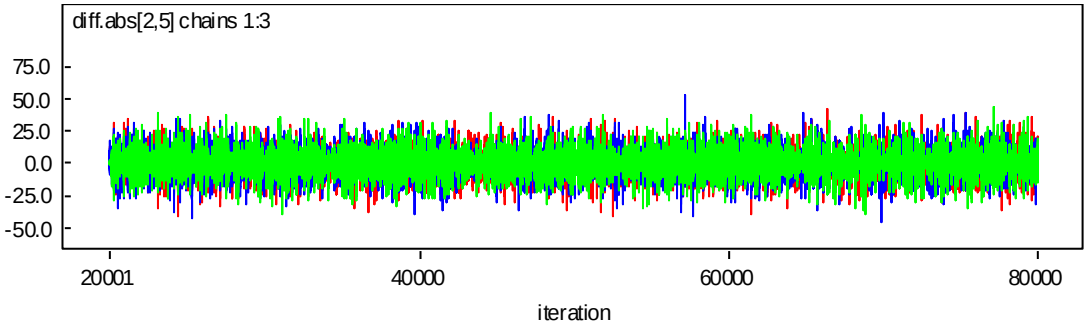


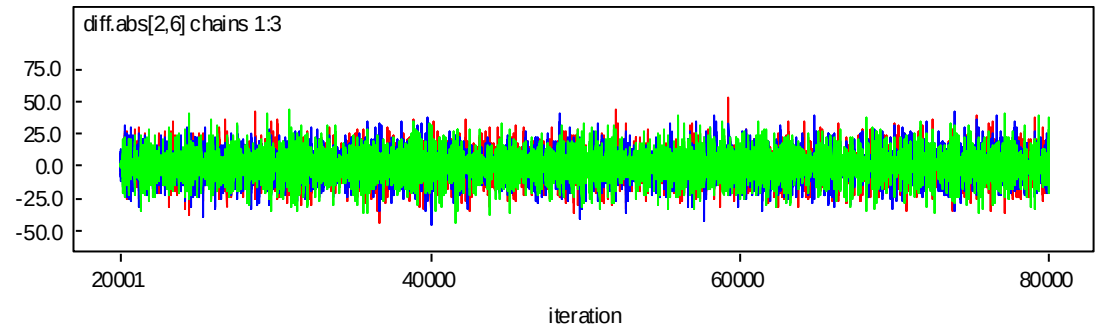
Time series Plots:







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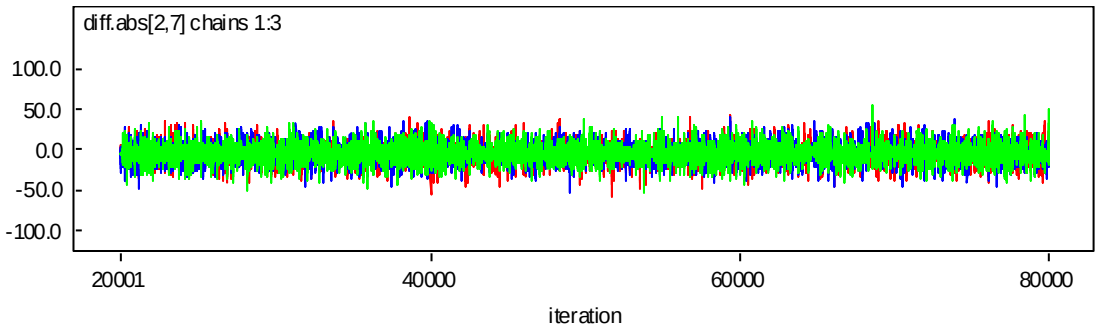
25.0
0.0
-25.0
-50.0
20001
40000
60000
80000
iteration


diff.abs[2,7] chains 1:3
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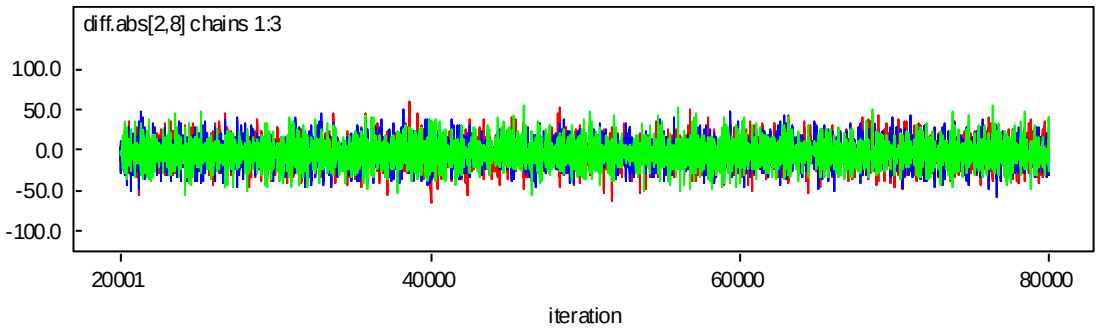
-50.0
-100.0
20001
40000
60000
80000
iteration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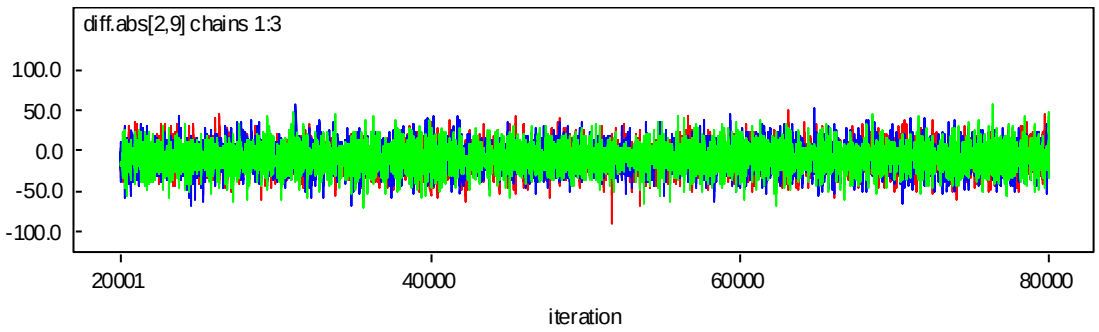
40000
60000
80000
iteration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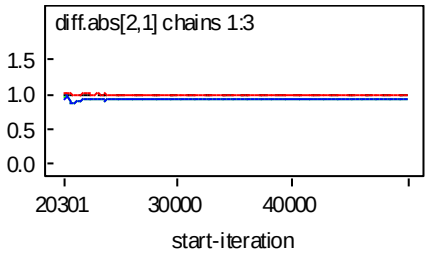
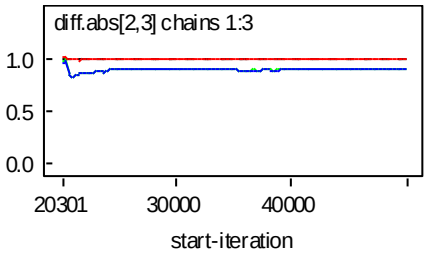
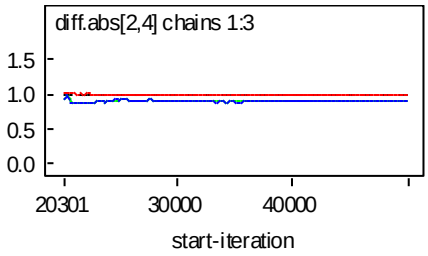
20001
40000
60000
80000
iteration

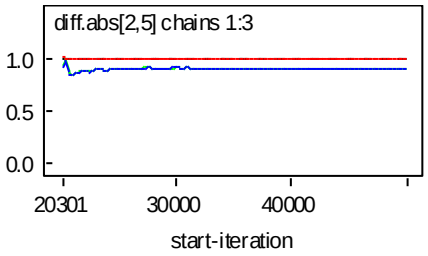
Body Weight CFB REM

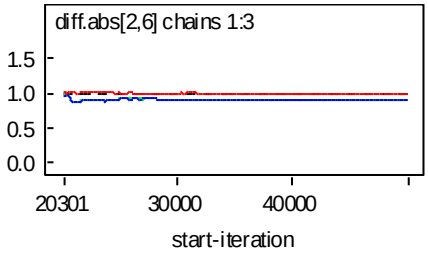
BGR Plots for model convergence:

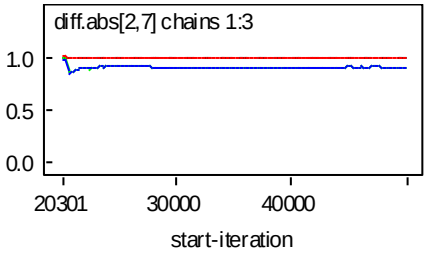


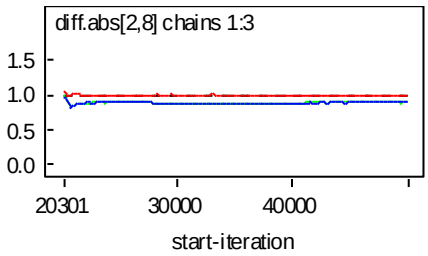


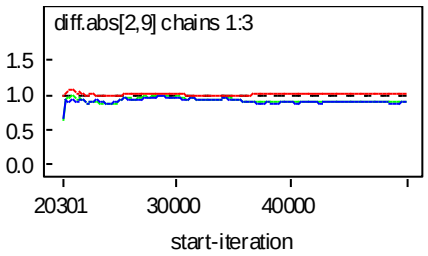












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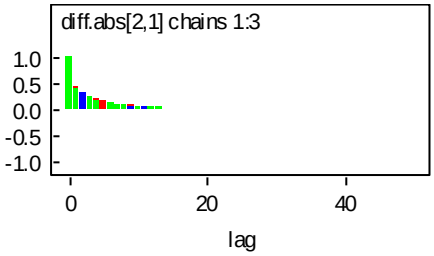

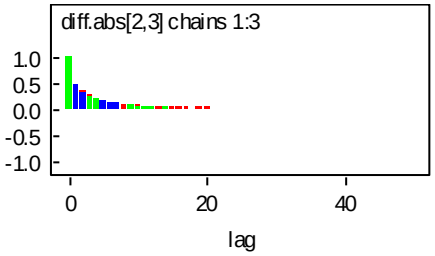

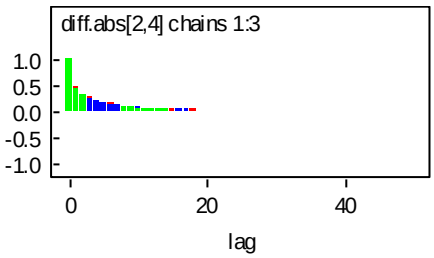

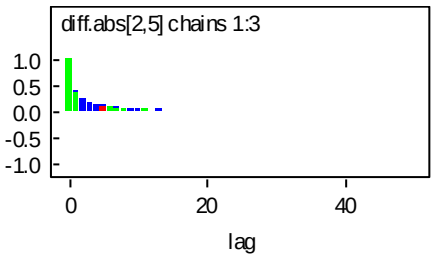

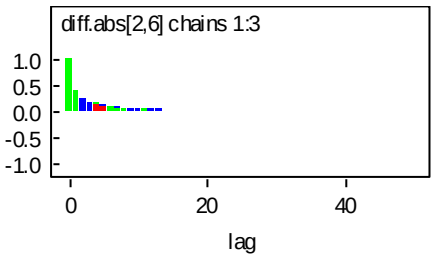

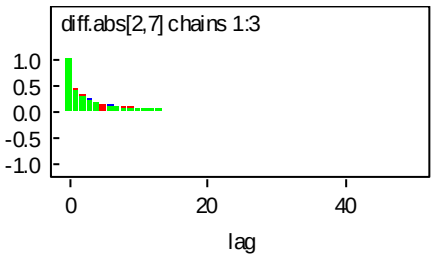

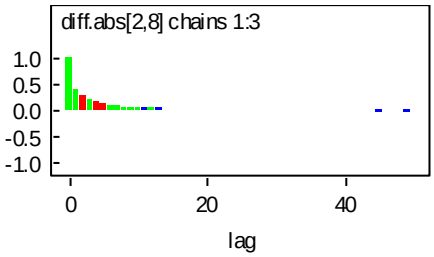

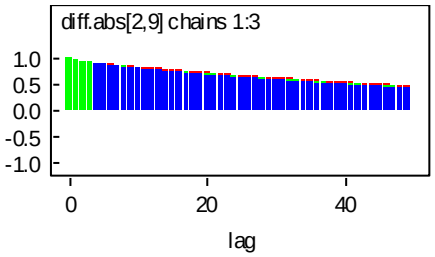

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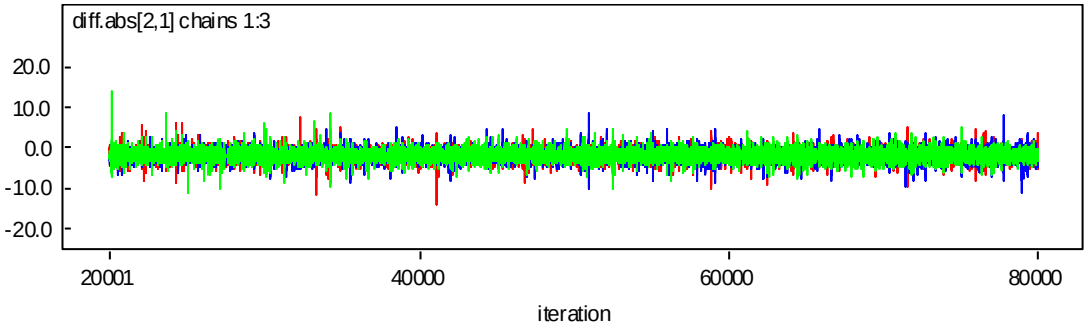

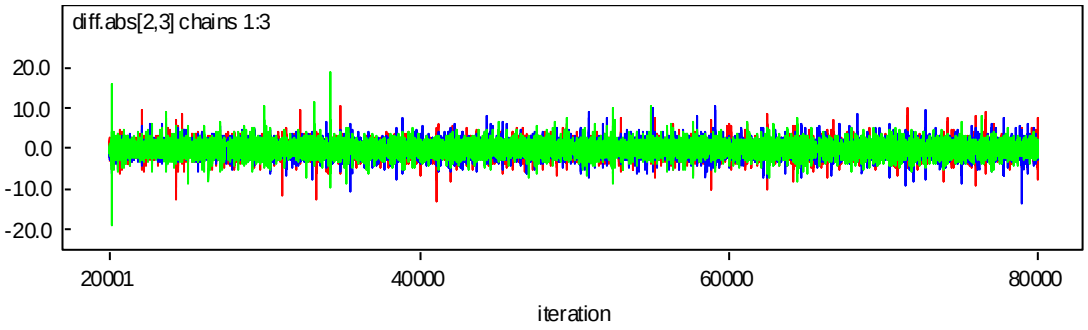

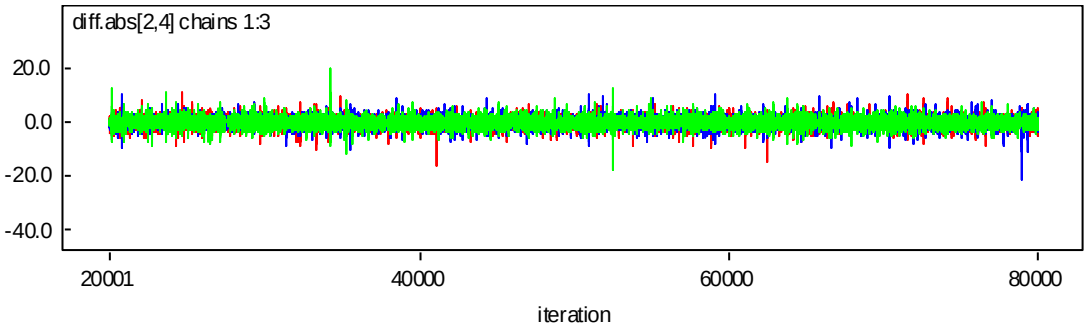

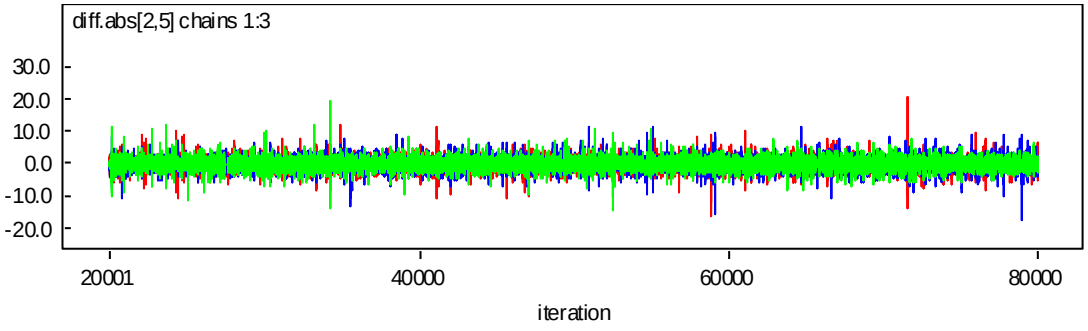

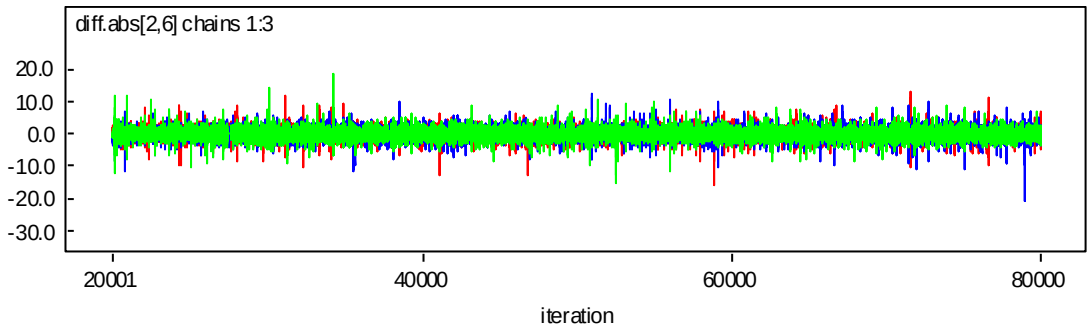
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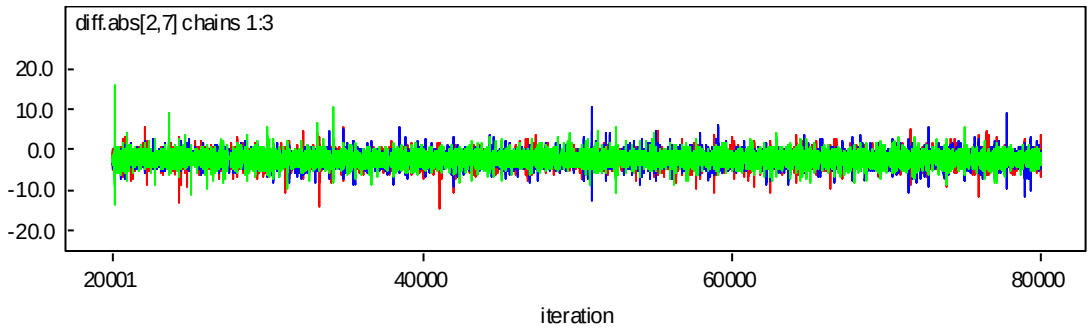
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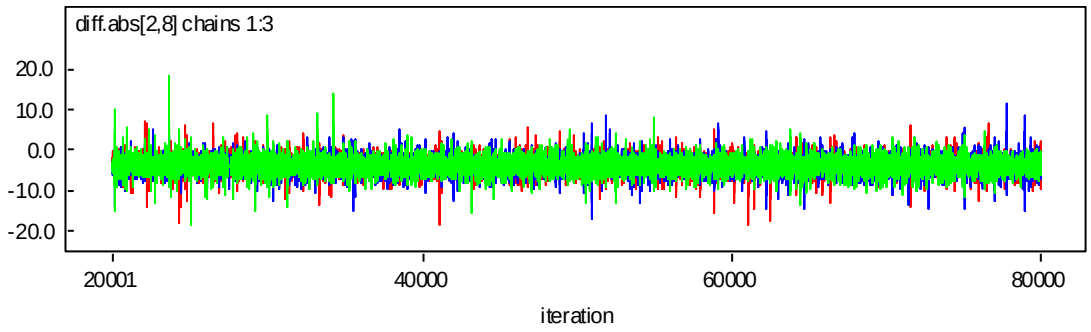
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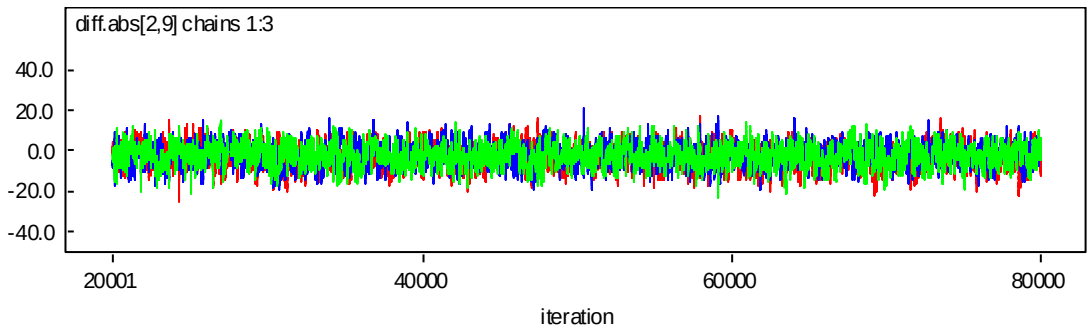
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20.0
0.0
-20.0
-40.0
20001
40000
60000
80000
iteration

Treatment code

Treatment name	Code
MET+SU	1
DAPA+MET+SU	2
CANA300mg+MET+SU	3
CANA100mg+MET+SU	4
EMPA25mg+MET+SU	5
EMPA10mg+MET+SU	6
DPP4+MET+SU	7
TZD+MET+SU	8
Basal insulin+MET+SU	9

1. The company in response to A7 states that "Should results also be required for each of the four networks… please let us know and we can provide these". Could the company please provide the

corollary of the Dapa_TOT_CE_model_inputs_Restricted_networks_endpoints_FINAL_Base_case spreadsheet for the 24 week, 52 week, study endpoint and base case analyses for both the fixed and the random effect analyses.

2. Furthermore, the Dapa_TOT_CE_model_inputs_Restricted_networks_endpoints_FINAL_Base_case spreadsheet provides the data relative to MET+SU while e.g. table 28 provides results relative to DAPA.

Table 28 appears to suggest a relative effect of 1.05 for CANA300 compared to DAPA but the spreadsheet suggests estimates for CANA300 -3.070 of and for DAPA of-2.038, which suggests a net effect of 1.03. There appear to be other discrepancies throughout if the ERG has interpreted the company method correctly. Could the company clarify this please and reconcile the data in tables 26, 27,28 and 29 for the base case random effects model with that of the

Dapa_TOT_CE_model_inputs_Restricted_networks_endpoints_FINAL_Base_case spreadsheet.

Norman and Ewen

Warwick Evidence and McMDC

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Norman and Ewen

Warwick Evidence and McMDC

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962] - Further clarification

Please find below the response for query 2.

2. Furthermore, the *Dapa_TOT_CE_model_inputs_Restricted_networks_endpoints_FINAL_Base_case* spreadsheet provides the data relative to MET+SU while e.g. table 28 provides results relative to DAPA. Table 28 appears to suggest a relative effect of 1.05 for CANA300 compared to DAPA but the spreadsheet suggests estimates for CANA300 -3.070 of and for DAPA of-2.038, which suggests a net effect of 1.03. There appear to be other discrepancies throughout if the ERG has interpreted the company method correctly. Could the company clarify this please and reconcile the data in tables 26, 27, 28 and 29 for the base case random effects model with that of the *Dapa_TOT_CE_model_inputs_Restricted_networks_endpoints_FINAL_Base_case* spreadsheet.

The base case relative results from the NMA presented in tables 26 to 29 in the submission dossier and those presented in the model input spreadsheet have been obtained as an output from Winbugs; no manual calculations were involved.

The only difference between these results is the way they have been presented i.e. in the submission dossier tables, effect sizes have been presented as dapagliflozin vs. all comparators while in the spreadsheet the effect sizes have been presented as all comparators vs. placebo (MET+SU). Additionally, in the submission tables, the effect size values have been rounded off to 2 decimal places.

The differences in effect size results between spreadsheet calculation and Winbugs output are observed at the second and third decimal place (please refer to attached Excel sheet [NICE query 2]). These differences may be due to fact that the output from Winbugs involves sample iterations and also considers both median/mean and SE values.

These differences are not clinically meaningful; and would be expected to have no or negligible impact on the results of the economic modelling. Indeed, univariate sensitivity analyses already presented demonstrate that dapagliflozin remains highly-cost effective or dominant with variation of treatment effects by ±25%.

For hypoglycaemia, effect sizes have been presented as odds ratio; so it cannot be manually calculated to assess net estimate of dapagliflozin vs. other therapies.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for treating type 2 diabetes [ID962]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

XXXXXXXXXXXXXX

Name of your organisation

Honorary Associate Clinical Professor, Warwick Medical School, University of Warwick

[redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

I am a Profesional member of Diabetes UK and the Primary Care Diabetes Society

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Diabetes Mellitus is treated and managed across both primary & secondary care in the UK. There is evidence of a degree of variation between practices and between CCG's demonstrated in the National Diabetes Audit of which I am the GP Clinical Lead.
Management is guided by NICE Clinical guidelines which have recently been updated for both Type 1 Diabetes in children & adults and for Type 2 Diabetes in adults. Both sets of guidelines were published in 2015.
The NICE type 2 guideline published in Dec 2015 includes statements about the group of oral agents called SGLT2 inhibitors of which dapagloflozin, the agent under consideration in this appraisal, is an example.
NICE has also recently published a technology appraisal of the use of SGLT2 agents in monotherapy management of type 2 diabetes. There have also been TA's on the use of 2 other SGLT2 agents iemplafloflozin and canagloflozin n combination therapy for type 2 diabetes.

The position of the SGLT2 agents in the treatment algorithm for type 2 diabetes is in my opinion, undergoing change even since the T@ guideline was published in 2015.
Recently in 2016 he EMPRA -REG study of the SGLT2 agent emplagloflozin, showed that use of this agent reduced CVD mortality and so clinicians may feel now that the earlier use of SGLT2 agents, perhaps second to metformin, is now more justified., as is their role as third line agents with metformin and one other glucose lowering therapy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Dapagloflozin as an SGLT2 agent has a similar side effect profile to the other SGLT2 agents licensed for use in combination. Its advantages and disadvantages are therefore similar to the others in the class which have received their TA"s for use in combination.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

The evidence required for Dapagloflozin should be similar to that for the other SGLT2 agents that have received TA's for use in combination

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No.
This agent is similar to other SGLT2 agents in the class that already have TA's so there are in my opinion no additional resource implications

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for treating type 2 diabetes [ID962]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Chelsea & Westminster NHS Foundation Trust, London

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **NO**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **NO**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? **THERE ARE SEVERAL DRUG CLASSES AVAILBLE FOR THE MANAGEMENT OF TYPE 2 DIABETES. DRUG COMBINATIONS ARE OFTEN REQUIRED TO ACHIVED IMPROVED GLUCOSE CONTROL. WHILE THE DRUG CHOICE OFTEN IS DRIVEN BY GUIDLEINE STEPS, INDIVIDUALISATION OF THERAPY IS REQUIRED DUE TO VARIATION IN RESPONSIVENESS AND KEY CLINICAL FACTORS SUCH AS EFFECTS ON WEIGHT AND HYPOGLYCAEMIC RISK.**

OF PARTICULAR IMPORTANCE IS THE HIGH PREVALENCE OF HIGH BMI IN THIS PATIENT GROUP, WHERE OVER 75% ARE EITHER OVER-WEIGHT OR OBESE WHICH HAS A KEY DETERMINANT OF DRUG CHOICES AFTER METFORMIN THERAPY. Dapagliflozin WAS FIRST IN MARKET OF THE FLOZIN CLASS WHICH HAS EFFECTIVE WEIGHT REDUCTION AS WELL AS GLUCOSE LOWERING. ITS USE IN TRIPLE THERAPY WOULD ALLOW THE MOST COMMONLY PRESCRIBED DRUG IN CLASS TO BE EASILY USED IN TRIPLE COMBINATION IF REQUIRED.

ADDITIONAL BENEFIT- TO SIMPLIFY THE GUIDANCE ALGORITHM FOR GLUCOSE LOWERING TYPE 2 DIABETES

Is there significant geographical variation in current practice? **YES**

Are there differences of opinion between professionals as to what current practice should be? **VARIES UPON EXPERIENCE WITH THE SEVERAL DRUG CLASSES**

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

1. **HIGHER DOSE OF EMPAGLIFLOZIN HAS A WEAKER GLUCOSE LOWERING EFFECT THAN LOWER DOSE**
2. **CANAGLIFLOZIN AND EMPAGLIFLOZIN MAY BE PRESCIBED WITH EGFR DOWN TO 45 WHILE DAPA ABOVE EGFR 60**

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? **RESPONDER VERSUS NON- OR POOR RESPONDER**

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? **NOT KNOWN**

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? **FOR ALL PRACTICES PARTICULARLY WITH OVERWEIGHT TYPE 2 DIABETES**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? **ALREADY ON MARKET- EASY TO ADMININSTER AS SINGLE DRUG**

If the technology is already available, is there variation in how it is being used in the NHS? **SIMPLIFIES THE USE OF FLOZINS - AS DAPAGLIFLOZIN WAS THE FIRST TO MARKET-**
Is it always used within its licensed indications? If not, under what circumstances does this occur**? COMBINED WITH GLP-I FOR OBESE??**

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

RECENT ADA/EASD GUIDELINES FOR TYPE 2 DIABETES-

ESTABLISHED FROM DIABETES ASSOCIATIONS IN U.S.A. AND EUROPE

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
EASIER TO USE FOR COMBINATION THERAPIES TO MAXIMISE INDIVIDUAL BENEFIT

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
CESSATION IF NO EFFECT OVER 3 MONTHS OR EARLIER WITH CLINICALLY IMPORTANT ADVERSE EFFECTS EG INCREASE D DIURESIS

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life?

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

FEWER SKIN INFECTIONS BUT INCREASED URINE FLOW ISSUES

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

WITHIN THE KNOWN CAUTIONS

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

A MC GOVERN ET AL. ***BR J DIAB VASC DIS 2014 ; 14; 138-143***

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

EASY TO ADMINISTER SINGLE ORAL THERAPY

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Patient/carer expert statement (STA)

Dapagliflozin in combination therapy for treating type 2 diabetes (ID962)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: Diabetes UK
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☒ No

Do you wish to agree with your nominating organisation's statement?

☒ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☒ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?
-

☒ Yes ☐ No

Do you have experience of the treatment being appraised?

☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

- There are good days and not so good days. Some days I forget all about having diabetes and other days it is a really annoying. Having to make sure I eat within certain times can be difficult if people I am out with don't understand the difference between feeling a bit light-headed and needing something to eat and feeling hungry.

- Sometimes, it is difficult in getting some people to understand I have diabetes due to a high family history of diabetes and not because I ate too many sweet, sugary and inappropriate meals. I have never been overweight. I do not buy ready-made meals from the supermarkets.

- It is frustrating when I receive poor advice/mixed messages from those involved with my diabetes care but who don't have enough knowledge of diabetes or the newer medications.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

- Improved blood sugar control which reduces my risk of complications.

- Minimum side effects from medication.

- Not having to take insulin – I have a fear of injections.

- Feeling more confident and healthier when blood glucose levels are improved.

- Greater flexibility in my lifestyle means I am able to lead a normal life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

- I prefer taking tablets as I do not want to take insulin. Insulin would be very restrictive on my life and cause me a lot of worry and stress.

- Some of those involved in diabetes care have more knowledge than others about diabetes and the medications available. This makes it difficult to discuss or find out about newer medications which might be more suitable or appropriate.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

- Positive effect on my blood glucose levels.
- Less worry and stress of having high blood glucose readings.
- I can take this medication at a time convenient to me with or without food.
- If I don't have the tablet with me when I normally take the medication, I can take it when I get home.
- It is easy to take.
- Feel healthier and blood glucose levels will be improved.
- Better quality of life as I no longer worry about high blood glucose levels.
- I don't need blood pressure medication as Dapagliflozin has had a positive effect in lowering my blood pressure.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

- Positive effect on my blood glucose levels which has made me feel healthier and more confident.
- I have a positive outlook.

- No worry and stress of having high blood glucose readings.
- Since taking Dapagliflozin, my blood pressure has improved and I don't require blood pressure reducing medication.
- I can take this medication at a time convenient to me.
- Tablets are easy to swallow.
- Better quality of life.
- Other medications are quite restrictive eg insulin.
- No fear of having daily or multiple injections.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

- I have been told by a member of the diabetes support group that she experienced thrush.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Disadvantages – Thrush in some patients; need to use the toilet more often due to the increased requirement to drink more water.

Please list any concerns you have about current NHS treatments in England.

- Are patients given the correct drug as a priority or are the GP surgeries looking at costs first.

Please list any concerns you have about the treatment being appraised.

- Drug might be withdrawn due to costs.
- Other yet unknown health risks.
- Ensuring patients drink enough to avoid dehydration due to the way the drug works.
- GP surgeries not giving a person enough information about the treatment and how it works.
- Patients not complying with taking the medication as some people want immediate results.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Only thrush and needing to drink more water. I had no problems.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

- Some Type 2 patients who are overweight might find their weight is reduced.
- Reduced blood glucose levels and weight means that a person can lead a healthier life and perhaps start exercising.
- Reduced blood glucose levels will improve a person's overall health which will save the NHS a lot of money in the long term.
- Better diabetes control makes someone feel better in themselves and give them more confidence as sometimes, there does not seem to be a reason why glucose levels are high.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

- Those who have kidney problems or are unable to take the medication due to other health problems they might have.
- Those who don't like taking tablets.
- Some people don't like to try newer medications if they are happy on older medications.
- People taking numerous tablets might not want to add another tablet to the amount they already take.
- Those who are near the top or bottom of the age range for the medication.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Not to my knowledge

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

- Prevent or delay the need to take insulin.
- If, for example, the medication was forgotten in the morning it can be taken as soon as the person realizes, at any time of the day, without the need for food.
- It is easy to take and does not 'melt' in the mouth or leave an unpleasant taste in the mouth.
- No obvious side effects.

Is there anything else that you would like the Appraisal Committee to consider?

- This medication has had a positive impact on me by making me more confident as I know my blood glucose levels have improved.
- I feel healthier and am more active.
- I am happier knowing my diabetes is under better control.
- My family are less stressed knowing my blood glucose levels have improved.
-

10. Key messages

In no more than 5 bullet points, please summarise the key messages of

your submission.

- Improved blood glucose levels
- Lead a healthier lifestyle
- More confident
- No longer stressed about blood glucose levels
- Seem to have a more flexible lifestyle

ERG report: 18th July 2016

Dapagliflozin in triple therapy for type 2 diabetes: ERG report

NICE reference ID962

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1 SUMMARY

1.1 Scope of the AstraZeneca submission

The AstraZeneca submission addressed the clinical and cost-effectiveness of dapagliflozin, one of the sodium-glucose cotransporter 2 (SGLT2) inhibitors, in triple oral therapy in type 2 diabetes. The submission did not match all that was in the NICE scope, but justifications for omissions were presented. The main difference was that the AstraZeneca submission focused on triple therapy when dual therapy with metformin and sulfonylureas were insufficient, and did not examine in any detail, failure of dual therapy with metformin and a dipeptidyl peptidase-4 (DPP4) inhibitor. Another difference was that AstraZeneca did not regard insulin or glucagon-like peptide 1 (GLP-1) mimetics as comparators. The ERG agrees, but we note that the NICE guideline includes insulin and GLP-1 mimetics as options for triple therapy.

The NICE scope did not include adding third drugs when people were not getting adequate control on dual therapy with metformin and pioglitazone.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The AstraZeneca submission provided two main sources of evidence. Firstly, it provided a detailed account of the trial by Matthaei and colleagues which compared dapagliflozin and placebo, both in combination with metformin and sulfonylureas. Secondly, it presented results of a network meta-analysis (NMA), focusing mainly on a comparison with DPP-4 inhibitors, but also comparing dapagliflozin indirectly with canagliflozin and dapagliflozin.

The Matthaei trial showed that by 24 weeks, glycaemic control as reflected in glycated haemoglobin (HbA1c), the usual indicator of glycaemic control, had improved (reduced) by 0.69% from a baseline level of 8.08%, compared to placebo. Weight loss of 2.7kg occurred with dapagliflozin compared to 0.6kg on placebo. Systolic blood pressure (SBP) fell by 4.0 mmHg on dapagliflozin and by 0.3mmHg on placebo.

At 52 weeks, the reduction in HbA1c was sustained, with HbA1c difference of 0.7%. Weight loss was partially sustained with reduction compared to baseline of 1.9kg. However much of the reduction in SBP was lost. Cholesterol levels showed very little change.

Genital tract infections (GTIs) were more frequent in the dapagliflozin group, especially amongst women (14% by 52 weeks on dapagliflozin, 2% on placebo). Rates of urinary tract infections (UTIs) were similar. No serious hypoglycaemic episodes occurred.

The AstraZeneca submission reported the results of the NMA as showing;

- Compared to pooled DPP-4 inhibitors, dapagliflozin provided a slightly greater reduction in HbA1c (0.85% versus 0.79%); weight loss of 2.2kg compared to no significant change; and a reduction in SBP of 3.13mmHg compared to a rise of 1.85mmHg on DPP-4 inhibitors
- Few differences amongst three SGLT2 inhibitors considered by NICE (dapagliflozin, canagliflozin and empagliflozin - the flozins), with only canagliflozin 300mg showing slightly greater effect sizes.
- Probabilities of severe hypoglycaemia of 0.04 on the flozins, 0.034 on DPP4s, and 0.022 on intensive insulin therapy.

1.3 Summary of ERG critique of clinical effectiveness evidence submitted

The ERG has little to add to the AstraZeneca submission on the Matthaei trial. The ERG considered it to be a good quality trial showing that compared to placebo, dapagliflozin significantly improves glycaemic control and promotes modest but useful weight loss.

The ERG felt that data from other trials by Weber and colleagues, Leiter and colleagues, and Cefalu and colleagues, of dapagliflozin versus placebo, could have been used, by extracting the data on the subgroups of patients failing to achieve control on metformin and sulfonylureas and having triple therapy with those drugs and dapagliflozin.

The ERG does have concerns about the NMA results, because some of the main outputs do not seem compatible with the results of the Matthaei trial, which was the only dapagliflozin trial included. The ERG does not think it is credible that the risk of severe hypoglycaemia should be higher on dapagliflozin (probability 0.04) than on intensive insulin therapy (0.022). The ERG does not regard dapagliflozin as causing hypoglycaemia, which is only seen when dapagliflozin is used in combination with drugs that do cause hypoglycaemia, sulfonylureas and insulin.

The AstraZeneca NMA showed canagliflozin 300mg to have slightly greater effects. However in the trials, patients started on canagliflozin 300mg, whereas in routine care according to the licence, patients would start on canagliflozin 100mg and only progress to 300mg daily if the drug was well tolerated but effect was insufficient. Patients in whom 100mg is insufficiently effective may not achieve the same effect on 300mg as did the unselected patients in the trials.

The main flaw with the AstraZeneca submission is an attempt to ignore pioglitazone as a comparator, on the incorrect grounds that pioglitazone use is rare in the UK. Pioglitazone is effective in lowering HbA1c and reduces cardiovascular risk, with the exception that it can cause oedema and can precipitate heart failure. It can also cause macular oedema, weight gain and occasional fractures. However, pioglitazone is useful in non-alcoholic fatty liver disease, recognised to be an increasing

problem amongst people with type 2 diabetes, and which can progress to cirrhosis of the liver. It is also now available in inexpensive generic forms, though the price has fluctuated during 2016.

1.4 Summary of cost-effectiveness evidence submitted by AstraZeneca

The company uses the CARDIFF model run over a sample of 5,000 patients. The CARDIFF model is an individual patient simulation in C++ which attempts to largely replicate the UKPDS model of UKPDS 68 or the more recent UKPDS 82 depending upon user choice. The company base case applies the more dated UKPDS 68 equations. If the more recent UKPDS 82 event equations are applied, the risk factor evolution equations of the UKPDS 68 are retained as these have yet to be updated by the UKPDS. Triple therapy weight changes are assumed to last for only one year, after which weight is assumed to increase by 0.1kg per year.

The cost effectiveness of dapagliflozin is estimated against the following in pairwise comparisons.

- A pooled DPP-4i comparator, the effectiveness of which is mainly drawn from the NMA with the direct drug cost being weighted by market share
- Empagliflozin 10mg
- Empagliflozin 25mg
- Canagliflozin 100mg
- Canagliflozin 300mg

Patients start on these therapies and intensify to insulin when their HbA1c is modelled as breaching the 7.5% threshold. Patients are assumed to cease their relatively expensive oral therapies when intensifying to insulin. Patients move onto intensified insulin if their HbA1c subsequently breaches the 7.5% threshold

Patient baseline characteristics are taken from the pivotal trial. The triple therapies are associated with changes in HbA1c, SBP and weight based upon the company NMA. They are also associated with treatment specific:

- discontinuation rates
- non-severe hypoglycaemia events
- severe hypoglycaemia events
- UTIs
- GTIs

Intensifications to insulin are also associated with estimates for the above, though UTI and GTI rates are zero.

Quality of life values are drawn from a range of sources, with the baseline value for patients with no complications of 0.87 being derived from Health Survey for England data. This is further age adjusted as the patient ages.

- The disutilities for the main complications of diabetes are taken from the UKPDS 62.
- The disutilities associated with hypoglycaemic events are taken from the industry sponsored Currie et al (2007) paper that maps rates of hypoglycaemia events to the Hypoglycaemie Fear Index (HFS), and separately maps the HFS to EQ-5D values.
- The disutilities for UTIs and GTIs are taken from the same source as the company submission to the NICE MTA of SGLT2-is for monotherapy [TA390].
- The disutility associated with weight gain is taken from Bagust & Beale (2005) and has been used in numerous NICE assessments of treatments for diabetes.

The annual direct drug cost of £477 is the same for all the SGLT2-is. This is £53 or 12.5% higher than the £424 market share weighted cost of the DPP4-is that is applied in the modelling. The direct drug cost for those on insulin is estimated to be £181, and for those on intensified insulin £269. One off renal function monitoring costs of £49 are applied to dapagliflozin.

The average outpatient and inpatient costs for patients with no complications and patients with complications are drawn from the UKPDS 65 rather than the more recent UKPDS 84. UTIs and GTIs are assumed to require one GP visit at a cost of £45. Severe hypoglycaemia events are costed at £380 which is in line with the recent NICE clinical guideline.

For the comparison of dapagliflozin with the DPP4-is, event rates are slightly higher in the DPP-4i arm causing slightly more deaths from complications and a small survival gain for dapagliflozin. The greater HbA1c effect of dapagliflozin also causes patients to tend to remain on the expensive triple therapy for slightly longer which raises treatment costs, but this is more than offset by the reduced costs of complications and in particular the costs of nephropathy resulting in a net lifetime saving of £113. Given the weight loss associated with dapagliflozin compared to the slight weight gain associated with the DPP-4is, this further increases the QALY gains from dapagliflozin to 0.032 QALYs resulting in dapagliflozin dominating the DPP-4is.

Dapagliflozin is estimated to be broadly clinically equivalent to, and the same cost as, empagliflozin 10mg and empagliflozin 25mg.

Compared to canagliflozin 100mg, dapagliflozin has slightly poorer effects upon HbA1c and SBP. This causes slightly higher complication rates and so both higher costs and a slightly worse survival.

There is a smaller difference in net QALYs than in net life years, which is probably due to dapagliflozin's slightly superior weight profile. Canagliflozin 100mg is estimated to formally dominate dapagliflozin. But the additional net lifetime cost of £67 and the net -0.001 QALYs associated with dapagliflozin are very small.

Compared to canagliflozin 300mg, dapagliflozin also has slightly poorer effects upon HbA1c and SBP. However the better HbA1c profile of canagliflozin 300mg is sufficient to cause patients to remain on it for longer than dapagliflozin. The cost increases of the higher complication rates for dapagliflozin are more than offset by the reduced treatment costs and hypoglycaemia costs associated with the faster move onto insulin therapy. Dapagliflozin is estimated to save £193. There is also a very small 0.003 QALY gain from dapagliflozin despite canagliflozin 300mg providing a slight increase in life expectancy. As a consequence, dapagliflozin is estimated to dominate canagliflozin 300mg.

The company estimates that canagliflozin 100mg formally dominates the other treatments, but the differences in costs and QALYs are small.

Scenario analyses broadly maintain the results for the comparison of dapagliflozin with the DPP4-i. There is some sensitivity to whether patients are assumed to continue with their oral therapies when intensifying to insulin and to using the more recent UKPDS 82 to model events and deaths.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG cannot check the model implementation as it is in C++. It has been used for previous NICE assessments and the C++ was checked by the DSU during a previous dapagliflozin STA. The model interface is slightly cumbersome and lacks transparency. Having altered the Excel front end inputs there is no ready cross check of whether these are the values being used within the model. The model also takes a considerable time to run, which limits cross checking via this route. As a consequence, the ERG cannot cross check all the analyses of the company or all its own analyses.
The summary of the main points of the ERG critique of the cost effectiveness is presented in sections 1.6.1 and 1.6.2 below.

1.6 ERG commentary on robustness of evidence submitted by AstraZeneca

1.6.1 Strengths

The company presents a good range of NMA analyses within the clinical effectiveness section, though these are not fully explored within the economic section. But a good range of scenario analyses which

are not mechanistic applications of confidence intervals and explore the true sensitivity of results to key assumptions is presented.

The CARDIFF model has been presented in a number of other NICE assessments and is routinely part of the Mt. Hood challenge. It is largely based upon the UKPDS, which has often been the preference in NICE assessments due to it providing a single cohesive set of equations rather than being an amalgam of equations drawn from disparate sources.

Most cost and quality of life values are also from recognised sources, though the ERG tends to prefer the updated versions of these where they exist.

The submission is clear with few areas of ambiguity.

1.6.2 Weaknesses and areas of uncertainty

The previous MTA of the SGLT2-is for monotherapy concluded that patients tend to remain on their oral therapies when intensifying to insulin. Given the company involvement in the MTA it seems disappointing for the company base case in this STA to assume that patients discontinue their oral therapies when intensifying to insulin.

There are a number of inconsistencies between the stated model inputs and those that the company actually applied. While not large some of these appear to tend to reduce the patient downside and the costs of moving onto insulin. This may tend to benefit dapagliflozin compared to the DPP4-i due to its higher discontinuation rate, and compared to canagliflozin 300mg due to its lesser HbA1c effect. Both tend to cause those on dapagliflozin to intensify to insulin earlier that those on the DPP4-is and canagliflozin 300mg.

The company modelling relies upon the more dated event equations of the UKPDS 68 rather than the relatively recent UKPDS 82.

Similarly the company modelling relies upon the more dated costs of the UKPDS 65 rather than the relatively recent UKPDS 84. The company model also does not easily accommodate the structure of these costs, which provides costs for patients with none of the modelled complications and costs for patients with the complications. The modelling assumes these are additive which will exaggerate the cost impacts of the complications.

Despite being an individual patient model, there is no sampling of patient heterogeneity within the company base case and scenario analyses. This may tend to exaggerate some of the estimated

differences in treatment costs when the differences in HbA1c effect are relatively large such as in the comparison with canagliflozin 300mg. But it seems likely that it will also have tended to unreasonably equalise them when the differences in HbA1c are not quite as large as is the case with canagliflozin 100mg and perhaps also the DPP-4i.

Exploratory work by the ERG that samples patient heterogeneity results in peculiar and unintuitive results. This may be due to model convergence issues, or there may be deeper issues.

The model assumes that weight losses and gains associated with triple therapies only persist for one year and then rebound to natural history. This may be unduly pessimistic and may slightly bias the analysis against dapagliflozin in the comparison with the DPP4-is. If weight gains persist and there is a permanent upward shift in weight with no convergence to natural history, the bias for any comparison with pioglitazone may be larger.

At clarification the company has presented an NMA of discontinuation rates. The central estimates of these suggest somewhat higher overall discontinuation rates for dapagliflozin, but lower adverse event related discontinuation rates. But the confidence intervals around these are very wide and it may be questionable to differentiate treatments by discontinuation rates.

The costs of metformin and sulfonylurea are omitted from the model. The costs of self-monitoring of blood glucose and needles for those on insulin are also omitted from the company model.

Pioglitazone is not considered as a comparator despite being within the company NMA.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has made a number of revisions to the company model, which are itemised in section 5.4. The main changes are to:

- Assume that oral therapies are continued when intensifying to insulin.
- Apply the UKPDS 82 event equations.
- Apply the UKPDS 84 costs.
- Apply the costs of metformin and sulfonylurea.
- Apply the costs of self-monitoring of blood glucose and needle use for those on insulin.
- Apply the costs and quality of life impacts of hypoglycaemia for those on insulin.

The ERG revisions suggest that dapagliflozin results in additional costs of £615 compared to the DPP4-is, due largely to an increase in treatment costs. Patient benefits are muted at 0.017 QALYs resulting in a cost effectiveness estimate of £37,997 per QALY.

If dapagliflozin and the DPP-4is are discontinued when patients intensify to insulin the additional annual cost from dapagliflozin is experienced for a much shorter period. Net costs fall to £143 and the cost effectiveness improves to £8,351 per QALY. These results are similar to SA10 of the company scenario analysis, though the net treatment costs are higher possibly due to the ERG addition of the costs of consumables to insulin.

The UKPDS 68 event equations suggest more events are avoided with dapagliflozin than the UKPDS 82 event equations. This provides larger cost offsets and the net cost falls to £495 compared to the DPP4-is while the patient gains increase to 0.020 QALYs, improving the cost effectiveness estimate to £25,329 per QALY.

The company NMA results worsen the effectiveness estimates for dapagliflozin compared to the DPP-4is to around £60k per QALY though this rests upon very small QALY differences. More robust may be that the net costs increase to around £725.

The ERG revisions and scenario analyses suggest virtual equivalence between dapagliflozin and empagliflozin.

The ERG revisions suggest cost savings of around £124 from dapagliflozin compared to canagliflozin 100mg, though these are in part a function of assumptions around differing rates of severe hypoglycaemia. In general there are relatively limited differences in costs, with patient effects ranging between a gain of 0.022 QALYs and a loss of 0.009 QALYs. The ERG clinical assumptions suggest

the dapagliflozin formally dominates canagliflozin 100mg, while the company NMA results in the context of the other ERG revisions suggest that canagliflozin 100mg formally dominates dapagliflozin. But in the context of a lifetime of diabetes the differences in costs and QALYs are minor.

The ERG revisions cause dapagliflozin to be more expensive than canagliflozin 300mg by £110 for the base case. Gains of 0.009 QALYs are small (about 3 days), but suggest a cost effectiveness of £12,875 per QALY. The cost increase is due to the ERG assuming the oral therapies are retained when intensifying to insulin. If they are not dapagliflozin is cost saving and dominated canagliflozin 300mg. The QALY gains fall to only 0.001 QALYs if triple therapy hypoglycaemia does not apply. The company NMA results in the context of the other ERG revisions suggest that canagliflozin 300mg formally dominates dapagliflozin.

The company did not consider pioglitazone as a comparator within the economics despite it being within the company NMA. The clinical effectiveness estimates suggest very small patient gains will occur from pioglitazone, though these are in the context of weight gains and losses being assumed to persist for only one year. More concretely, dapagliflozin has considerably higher treatment costs. Net cost estimates are £4,834 for the base case, £2,341 if annual pioglitazone annual drug costs are £225 and £1,154 if patients discontinue their oral therapies when intensifying to insulin.

1.8 Summary of additional work undertaken by ERG

The ERG extracted data on;

- Sulfonylureas used in the various trials, because different sulfonylureas have different effects, with gliclazide being our sulfonylurea of choice, and also the most used in the UK. In the trials used in the NMA, glimepiride was the commonest sulfonylurea, with only two trials having significant minorities on gliclazide, Matthaei 2014 (42% on gliclazide) and Round 2013/Moses 2016 (40%)
- Reduction in HbA1c on placebo and active drugs in the restricted NMAs, to look for variation in HbA1c changes on placebo. In the appraisal of the flozins in monotherapy, much of the apparent difference in HbA1c lowering between canagliflozin and dapagliflozin occurred because in the dapagliflozin trials, HbA1c fell in the placebo group whereas in the canagliflozin trials, HbA1c rose on placebo. In the triple therapy trials, mean HbA1c decreased in the placebo arm of 8 trials (range -0.01% % - 0.47%) and increased in 3 trials (range 0.28% to 0.33%), with no change in 1 trial. So heterogeneity occurred in the trials, with the effect of placebo on HbA1c ranging from a fall of 0.47% to a rise of 0.33%.

- Lipid changes in the NMA trials, to explore whether the NMA could have produced comparative data on lipid changes. We concluded that there was sufficient data from some trials to use in the NMA but the omission of lipid changes is probably unimportant because the flozins cause little change in lipid levels.
- Whether the trials reported proportions on statins. Only one relevant trial did.
- Quality of trials to check on the AstraZeneca assessment. The ERG quality assessments agreed with most of the company assessments, although there were some differences as noted in the comments in Appendix 3

The ERG also extracted data from the NMA trials to replicate the AstraZeneca inputs for the modelling reported in AstraZeneca Table 38, considered alternative values for some variables, and re-ran the model with the alternative values.

1.9 Conclusions

The clinical effectiveness of dapagliflozin in triple therapy is not in doubt. The AstraZeneca submission argues that it is similar in efficacy and adverse effects to the two flozins already recommended by NICE for triple therapy, canagliflozin and empagliflozin, and the ERG broadly agrees with this. There are two adverse effect alerts currently issued for canagliflozin but not for dapagliflozin, amputations and fractures. There has been a warning about acute kidney injury with canagliflozin and dapagliflozin but not with empagliflozin.

Compared to the DPP-4 inhibitors, the main advantage of dapagliflozin is weight loss. The DPP-4 inhibitors do not cause weight gain or weight loss.

In cost-effectiveness, the ERG regards dapagliflozin and empagliflozin as equivalent. When compared to canagliflozin, there can be very small differences in costs and QALYs which can lead to fluctuating ICERs. When compared to pioglitazone, there are small differences in effectiveness but considerable differences in costs, but the AstraZeneca modelling pessimistically assumes that weight loss with dapagliflozin may be lost after one year.

2 BACKGROUND

Dapagliflozin has already been appraised and recommended by NICE for use in monotherapy, dual therapy and in insulin-containing regimens. Members of the Appraisal Committee will be familiar with its mechanism of action and adverse effects, but in brief;

- Dapagliflozin inhibits conservation of glucose in the kidney by the SGTL2 transport system. Glucose is lost in the urine leading to lowering of blood glucose levels
- The loss of glucose and the associated calories leads to weight loss
- The presence of glucose in the urine leads to an increase in urinary and genital tract infections, mainly in women, but these are usually mild and easily treated
- Dapagliflozin has a diuretic effect which leads to a modest reduction in blood pressure, and which may explain the reduction in heart failure admissions seen in people on the drug
- Hypoglycaemia is not a problem with dapagliflozin monotherapy, and is only seen in combination therapy when dapagliflozin is used with other drugs that cause hypoglycaemia such as insulin or sulfonylureas

The SGLT2 inhibitors (the flozins) have a number of attractions for use in type 2 diabetes, because people with the disease tend to have other metabolic issues such as hypertension and hyperlipidaemia. Treating these has more effect on cardiovascular risk than reducing blood glucose.[1, 2] The flozins have modest but useful effects on blood pressure and weight. They reduce triglyceride levels (probably by the weight loss) and increase high density lipoprotein (HDL) cholesterol. Low density lipoprotein (LDL) cholesterol is also raised but the LDL/HDL ratio is unchanged.

The indications for the flozins vary. Canagliflozin and empagliflozin can be used with pioglitazone but dapagliflozin cannot. Canagliflozin can be used in the elderly but dapagliflozin is not recommended in the over 75s, and empagliflozin is not recommended in the over 85s, both because of lack of evidence.

2.1 Decision problem

NICE identified comparators as follow;

- Other SGLT2 inhibitors (the flozins)
- DPP4 inhibitors (the gliptins)
- Pioglitazone
- GLP-1 mimetics
- Insulin
- Sulphonylureas

2.1.1 Critique of AstraZeneca approach to decision problem

Population

The final scope from NICE describes the population as adults with type 2 diabetes that is inadequately controlled with dual therapy with either;

- Metformin with a sulfonylurea
- Metformin with a DPP4 inhibitor

AstraZeneca have focused on triple therapy based on the first of these dual combinations, on the grounds that there is much less evidence on third drugs added to metformin and a DPP4 inhibitor, and that an NMA would not be possible. However data on two trials in which dapagliflozin was added to metformin and sitagliptin (Jabbour Diabetes Care 2014/37/740-750) or to metformin and saxagliptin (Mathieu Diabetes care 2015/38/2009-2017) were described in an appendix. It is worth noting that triple therapy with both a flozin and a gliptin would cost over £900 a year, which takes the cost into the same range as long-acting, once-a-week, GLP-1 mimetics.

Intervention

The AstraZeneca submission matches the scope.

Comparators

Astra Zeneca did not regard insulin or GLP-1 mimetics as comparators. The ERG agrees, on the grounds that oral options should be tried first, before injectables, and taking into account the much higher cost of the GLP-1 mimetics. It could be argued that the newer once-a-week injectables are more acceptable.

The NICE guideline on type 2 diabetes states that at second intensification to triple therapy, options to be considered in combination with metformin are two of sulfonylureas, pioglitazone, gliptins and the flozins inhibitors.[3]

The other two licensed flozins have been approved by NICE for triple therapy. Dapagliflozin was not approved when it was appraised for combination therapy because there was no RCT evidence at the time.

Pioglitazone

The main problem with the AstraZeneca approach is that they did not consider pioglitazone to be a comparator on the grounds (page 13) that “pioglitazone is rarely used in the UK”. This is not correct.

Prescription Cost Analysis data for England[4] show that there were over 1 million prescriptions of pioglitazone in 2015, as shown in Table 1.

Table 1 Prescriptions for selected diabetes drugs, England, 2015

	Items (1000s)
Sitagliptin	2322
Pioglitazone	1062
Linagliptin	882
Dapagliflozin	489
Saxagliptin	355
Canagliflozin	133
Alogliptin	94
Vildagliptin	90
Empagliflozin	24

So to say its use is rare, is incorrect, and the ERG view is that it should be considered as a comparator.

However, the use of pioglitazone has declined, probably because of concerns about adverse effects, which include;

- Bladder cancer
- Fractures
- Oedema which can lead to heart failure and macular oedema

We consider each of these in turn. We also consider benefits of pioglitazone other than glycaemic control, including cardiovascular risk reduction and the effect on non-alcoholic fatty liver disease (NAFLD).

Bladder cancer

In 2012, a French study reported a doubling of a very small risk of bladder cancer.[5] In France, pioglitazone use was suspended in 2011.[6]

The European Medicines Agency (EMA) concluded that pioglitazone was associated with an increase in the small risk of bladder cancer, from 7 in 10,000 in people with diabetes not treated with pioglitazone to 15 per 10000. The EMA issued a statement in 2011 saying that there was a small increased risk of bladder cancer but that on balance pioglitazone could still be used as a second and third line treatment.[7] The MHRA concurred. (Medicines and Healthcare products Regulatory Agency.[8]

However the evidence is inconsistent. Azoulay and colleagues[9] using UK data from 1988 to 2009 from the General Practice Research Database (GPRD), reported an increased risk of 1.83 (95% CI 1.10-3.05), and a second paper from the same group[10], also using the GPRD, now renamed as the Clinical Practice Research Datalink, but for 2000 to 2013, reported a hazard ratio (HR) of 1.63 (95% CI 1.22-2.19). It has been argued by Gallagher and Winocour, and Ryder that there may be higher use of pioglitazone in patients at higher risk of bladder cancer because of obesity and poor control.[11]

Another study that used the GPRD data from 2001 to 2010, with propensity matching in a cohort of over 200,000 patients, found no significant increase in bladder cancer.[12]

The Kaiser Permanente study from the USA of a cohort of 193,099 people aged 40 or over reported an increase in risk with pioglitazone with relative risk (RR) of 1.18 but this was not statistically significant.[13] The PrOactive trial reported a RR of 2.83 ($p = 0.04$) but once cases of bladder cancer diagnosed in the first year were excluded there was no difference.[14] Some of the bladder cancers in the PROactive trial were diagnosed within weeks of starting pioglitazone. It was argued that cancers diagnosed with a year of starting the drug must have been there before. However Gale has argued that pioglitazone could be acting as a growth promoter in latent tumours.[15]

Another very large study by Levin and colleagues mainly in the UK, Finland and British Columbia (one million people with type 2 diabetes, almost 6 million person years of observation) found no increased risk of bladder cancer, providing further reassurance.[16]

In the Insulin Resistance after Stroke (IRIS) trial in 3876 patients, of pioglitazone in secondary prevention after stroke or TIA, 94% of whom were not diabetic but all of whom were insulin-resistant, there were slightly more bladder cancers in the pioglitazone group (12) than the placebo group (8) but this difference was not significant. The main outcome of the trial was myocardial infarction or stroke, which occurred in 9% of the pioglitazone group and 11.8% of the controls.[17]

It should be noted that diabetes itself has been reported in a very large meta-analysis to increase the risk of bladder cancer with RR 1.35 (95% CI 1.17-1.56), though this applied only to those within 5 years of diagnosis. Amongst those with duration over 5 years, relative risk was 1.08.[18]

In summary, recent evidence on pioglitazone and bladder cancer has been largely reassuring.

Fractures

There is an increased risk of fractures amongst people taking pioglitazone. The fractures were originally reported as being atypical fractures of long bones[19], possibly because of the relatively young age of people in trials, but Scottish data also show an increase in hip fractures.[20] This might suggest

that pioglitazone should not be used in people at increased risk of fracture, such as older people with osteoporosis.

Oedema

Pioglitazone can cause oedema, which can precipitate congestive heart failure, which is a common cause of admission to hospital, and the second commonest first presentation of cardiovascular disease (after peripheral arterial disease).[21] There is clearly an increased risk of heart failure.[14, 22] Regular monitoring with BNP might be useful for the safest use of this drug [23] but this is not done routinely due to cost and availability. Patients are advised of possible side-effects and advised to stop if oedema or shortness of breath develops. If there are concerns regarding heart failure, echocardiography is often carried out, to check that left ventricular function is satisfactory, before starting pioglitazone. A five-fold risk of macular oedema has also been reported.[24]

Cardiovascular effects

There are some cardiovascular benefits from pioglitazone (the reverse of what was seen with rosiglitazone) with a reduced risk of myocardial infarction.[14]

NAFLD

Many people with type 2 diabetes are considerably overweight and may develop non-alcoholic fatty liver disease (NAFLD). An Edinburgh study by Williamson and colleagues[25] found that in 939 randomly selected people with type 2 diabetes, 43% had hepatic steatosis, with no other known cause. A recent editorial from the USA reported that NAFLD is now the commonest cause of chronic liver disease in the USA and other industrialised countries.[26] Cusi and colleagues from the USA report that NAFLD is frequently undiagnosed, and that most obese patients with type 2 diabetes have NAFLD on imaging. Many have normal liver enzymes (aminotransferases).[27]

Pioglitazone has been reported to improve NAFLD[28] so if attempts at weight loss are unsuccessful, pioglitazone may be useful. NAFLD is a spectrum of disease ranging from an increased fat content in the liver (steatosis) to inflammation (non-alcoholic steatohepatitis) and possibly on to cirrhosis. Simple steatosis may not progress to more serious liver damage, but progression to fibrosis and cirrhosis is more likely in people with type 2 diabetes.[26, 29] In type 2 diabetes, NAFLD is associated with a higher risk of cardiovascular disease.[30]

Cusi and colleagues carried out a 18-month RCT of pioglitazone in patients with non-alcoholic steatohepatitis (NASH) and type 2 diabetes or pre-diabetes, followed by an 18-month open label extension.[27] The primary outcome was a reduction of 2 or more points in the NAFLD activity score

based on histology of liver biopsies. This was achieved by 58% of the pioglitazone group and by 17% of the placebo group. There was less fibrosis progression in the pioglitazone group.

Hence pioglitazone may actually have an increasing role in type 2 diabetes in order to counter the NAFLD epidemic. The NICE guideline on NAFLD summarised the evidence as shown in Box 1.[31]

Box 1: Extract from NICE guideline on NAFLD.

Pioglitazone:

The GDG noted that in the largest double-blind RCT identified (comparing pioglitazone [30 mg/day] to placebo as treatment to slow the histological progression of NASH in adults when used over 96 weeks), participants randomised to taking pioglitazone achieved greater reduction in hepatocellular ballooning, steatosis, lobular inflammation, and total NAS score (as well as significantly higher rates of resolution of NASH) compared to participants taking placebo; all of which the GDG considered to be of relevant clinical benefit. The GDG also noted that no participants within this study had diabetes but felt that there was no strong reason for suspecting that these results should be any different for adults with NASH and diabetes.

The other evidence for pioglitazone in adults with NASH that was considered by the GDG also demonstrated histological improvement in many clinically relevant domains; however, the evidence was more consistent for pioglitazone causing a reduction in steatosis and inflammation and stabilisation of fibrosis, rather than any definite improvement in fibrosis. There was also evidence of an improvement in liver enzymes related to the use of pioglitazone. The GDG noted that participants in one study all had impaired glucose tolerance or type 2 diabetes mellitus.

Collectively, the GDG felt that there was sufficient evidence to conclude that pioglitazone does have evidence for clinical effectiveness in slowing or reversing progression in adults with NASH, regardless of whether they are diabetic or not. However, the GDG also noted the recent concerns that had arisen about the safety of pioglitazone, along with other members of the glitazone family. The GDG also discussed the evidence for glitazones causing fluid retention and therefore potentially precipitating cardiac failure; this is clearly particularly a limitation for a condition such as NAFLD, where cardiovascular events are the major cause of morbidity and mortality. Concerns have also been raised about an elevated fracture risk in women and a possible increased rate of bladder cancer in relation to the use of the medication.

The GDG concluded that there is a potential role for pioglitazone in treating adults with NASH.

The cost of pioglitazone is much lower than those of the newer drugs, though the costs of adverse effects need to be considered. However the costs of pioglitazone have risen 10-fold over the last year. In March 2016, the price of a 28-tablet pack of pioglitazone 30mg tablets was £1.31. In April 2016,

the price was £10.99. For a pack of 45mg pioglitazone, the cost rose from £1.47 in March to £33.81 in April.

The most recent prices (July 14th), from eMIMs and the drug tariff both currently suggest

- 15mg, 28=£13.31
- 30mg, 28=£14.81
- 45mg, 28=£17.29

Figure 1 provides a comparison of costs in June 2016.

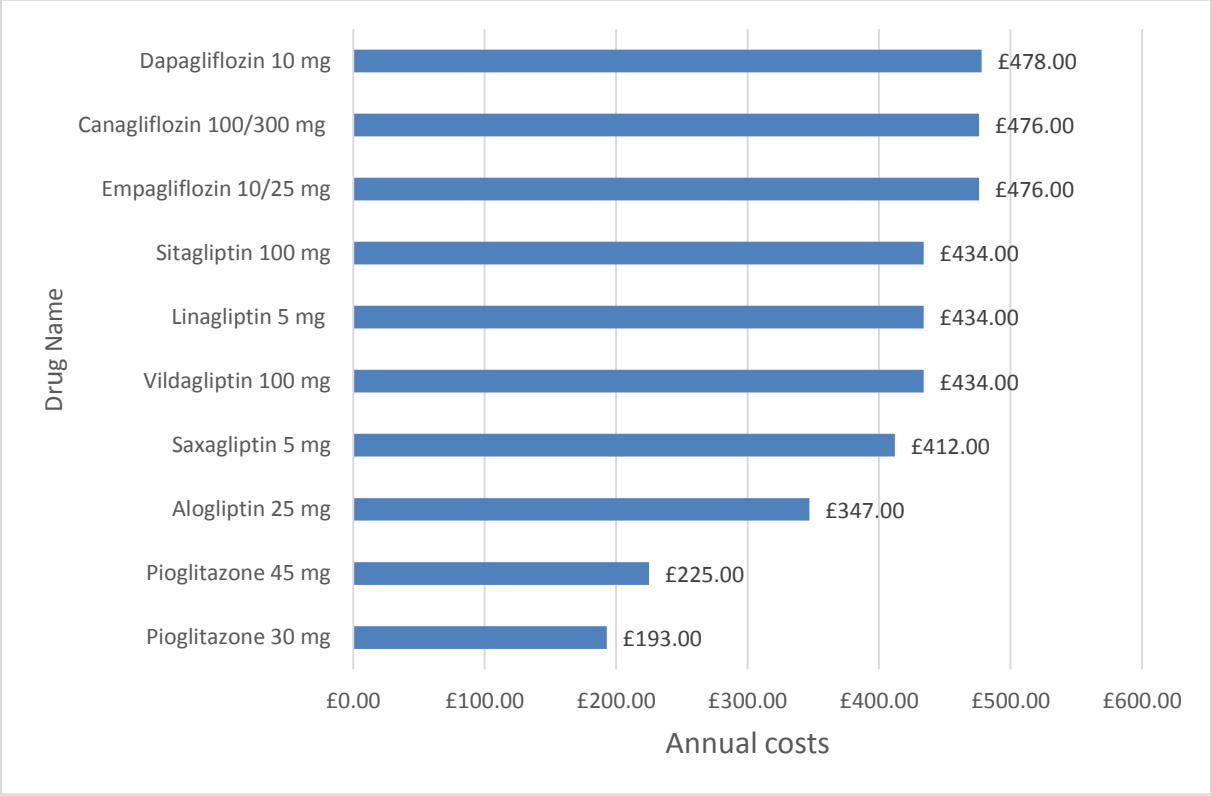


Figure 1 Comparison of drug costs in June 2016

The flozins and NAFLD

There is some evidence on the effect of the flozins on liver function. For canagliflozin, Leiter and colleagues[32] reported data from four pooled trials of both the 100mg and 300mg doses. They found improvements in liver function tests but these were fully explained by weight loss. Conversely, Yadagiri and colleagues from the ABCD Dapagliflozin Audit group reported, so far only in a conference abstract, that improvements in the liver enzyme ALT seen after dapagliflozin treatment did not correlate with weight loss.[33]

Outcomes

The outcomes in the final scope from NICE include glycaemic control, which is measured using HbA1c. The results can be expressed either as placebo-adjusted reduction (improvement) or as proportions achieving the target level of HbA1c. It is generally accepted that HbA1c must be reduced by at least 0.5% to be clinically significant. However if baseline HbA1c is high, then even reductions in HbA1c of 1% may not be sufficient to achieve target, in which case the NICE type 2 guideline recommends further intensification of treatment.

A key issue here is what assumptions should be made about clinical practice in England. If the NICE guideline is followed, than patients will be closely monitored with regular HbA1c testing, and treatment intensified once HbA1c rises above 7.5%. Generally speaking, reductions in HbA1c after intensification are correlated with baseline HbA1c, so we would expect a smaller reduction from intensifying treatment at HbA1c of, say, 7.7%, than from intensifying at, say, 8.2% (the baseline in the Matthaei trial of dapagliflozin in triple therapy).[34]

The AstraZeneca submission provides results for the proportions achieving target for the Matthaei trial (Matthaei 2015a and 2015b)[34, 35] of adding dapagliflozin to metformin and sulfonylureas, but not for the two trials (Jabbour[36] and Mathieu[37]) of adding dapagliflozin to metformin and a DPP4 inhibitor. The ERG requested such data but AstraZeneca declined to provide it, on the grounds that;

"we would like to clarify that the key trial of the submission is the Matthaei 2015 trial (dapagliflozin on a background of MET + SU) for which the information requested is already published.

The data is requested for the triple therapy groups (stratum B) in the Jabbour and Mathieu trials of adding dapagliflozin to metformin and a gliptin. However, at this time we do not feel it is relevant to provide this information as these trials are not key to the appraisal as they assess dapagliflozin on a background of MET + DPP4-i; which is not a focus of the submission."

The publications from the Matthaei trial[34, 35] do not give proportions achieving target by bands of baseline HbA1c.

Other outcomes in the NICE scope were;

- Mortality and complications of diabetes. Data on these are not available in the short-term trial presented in the submission, but this is common to nearly all new diabetes interventions, and the AstraZeneca submission addresses the data gap by modelling based on glycaemic control and other variables. The submission also provides the results of a meta-analysis of 21 trials with over 9,000 patients which showed a decrease in a primary composite outcome of cardiovascular events which did not quite reach statistical significance – HR 0.787 (CI 0.579 to 1.070). However hospital admissions for heart failure were greatly reduced – HR 0.361 (CI 0.156 to 0.838).
- Body mass index (BMI). The submission presents data on weight changes in kilogrammes rather than BMI, because that is how most trials report weight.
- Frequency and severity of hypoglycaemia – data presented
- Changes in cardiovascular risk factors. Data are presented on blood pressure but not on lipid effects. Total cholesterol, LDC and HDL changes, and the LDL/HDL ratio were reported in the trial. Details are given later in this report.
- Adverse effects – data provided
- Health related quality of life – data were reported in brief.

3 CLINICAL EFFECTIVENESS

3.1 The Matthaei 2015 trial [34, 35]

The AstraZeneca submission present data from the trial by Matthaei and colleagues, referred to as Study 5. This randomised 219 patients in 45 centres, an average of 4.5 patients per centre.

3.1.1 Quality assessment

Details of risk of bias assessment are shown in Appendix 1. The trial by Matthaei and colleagues [34, 35] had a low risk of bias, fulfilling 8 of the 9 quality criteria. Trial used adequate randomisation procedures, allocation concealment and adequate blinding of patients, personnel and outcome assessors. There was an imbalance in baseline characteristics with a higher proportion of women in the dapagliflozin group. Withdrawals and losses to follow-up were described with a low non-completion rate of 7% at 24 weeks. The trial used intention-to-treat analysis, including all patients having received at least one dose of drug and with at least one baseline and post-baseline measurement. However, Matthaei 2015 used this only for the outcomes measured at 24 weeks but not for the outcomes measured after the extension at 52 weeks. The trial reported all outcomes as specified on clinicaltrials.gov. No power analysis was reported. No other potential sources of bias were identified.

Details of study characteristics of the trial by Matthaei and colleagues (2015) are shown in Table 2. The authors compared participants with type 2 diabetes on a background medication of metformin (≥1500 mg/day) and sulphonylurea (maximum tolerated dose) who received either 10 mg dapagliflozin once daily or a matched placebo. The trial was a commercially sponsored double-blind parallel randomised controlled trial carried out in five countries in Europe and in Canada. The main study duration was 24 weeks and the trial had a 28 week double-blind extension, with final outcomes assessed at 52 weeks.

3.1.2 Baseline characteristics

The mean age of patients was 61 years. There were more women in the dapagliflozin group than in the placebo group (57% versus 44%). Most participants where white (94 to 96%) and most had a history of cardiovascular disease (84 to 88%). Diabetes duration was between 9.3 and 9.6 years. Baseline HbA1c was between 8.1 and 8.2% and baseline BMI was 32 kg/m^2. The majority of patients were on antihypertensives and angiotensin receptor blockers and/or ACE. For details see Table 2.

3.1.3 Results

Results are shown in Table 3. After 24 weeks of intervention, HbA1c with dapagliflozin was reduced by 0.69% more than with placebo ($p<0.0001$) and the proportion of participants achieving HbA1c <7.0% was 32% with dapagliflozin versus 11% on placebo ($p<0.0001$).

The reduction in HbA1c varied by baseline level;

- Baseline HbA1c <8%, lowering 0.44% at 24 weeks (placebo adjusted)
- Baseline 8 to <9%, lowering 0.84%

Weight was reduced by 2.1 kg more with dapagliflozin than with placebo ($p<0.0001$) and systolic blood pressure was reduced by 3.8 mmHg more with dapagliflozin than with placebo ($p=0.025$). Increases in total cholesterol, LDL cholesterol and HDL cholesterol were seen compared to placebo, but there were no significant changes in the LDL/HDL ratio and in triglyceride levels.

Significantly more patients on dapagliflozin experienced hypoglycaemia than patients on placebo ($p=0.024$, none major). More genital tract infections were seen with dapagliflozin than with placebo (mainly in women, $p=0.0029$). There were no notable differences in urinary tract infections.

For the 52 week results, significance values were not provided. After 52 weeks of intervention, the effect of dapagliflozin on HbA1c was sustained (difference between groups -0.70%) and more participants on dapagliflozin reached HbA1c <7.0%. Again, patients with a higher baseline HbA1c value had a greater reduction in HbA1c (1.17%) than participants with a lower baseline HbA1c (0.48%); there was no effect of baseline BMI on HbA1c reduction. Similarly, the weight reduction with dapagliflozin compared to placebo was sustained. After the first 24 weeks of intervention, systolic blood pressure increased again in both groups, with the changes being similar regardless of the class of concomitant antihypertensive medication. The difference between the two groups in lipid levels became smaller after 52 weeks of intervention. Episodes of hypoglycaemia were experienced by 15.6% of patients on dapagliflozin and 8.3% of patients on placebo but there were no severe episodes. Hypoglycaemia occurred more frequently in patients receiving the sulphonylurea glyburide than in patients receiving gliclazide or glibenclamide. Genital tract infections (mainly in women) at 52 weeks were again more frequent with dapagliflozin (14%) than with placebo (2%), while there was no notable difference in urinary tract infections.

3.2 Comments on AstraZeneca submission

- The submission (Table 2, page 17) shows tiny QALY differences amongst the flozins. A QALY difference of 0.001 means about 8 hours. We should regard this table as showing no differences amongst the flozins.

- Page 19 of the submission states that dapagliflozin has "a low propensity to cause hypoglycaemia". AstraZeneca is being cautious or conservative here, and it could be argued that dapagliflozin does not cause hypoglycaemia. It is only seen when dapagliflozin is combined with other drugs that cause hypoglycaemia.
- Page 45, last observation carried forwards (LOCF) may be unsound. People are not missing measurements at random.
- Discontinuations (page 48, figure 4) in trials include trial-specific reasons which would not occur in routine care, so we should base discontinuation more on adverse events.
- Page 49 reports that "patient characteristics were similar in both arms" but there were more women in the dapagliflozin group as shown in Table 2. This is unlikely to matter because in a pooled analysis of 10 dapagliflozin studies (none on triple therapy), the effects of dapagliflozin on HbA1c, body weight and SBP did not vary by gender.[38]
- Page 50 "Per protocol population was used for efficacy analysis and ITT population was used for safety analysis". According to the published reports, efficacy analysis was carried out for all patients with at least one baseline and one post-baseline value and safety analysis for all randomised patients at 24 weeks while a per protocol analysis was done for the efficacy data at 52 weeks.
- Page 50 "Patients included in the study are thought to reflect patients in the UK clinical practices." The study did not include any patients from the UK and only two Western European countries (Germany and Spain) recruited patients.
- Page 54 reports that only 32% reached target HbA1c of < 7.0%. It would have been useful to know how many reached <7.5%, the NICE intensification threshold.
- Table 15 on page 55 reports that the SBP reduction on dapagliflozin at 24 weeks was mostly lost by 52 weeks. The submission argues that this finding was at odds with other evidence from the dapagliflozin development programme. However the ERG does not find the proposed explanation on page 57 convincing. The two studies quoted in support of the explanation were only for 12 weeks, so don't provide support. One study long enough to have provided support is the extension to 52 weeks of the trial by Mathieu and colleagues[39]of triple therapy with dapagliflozin added to metformin plus saxagliptin, but this trial did not report blood pressure at 52 weeks. A pooled analysis by Fioretto et al[40] of nine dapagliflozin trials (none in triple oral therapy) reported differences in SBP at 102 weeks of 1.43mmHg in patients under 65, and of 6.4 mm Hg in those 65 and over. The older group had slightly higher baseline BP.
- Page 55.The industry submission reports results for health-related quality of life measures, but these are not reported either in the published papers or on clinicaltrials.gov, so cannot be checked. There were no significant differences between the groups or over time.

- Table 28 on page 87. The 52 weeks SBP data don't match the trial results, which is strange since only one trial of dapagliflozin was included. The difference compared to DPP4-is is larger than expected and may be driven mainly by the Schernthaner trial[41] which used canagliflozin 300mg.
- Page 92 and page 121 states that there is evidence that the gliptins are non-inferior to each other, but the reference cited on page 121 only included sitagliptin and vildagliptin. However a systematic review and network meta-analysis by Craddy and colleagues[42] found no differences in efficacy amongst the gliptins.
- Pages 94-95. The large reduction in HbA1c in triple therapy in routine care was from a high baseline of 9.36% and even a drop of 1.18% would not reach anywhere near target.
- Table 34, page 110. The Shyangdan report is not relevant to this review. It was the ERG report on liraglutide.[28] The details in the reference list are incorrect.
- Page 131, para 2. The ERG agrees that the weight loss assumption is conservative because it would be reasonable to assume that weight loss lasted longer than one year. In the pooled analysis by Fioretto and colleagues[40] weight differences of 2.5kg and 1.9 kg (<65 years and 65 and over respectively) persisted to 104 weeks
- On page 147, the effect of renal function on the effectiveness of dapagliflozin is mentioned. This is also reported in a recent abstract from the American Diabetes Association meeting. Heerspink and colleagues (mainly from AstraZeneca)[43] reported placebo adjusted HbA1c lowering of 0.57% in patients with eGFR 90ml/min or over, 0.47% in those with eGFR 60 to 89 ml/minute, and 0.27% in those with GFR of 45 to 59. These results come from 11 pooled trials, not just in triple therapy.

Table 2 Study characteristics

Matthaei 2015[34] **Setting:** 45 centres in 6 countries (Canada, Czech Republic, Germany, Poland, Slovakia, Spain) **Design:** RCT, double blind, parallel group, 1:1 **Duration:** 52 weeks**,** primary endpoint at 24 weeks **Sponsor:** Bristol Myers-Squibb and Astra Zeneca, manufacturers of dapagliflozin	**N:** 218 (101 completers at 24 weeks and 95 at 52 weeks with dapagliflozin; 101 completers at 24 weeks and 95 at 52 weeks with placebo) **Inclusion criteria:** age >18 years; type 2 diabetes mellitus, stable dose combination therapy of metformin ≥1500 mg/day and a maximum tolerated dose (at least half the maximum dose according to local use) of sulphonylurea for at least 8 weeks prior to enrolment; inadequate glycaemic control (HbA1c ≥7.0% to ≤10.5% at randomisation); systolic blood pressure <160 mmHg and diastolic blood pressure <100 mmHg at the end of placebo run-in; not of child-bearing potential or using highly effective method of contraception **Exclusion criteria:** BMI ≥45 kg/m^2 ; measured serum creatinine value of ≥1.5 mg/dL for men or ≥1.4 mg/dL for women, unstable or rapidly progressing renal disease, cardiovascular events within 2 months prior to enrolment, congestive heart failure (New York Heart Association Class IV), systolic blood pressure ≥160 mmHg, or diastolic blood pressure ≥100 mmHg at randomisation **Age (years):** *Dapa:* 61.1 SD9.7; *Pla:* 60.9 SD9.2 **Sex (%women):** *Dapa:* 57.4%; *Pla:* 44.4% **Ethnicity:** *Dapa:* 96.3% White; *Pl:* 94.4% White **Diabetes duration (years):** *Dapa:* 9.3 SD6.5; *Pla:* 9.6 SD6.2 **HbA1c (%):***Dapa:* 8.08 SD0.91 %; *Pla:* 8.24 SD0.87 % **BMI (kg/m^2):** *Dapa:* 31.9 SD4.8; *Pla:* 32.0 SD4.6 **Comorbidities:** *Dapa:* 84.3% prior history of cardiovascular disease; *Pla:* 88.0% prior history of cardiovascular disease **Baseline co-medication:** *Dapagliflozin:* 81.7% antihypertensives, mostly thiazide diuretics 27.5% and angiotensin receptor blocker and/or	**<u>Intervention</u>** **Dapa (n=108):** dapagliflozin 10 mg once daily **Pla (n=108):** matched placebo once daily **Run-in:** 3 week screening period; 8 week placebo run-in (with adjustment of concomitant antihypertensive medication as required) **All groups:** metformin and sulphonylurea treatment as before randomisation; sulphonylurea could be down-titrated only once during the treatment period to mitigate the risk of recurrent hypoglycaemic events at the discretion of the investigator; open-label rescue therapy was administered with the patients' study medication if FPG ≥13.32 mmol/L between weeks 4 and 16 ≥11.10 mmol/L between weeks 16 and 24 **Extension:** 28 week double-blind extension **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** fasting plasma glucose, proportion reaching HbA1c <7.0%, body weight, systolic blood pressure **Other outcomes:** total, LDL- and HDL-cholesterol, triglycerides, need for rescue therapy, hypoglycaemia, adverse events, serious adverse events, genital infections, urinary tract infections

	ACE 68.8%; *Pla:* 87.2% antihypertensives, 76.1% angiotensin receptor blocker and/or ACE, 26.6% thiazide diuretics	

Table 3 Results - Matthaei 2015

Outcome	**Dapagliflozin (n=108)**			**Placebo (n=108)**		
	Baseline	24 weeks	52 weeks	Baseline	24 weeks	52 weeks
HbA1c (%)	8.08 SD0.91	-0.86 SD0.74	-0.80 SD0.94	8.24 SD0.87	-0.17 SD0.77	-0.10 SD0.71
% reaching HbA1c <7.0%	-	31.8 SD44.8	27.3 SD43.7	-	11.1 SD30.2	11.3 SD30.1
Weight (kg)	88.6 SD17.6	-2.7 SD2.9	-2.9 SD3.3	90.1 SD16.2	-0.6 SD2.7	-1.0 SD3.0
Systolic blood pressure (mmHg)	134.7 SD12.7	-4.0 SD12.5	-1.0 SD12.2	136.6 SD14.4	-0.3 SD12.5	+1.1 SD11.5
Total cholesterol (mmol/L)	4.6 SD1.2	+0.17 SD0.82	+0.16 SD0.76	4.5 SD0.9	-0.13 SD0.83	+0.06 SD0.71
HDL cholesterol (mmol/L)	1.2 SD0.3	+0.05 SD0.17	+0.08 SD0.2	1.2 SD0.3	0.00 SD0.17	+0.01 SD0.18
LDL cholesterol (mmol/L)	2.5 SD1.0	+0.14 SD0.72	+0.12 SD0.76	2.4 SD0.8	-0.15 SD0.73	+0.02 SD0.67
Triglycerides (mmol/L)	2.1 SD1.4	-0.14 SD1.01	-0.17 SD0.82	2.2 SD1.7	+0.04 SD1.02	+0.06 SD0.82
Hypoglycaemia (% patients)*	-	12.8% (none major)	15.6% (none major)	-	3.7% (none major)	8.3% (none major)
Urinary tract infections	-	3 men (6.5%), 4 women (6.3%)	3 men (6.5%), 8 women (12.7%)	-	1 man (1.7%), 6 women (12.2%)	1 man (1.7%), 11 women (22.4%)
Genital tract infections	-	1 man (2.2%), 5 women (7.9%)	2 men (4.3%), 9 women (14.3%)	-	0	0 men, 1 woman (2.0%)

*** Definition of hypoglycaemia:** *Minor episodes of hypoglycaemia*: either a symptomatic episode with a capillary or plasma glucose measurement <3.5 mmol/L, regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <3.5 mmol/L that did not qualify as a major episode; *Major episode:* a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol/L and prompt recovery after glucose or glucagon administration

The AstraZeneca submission (pages 93 to 95) gives data from use in routine care from the CPRD. In 255 patients on triple therapy for more than 90 days, HbA1c was reduced by a mean of 1.05% from a baseline of 9.36% before dapagliflozin was started, implying a reduction to an average of 8.31% - well above the NICE target level. The reductions in HbA1c shown in the CPRD data are greater than seen in the trials, reflecting the higher starting levels.

3.3 Other trials of dapagliflozin in triple therapy

The AstraZeneca submission presents results only from the Matthaei trial, in which 101 patients completed 24 weeks on dapagliflozin and 95 completed 52 weeks.

Weber 2015

A trial by Weber and colleagues (published in November 2015[44]) compared dapagliflozin and placebo as add on to metformin and sulfonylureas, but no data from the Weber trial are presented in the AstraZeneca submission, despite the trial being funded by the company along with Bristol-Myers Squibb. The trial is not mentioned at all in the submission.

Details of risk of bias assessment are shown in Appendix 1. The trial by Weber and colleagues 2015 had a low risk of bias, fulfilling 9 of the 9 quality criteria. It used adequate randomisation procedures, allocation concealment, and adequate blinding of patients, personnel and outcome assessors. There was a slight imbalance in baseline characteristics with a slight imbalance of participants with prior cardiovascular disease in individual subgroups. Withdrawals and losses to follow-up were described and the non-completion rate was low - 6.2% on dapagliflozin and 9.8% on placebo. The study used intention-to-treat analysis, including all patients having received at least one dose of drug and with at least one baseline and post-baseline measurement. All outcomes were reported as specified on clinicaltrials.gov. A power analysis was reported and the envisaged power was achieved. No other potential sources of bias were identified.

The Weber trial recruited patients who had both uncontrolled type 2 diabetes (HbA1c 7.0% to 10.5%) and uncontrolled hypertension (SBP 140 to 165 mmHg and DBP 85 to 105 mmHg). This trial recruited 449 patients in 311 centres, an average of 1.4 patients per centre. The numbers on metformin and sulfonylureas are not given, but the baseline data show that 203 patients assigned to dapagliflozin were on metformin and 105 were on sulfonylureas. So at least 83 and probably more patients were on both metformin and a sulfonylurea. The trial reported effects on both glycaemic control and hypertension. All patients had hypertension, but most patients in the Matthaei trial also had hypertension (about 84%).

The Weber trial lasted for only 12 weeks. The reduction in HbA1c was 0.61% (after adjustment for placebo effect). Results are not given separately for the subgroup on metformin and sulfonylureas. SBP fell by 4.3mm Hg more on dapagliflozin than placebo, and weight fell by a placebo-adjusted 0.85 kg.

The ERG asked AstraZeneca (on 29th March 2016, almost two months before the STA was due to start) to provide data on the metformin + sulfonylurea subgroup of the Weber trial but the company declined, for the reasons given below.

"The Weber 2016 trial mentioned is not relevant to the decision problem of this appraisal as it includes a broad population uncontrolled on oral antihyperglycaemic drugs, insulin, or both rather than a specific population failing on MET + SU at baseline as specified in the scope of this appraisal. Further, the Weber paper presents sub-group data based on type of anti-hypertensive medication rather than type of OAD medication." (AZ 5th April 2016)

While the comments on the content of the paper published by Weber and colleagues are correct, nevertheless AstraZeneca has a considerable amount of data from that trial which is relevant to the decision problem in this appraisal. Had data been provided, the numbers of patients providing evidence for the decision problem might have been almost doubled. The Weber paper states that the "funders were involved in the design, collection, analysis and interpretation of data".

Other trials

The Scottish Medicines Consortium (SMC) guidance (799/12) has data on dapagliflozin in triple therapy from two other trials, then unpublished.[45] The SMC guidance reports that two trials, studies 18 and 19, randomised patients to dapagliflozin 10 mg daily or placebo for 24 weeks. In these trials, 25% (227 patients) and 22% (214 patients) were taking metformin and sulfonylureas at baseline, and so were on the same form of triple therapy being evaluated in the appraisal. Placebo-adjusted reductions in HbA1c at 24 weeks were 0.6% in study 18 and 0.5% in study 19, slightly lower than reported by the Matthaei trial used as the source of evidence in the AstraZeneca submission. Mean placebo-adjusted changes in body weight were 2.2kg and 1.1kg.

These two studies could have contributed data from another 441 patients to this appraisal. They were sponsored by AstraZeneca and Bristol-Myers Squibb. One has been published by Cefalu and colleagues (including from AstraZeneca)[46] but that publication does not give results split by baseline therapy. The other has been published by Leiter and colleagues (including from AstraZeneca) in a pooled analysis[32] with the Cefalu trial.

3.4 Triple therapy with metformin + a gliptin + dapagliflozin

The submission makes clear that the focus is on triple therapy that include metformin and sulfonylureas. Two trials of adding dapagliflozin to metformin + a gliptin are mentioned in passing in the main text and described in full in AstraZeneca appendix 6. The trials report overall reductions in HbA1c of 0.4% [36] and 0.72% [37] but do not give proportions of patients achieving the target levels of HbA1c. In the Jabbour trial[36] (with sitagliptin) the subgroup of patients with HbA1c of 8-10% achieved a reduction in HbA1c of 0.8%. AstraZeneca was asked to provide details of proportions achieving targets but declined to do so. Both studies were sponsored by AstraZeneca and Boehringer and had authors from AstraZeneca.

AstraZeneca are not asking NICE to consider the use of dapagliflozin in combination with metformin and a gliptin, so we need not describe these trials in detail. Both trials compared dapagliflozin with placebo rather than an active comparator such as pioglitazone or gliclazide. Given the relative potencies and relative costs, it would be surprising if dapagliflozin would be cost-effective against those drugs, but there are patients with contraindications to pioglitazone and others in whom the risk of hypoglycaemia might be seen as too high with gliclazide. So there may be a place for triple therapy with a gliptin and a flozin, though the combination would come at quite a high cost (over £900 per year).

3.5 Other developments

Two fixed dose combinations are now available, which by reducing the number of tablets required, might improve adherence.

The EMA issued initial authorisation of a fixed dose combination of saxagliptin and dapagliflozin, known as saxa/dapa, on 26th May 2016.[47]

The AstraZeneca press release[48] dated 27th May 2016 states that there are three studies of the combination in type 2 diabetes. These seem to involve adding the combination to metformin compared to adding the single drugs to metformin, so that

metformin + dapagliflozin + saxagliptin

was compared to

metformin + dapagliflozin + placebo

and

metformin + saxagliptin + placebo.

These studies seem relevant to the decision problem but it would have been better if active comparators such as pioglitazone or gliclazide had been added instead of placebo. These studies were not included in the AstraZeneca submission.

There is also a combination tablet of metformin and dapagliflozin called Xigduo which has 5mg of dapagliflozin and 850mg of extended release metformin, to be taken twice daily. The Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for Xigduo for use in combination with other agents.[49]

3.6 Introduction to NMA

The clinical effectiveness section of the submission (section 4, starting page 29) reports that a systematic review was conducted. This used an extremely comprehensive search strategy with a very large retrieval that should not have missed any relevant studies relevant to the decision problem. Our independent search found the trial by Weber and colleagues that was not mentioned in the AstraZeneca submission. We also found the full paper by Moses et al[50] of the Round 2013[51] trial.

Trials had to have duration of > 4 weeks, which is much too short. Most trials that rely on HbA1c as an intermediate indicator, have minimum duration of 12 weeks. Our preference has been to include only trials of 24 weeks or longer.

The trials of dapagliflozin were funded by AstraZeneca and Bristol-Myers Squibb so all were known the company. The searches for the submission were mainly for the NMA.

The submission reports that 50 studies were found on metformin + sulfonylurea in triple therapy but many of these were not relevant because they were of the GLP-1 mimetics or insulins or acarbose.

The trials which are relevant should be;

- metformin + sulfonylureas + a flozin
- metformin + sulfonylureas + pioglitazone
- metformin + sulfonylureas + a gliptin

with metformin + sulfonylureas + placebo as comparator.

The studies selected for the NMA are reported in AstraZeneca Table 17, reproduced here (Table 4). The AstraZeneca submission reports that a number of different networks were created but that

"*the base case NMA focuses only on studies that evaluate comparators directly relevant to UK clinical practice: DPP4-is and other SGLT2-is*."

This approach was sensible in some ways since many of the other trials were not relevant, but the glaring weakness is the omission of pioglitazone.

Table 7 of the AstraZeneca submission includes many drugs not relevant to the decision problem as previously stated. Table 8 of the submission starts with those which were included in their restricted network, reproduced here.

Table 4 Summary of RCTs included in the restricted base case NMA

Author, Year	Country	Number randomised	Treatment duration (weeks)	Intervention
Haering 2015[52]	Multinational	669	76	Empagliflozin (25 mg) + MET + SU Empagliflozin (10 mg) + MET + SU Placebo + MET + SU
Hermansen et al., 2007[53]	Multinational	229	24	Sitagliptin + MET + SU Placebo + MET + SU
Hong et al., 2015[54]	South Korea	344	24	Vildagliptin + MET + SU MET + SU (Dose increase)
Ji et al., 2015[55]	Multinational	678	18	Canagliflozin (300 mg OD) + MET + SU Canagliflozin (100 mg OD) + MET + SU Placebo + MET + SU
Lukashevich 2014[56]	Multinational	318	24	Vildalgliptin + MET + Glimepiride Placebo + MET + Glimepiride
Liu et al., 2013[57]	Taiwan	120	24	Pioglitazone + MET + SU Sitagliptin + MET + SU
Matthaei et al., 2015[34, 35]	Multinational	219	52	Dapagliflozin + MET + SU Placebo + MET + SU
Moses et al., 2014[58]	Multinational	257	24	Placebo + MET + SU Saxagliptin + MET + SU
NCT01590771[59]	China	223	24	Sitagliptin + MET + SU Placebo + MET + SU
Nogueira et al., 2014[60]	Brazil	35	24	Sitagliptin + MET + Glyburide NPH insulin + MET + Glyburide
Owens et al., 2011[61]	Multinational	1058	24	Linagliptin + MET + SU Placebo + MET + SU
Round et al., 2013[51]	Asia-Pacific	427	24	Sitagliptin + MET + SU Placebo + MET + SU
Schernthaner et al., 2013[41]	Multinational	756	52	Canagliflozin + MET + SU Sitagliptin + MET + SU
Wilding et	Multinational	469	52	Canagliflozin (300 mg OD) + MET + SU

al., 2013[62]				Canagliflozin (100 mg OD) + MET + SU Placebo + MET + SU

NPH, neutral protamine hagedorn

The ERG has reviewed the inclusions and omissions, aided by our own search.

The ERG considered that 14 trials with a metformin + sulfonylurea + placebo arm, compared to metformin +sulfonylureas + one of a gliptin, a flozin and pioglitazone could have been included. There are;

Four trials of metformin + sulfonylureas + a flozin:

Haering 2015 [empagliflozin][52]
Ji 2015 [canagliflozin][55]
Matthaei 2015 [dapagliflozin][34]
Wilding 2013 [canagliflozin][62]

Two trials of metformin + sulfonylureas + pioglitazone:

Charpentier 2009[63]
Home 2015 (excluding the albiglutide arm)[64]

Eight trials of metformin + sulfonylureas + a gliptin

Hermansen 2007 [sitagliptin][53]

Hong 2015 [Vildagliptin] (Note met+su only, no placebo)[54]

Lukashevic 2014 [vildalgliptin][56]

Moses 2014 [saxagliptin][58]

Moses 2015 (sitagliptin) – the full publication of the Round 2013 study[51]

NCT01590771 [sitagliptin] (not provided)[59]

Owens 2011 [linagliptin][61]

In addition Liu 2013[57] should be included: pio + met + su versus sitagliptin + met + su

This gives three trials for a comparison with pioglitazone: Liu, Charpentier and Home.

The ERG would exclude Nogueira [NPH insulin compared to sitagliptin].

So if the ERG was able to do an NMA, the differences from the inclusions in the AstraZeneca restricted network would be the addition of Charpentier and Home, and the exclusion of Nogueira.

Liu 2013 compared pioglitazone and sitagliptin as add-on to metformin and sulfonylureas (91% glimepiride, and the rest gliclazide). There could be a comparison of relative effects on HbA1c and other outcomes of pioglitazone and dapagliflozin using the links pioglitazone + metsu > DPP4 +metsu > placebo + metsu > dapagliflozin + metsu. However this is not provided and AstraZeneca Table 26 gives no data on the relative effects of pioglitazone and dapagliflozin. Liu and colleagues reported a reduction in HbA1c of 0.94% on pioglitazone and 0.71% on sitagliptin, though the proportions reaching the target of <7.0% were similar at 29% and 28%.

The NMA for HbA1c includes Nogueira 2014 but this had no metformin and sulfonylurea arm – it compared sitagliptin with NPH insulin, so its inclusion is inappropriate. However it could have been used to provide a link with two trials of pioglitazone + MetSu versus NPH + MetSu (Aljabri [65] and Hartemann-Heurtier[66]) to allow further indirect comparison of pioglitazone and dapagliflozin.

The Moses 2015/ Round 2013 trial compared sitagliptin and placebo for 24 weeks, both added to metformin and sulfonylureas. After the 24 weeks, the placebo group started pioglitazone and the sitagliptin group received a placebo resembling pioglitazone for 30 weeks, allowing a comparison of sitagliptin and pioglitazone. The full paper (Moses) was published online on 1st December 2015 with EDAT date 2nd December. (EDAT is Entrez Date when the publication was added to PubMed.)

So pioglitazone and dapagliflozin could have been indirectly compared if Aljabri 2004 and, Hartemann-Heurtier 2009 had been included, and if all the data from Liu 2013 had been used.

With the canagliflozin 300mg dose, and to a lesser extent with empagliflozin 25mg, we have the problem that according to the licences, the larger dose should only be used if there has been an insufficient reduction in HbA1c with the smaller doses. Patients who do not respond well to the smaller doses may not get as large a response as patients in the trial, who started on the higher doses.

3.7 Review of statistical methods used in the AstraZeneca submission for the NMA of dapagliflozin in triple therapy regimens

The full critique is given in Appendix 2. Quality assessment of the trials is given in Appendix 3.

The AstraZeneca submission provided a network meta-analysis (NMA), which was critically appraised by the ERG using a standard approach. The NMA was of RCTs comparing triple therapy

combinations of dapagliflozin with MET and SU in adults with type 2 diabetes mellitus poorly controlled on MET and SU. With the exception of the flozins, the NMAs included classes of drugs within the same networks rather than considering individual drugs separately. It focused on the continuous outcomes of the difference in the mean change in HbA1c, weight and SBP and the binomial outcome of subjects with any hypoglycaemia using the odds ratio. Given differences in the time points at which the studies assessed outcomes, NMAs examined the outcomes at three different time points (i.e. 24 weeks, 52 weeks and study endpoint) and for a base case restricted network (i.e. a network incorporating only DPP4-is and SGLT2-is comparators only – regardless of study duration).

The evidence networks were presented through network diagrams, highlighting both the classes and individual drugs included. Although these clearly identified the studies that were included in the different networks, the diagrams were presented for the restricted base case NMAs and sensitivity analyses only. Evidence networks for the studies included for the 24 weeks, 52 weeks and study endpoint NMAs are not presented or the differences in included studies presented.

The submission states that it took the decision to group the comparator treatments into their respective drug classes rather than assessing the treatments individually. Although this is based on an assumption that some, if not all, the treatments are similar (i.e. non-inferior), it does lead to concerns regarding the NMA. The 'lumping' of evidence can affect consistency, lead to heterogeneity, difficulties in interpreting results and potential conflict between direct and indirect evidence. It would have been more appropriate if the NMA had considered the individual treatments separately as well as the class effect.

Limited data are provided on the baseline characteristics of the participants in the studies included in the NMA and the possible effects on the NMA. With studies differing on participant age (mean 55 to 62 years), sex (37.5% to 64.1 % male), average HbA1c (mean 8.1 to 8.8%) and duration of diabetes (mean 7.3 to 10.9 years), it may have been beneficial to incorporate these in NMAs using meta-regression. The network diagrams highlight that many of the links between the different treatment combinations are based on one study only, raising the issue of the possible effects of sparse evidence (i.e. wide credible intervals and global measures of fit having limited discriminatory powers). Sparse evidence and random-effects models may result in wider credible intervals, which may influence interpretation of the outcome of the NMA. Such issues can be assessed through increasing the evidence from an expanded network, examining the influence of vague and informative priors and through additional sensitivity analyses.

In summary, the AstraZeneca submission outlines many of the aspects of the methods used in its NMAs, but some uncertainty remains regarding some areas. Not all networks are clearly presented, meaning it is unclear the extent of the evidence that underpins the analyses. The NMA provides limited details regarding its approach to sensitivity analyses concerning elements of the modelling

process (e.g. prior distributions, link functions and priors for parameters). Although the submission does not provide an assessment of autocorrelation, diagnostic plots regarding model convergence or measures of model fit, these were presented as clarifications by AstraZeneca and provided limited concerns. The occurrence of heterogeneity was assessed through summary measures and sensitivity analyses, though only the effects of baseline levels of HbA1c were assessed through meta-regression. Other possible causes of heterogeneity were identified in the AZ submission, but these were not examined due to limited data. Limitations in the evidence base may mean that the NMA is affected by sparse data, which can influence the credible intervals and measures of fit. This may have been part of the rationale for presenting a NMA that included classes of treatments with individual treatments, rather than treatment classes and individual treatments separately. Such lumping may have led to concerns regarding consistency, heterogeneity, interpretation of results and potential conflict between the direct and indirect evidence. Although these possible shortcomings may influence the outcome of the NMAs, the nature and extent of the effect remains uncertain.

Table 5 Checklist with core issues

Checklist		**Response yes/no**
Does the MS present an MTC?		**Yes (NMA)**
Are the MTC results used to support the evidence for the clinical effectiveness of the intervention		**Yes**
Are the MTC results used to support the evidence for the cost-effectiveness of the intervention		**Yes**
Homogeneity		
	1. Is homogeneity considered?	Partially. The MTC clearly specifies the selection criteria for the systematic review that underpins the NMA and it provides a comparison of a limited subset of study characteristics (e.g. age, sex, duration of diabetes, HbA1c, interventions, treatment duration). The AZ submission identifies factors (e.g. patient populations, study design and study duration), and specific studies (i.e. Ji et al (2015), Hong et al (2015)), that may be a source of heterogeneity. Studies included participants with a mean age ranging from 55 to 62 years, male (37.5% to 64%), had a mean duration of diabetes of 7.3 to 11 years, a mean HbA1c of 8 to 8.8. Studies were RCTs with treatment duration ranging from 18 to 76 weeks.
	2. Are the studies homogenous in terms of patient characteristic and study design?	No
	3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Yes. The AZ submission uses I^2, tau and Cochran's Q statistics for pairwise comparisons, assesses key study characteristics and undertakes

		sensitivity analyses and meta-regression to assess effects.
	4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	Yes. The submission undertakes a priori sensitivity analyses to assess the effects of study quality, sub-group data, missing data and studies thought to increase heterogeneity. It also produces analyses for different treatment durations and different evidence networks. Meta-regression was used to assess the effects of baseline HbA1c, however other factors that have the potential to cause heterogeneity were not included.
Similarity		
	1. Is the assumption of similarity stated?	No – reference is made to the requirement for exchangeability and that this is likely not to have been met.
	2. Have they justified their assumption?	No
Consistency		
	1. Does the analysis explicitly assess consistency?	Yes – it calculates the inconsistency factor (R software) and presents these in an inconsistency check (Appendix 13).
	2. Does the method described include a description of the analyses/ models/ handling of potential bias/ inconsistency/ analysis framework?	No
	3. Are patient or trial characteristics compared between direct and indirect evidence trials?	No
	4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	Not applicable

Table 6 Extended checklist

Checklist		***Response yes/no/unclear***
i. Rationale and searches		
	1. Is the rationale for the MTC and the study objectives clearly stated?	No
	2. Does the reported study follow conventional guidelines for systematic reviews, as well as use explicit search terms, time frames, and avoid ad hoc data?	Yes, however details of elements of the systematic review process are not reported (e.g. aspects process for study selection)
	3. Are inclusion/exclusion criteria adequately reported?	Yes
	4. Is quality of the included studies assessed?	Yes, a quality assessment/risk of bias assessment is undertaken for the 14 RCTs used in the base case (CS Table 21)
ii. Methods		
Model		
	1. Is the statistical model described?	Yes

	2. Has the choice of outcome measure used in the analysis been justified?	Yes
	3. Has the choice of fixed or random effects model been justified?	Yes
	4. Has a structure of the network been provided?	Yes, network diagrams are presented for the base case models (not for 24 week, 52 week or study endpoint models) and for sensitivity analyses (appendix 14)
	5. Is any of the programming code used in the statistical programme provided (for potential verification)?	Yes, standard WinBUGS code is provided for random effects models for continuous and binomial data (Appendix 9)
Sensitivity analysis		
	1. Does the analysis conduct sensitivity analyses?	Yes, sensitivity analyses are presented for the effects of poor quality studies, sub-group studies, missing data and heterogeneity (Appendix 14)
iii. Results		
	1. Are the results of the MTC presented?	Yes, point estimates and credible intervals are presented for HbA1c, change in body weight, change in systolic blood pressure and hypoglycaemic events for fixed-effect and random-effects models at 24 weeks, 52 weeks, study endpoint and base case analyses. Results are presented for sensitivity analysis and meta-regression models.
	2. Does the study describe an assessment of the model fit?	Yes, model fit is assessed as part of model selection using Deviance Information Criterion, mean total residual deviance and between-studies standard deviation.
	3. If direct and indirect evidence is reported to be consistent, is the evidence combined and the results presented?	Yes
	4. Has there been any discussion around the model uncertainty?	No

	5. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes (credible intervals)
iv. Discussion		
Overall results		
	1. Does the study discuss both conceptual and statistical heterogeneity and incoherence?	Partial, heterogeneity is discussed a priori and explored in the analysis, however discussion of its effects on the outcomes is limited
	2. Does the discussion flow from the results seen?	No
Validity		
	1. Are the results from the indirect/MTC compared, where possible, to those just using direct evidence?	No, direct evidence is presented as part of the consistency check, however no discussion is presented comparing the results.
	2. Have the authors commented on how their results compare with other published studies (e.g. MTCs)?	No, although passing reference is made to its similarity to other NMAs, no discussion or reference is made to specific studies.

The ERG asked a number of clarification questions about the NMA methods. These, and the AstraZeneca replies, are in Appendix 4. The replies were considered satisfactory.

3.8 Additional work by ERG

In NMAs, it is important that the baseline characteristics of the patients are reasonably similar across the trials. The ERG therefore extracted data on some baseline characteristics as shown in Appendix 5. Baseline HbA1c was similar in the trials, ranging from 8.0% to 8.8%, but with most in the middle of that range. Mean ages were similar, ranging from 55 to 61 years. However there was heterogeneity in mean baseline weights, from 67 to 93kg, and in BMI, 26 to 33. The proportions of recruits who were white ranged from 23% to 94%.

It is also important that changes in the placebo group are reasonably similar. In our assessment report for the flozins in monotherapy report, we noted that in some dapagliflozin trials, HbA1c fell in the placebo group, whereas in some canagliflozin trials, HbA1c rose in the placebo group. We therefore extracted data on changes in intervention and placebo arms.

Table 7 shows the reductions in HbA1c in the placebo arms of the placebo-controlled trials included in the AstraZeneca restricted network and two ERG additional trials. Mean HbA1c decreased in the

placebo arm of 8 trials (range -0.01% % - 0.47%) and increased in 3 trials (range 0.28% to 0.33%), with no change in 1 trial). So there is heterogeneity amongst the placebo arms, with HbA1c changes ranging from a reduction of 0.47% to an increase of 0.33%.

Reductions in the intervention arms are also noted, and ranged from 0.59% to 1.2%.

Table 7 Reductions in HbA1c on placebo

Trial	Baseline HbA1c Placebo	Baseline HbA1c intervention	HbA1c change on placebo, mean (SD or 95% CI)	HbA1c change on intervention, mean (SD or 95% CI)
Haering 2015	8.2 (0.8) 8.1 (0.8)	8.1 (0.8) 8.1 (0.8)	-0.0 (0.1)	52w, Empa 10 mg: -0.8 (0.1) 52 w, Empa 25 mg: -0.7 (0.1) 76w, Empa 10 mg: -0.7 (0.1) 76 w, Empa 25 mg: -0.7 (0.1)
Hermansen et al., 2007	8.26 (0.68)	8.27 (0.73)	0.30 (0.14 to 0.45)	-0.59 (-0.74 to -0.44)
Ji et al., 2015	7.9 (0.9)	8.0 (0.9) 8.0 (0.9)	-0.47	Cana 100 mg: -0.97 Cana 300 mg: -1.06
Lukashevich 2014	8.8 (0.9)	8.7 (0.9)	-0.25	-1.01
Matthaei et al., 2015	8.2 (0.9)	8.1 (0.9)	24w: -0.17 (-0.31, -0.02) 52w: -0.1 (-0.3, 0.1)	24w: -0.86 (-1.00, -0.72) 52w: -0.8 (-1.0, -0.6)
Moses et al., 2014	8.2 (0.8)	8.4 (0.9)	-0.08 (−0.23, 0.07)	-0.74 (–0.89, −0.60)
NCT01590771	8.48 (0.91)	8.61 (1.06)	-0.45 (-0.60, -0.30)	-0.86 (-1.01, -0.71)
Owens et al., 2011	8.14 (0.81)	8.15 (0.84)	-0.10 (0.81)	-0.72 (0.84)
Round et al., 2013 / Moses 2016	8.4 (0.9)	8.4 (0.8)	-0.16 (-0.28, -0.03)	-0.84 (-0.97, -0.71)
Wilding et al., 2013	8.1 (0.9)	8.1 (0.9) 8.1 (0.9)	24w: -0.13 52w: -0.01	24w: Cana 100 mg: -0.85 24w: Cana 300 mg: -1.06 52w: Cana 100 mg: -0.74 52w: Cana 300 mg: -0.96
ERG additional trials:				
Charpentier et al., 2009	8.1 (0.7)	8.2 (0.6)	0.28	-0.9
Home et al., 2015	8.26 (0.98)	8.29 (0.88)	0.33 (0.86)	−0.80 (1.0)

3.9 Commentary on NMA

- Page 121, section 5.4 says lipid results not available. But they were measured in Matthaei 2015 and several other trials in the restricted NMA – see the ERG table of lipid results in Appendix 6. So the reason for omission of lipid effects is not convincing. However given the very small changes, the omission is probably unimportant.
- Page 124 says "SBP changes were informed by the NMA" but the NMA figure does not match the trial result.
- Page 125. Defining intensified insulin treatment as a 50% increase in daily dose is unusual. Basal insulin should be titrated to target. Intensified insulin therapy has different meanings but usually means using a combination of insulins, such as adding short-acting insulin at meal-times.
- Table 38. The ERG has concerns about the figures in AstraZeneca Table 38 which do not match the results in the Matthaei trial, which was the only trial of dapagliflozin in the NMA. Table 38 gives HbA1c reduction of 0.85%. The 52 week paper gives reductions of 0.8% and 0.72% (figure 1 of the publication). The weight change is given as -2.2kg but the paper says – 3.6kg. The SBP reduction in Table 38 is 3.13 mmHg ut in trial was 1.0. Table 38 says that the probability of severe hypos was 0.040 but there were none in the trial. It's very odd to have a lower hypoglycaemia risk (0.022) for intensified insulin than dapagliflozin.
    - Different sulfonylureas have different effects with gliclazide being our sulfonylurea of choice, and also the most used in the UK. Appendix 7 shows that in the trials used in the NMA, glimepiride was the commonest sulfonylurea, with only two trials having significant minorities on gliclazide, Matthaei 2014 (42% on gliclazide) and Round 2013/Moses 2016 (40%)

3.10 Adverse effects

Urogenital Tract Infections
Ptaszynska and colleagues[67] reported that in pooled analyses from 12 placebo-controlled studies of dapagliflozin as monotherapy or combination therapy, urogenital tract infections occurred more often with dapagliflozin treatment compared with placebo, but were mild or moderate in severity. Pyelonephritis was rare. Both UTIs and GTIs are more common in females.[68]

UTIs
Most urinary tract infections (UTIs) are mild and resolve with antibiotic treatment, but more severe infections can result in bacteraemia, sepsis and death.

Symptoms of UTI include dysuria (a burning feeling when urinating); frequency of urination; urgency (a feeling of an intense urge to urinate); pain or pressure in the back or lower abdomen; nausea and/or vomiting; cloudy, dark, bloody, or strange-smelling urine; feeling tired or shaky; fever or chills.

The presence of glucose in the urine (glycosuria) creates a suitable environment for the growth and proliferation of bacteria. By causing glycosuria, dapagliflozin increases the risk of UTI. [69]

Genital tract infections

Glycosuria in patients with T2DM predisposes them to develop genital tract infections (GTIs), in particular, genital mycotic infections i.e. vulvovaginal candidiasis in women and candida balanitis in men, as it provides a favourable growth environment for otherwise commensal genital microorganisms. Candida albicans is the most common cause, but Candida glabrata is also an important cause in women with T2DM..[70]

Symptoms of genital candidiasis can include itching; burning; genital discharge; pain during sexual intercourse; soreness; redness in the genital area; rash.

The frequency of urogenital infections was reviewed in depth in the assessment report for the SGLT2 monotherapy appraisal. In summary, dapagliflozin treatment is associated with a higher incidence of urogenital tract infections. These are generally mild to moderate in severity, tend to occur during the first 6 months of dapagliflozin therapy, are more common in women, but are amenable to standard treatment. Urogenital infection rates are similar in monotherapy and combination therapy.

Acute kidney injury

The US Food and Drug Administration (FDA) has issued a warning about acute kidney injury with dapagliflozin and canagliflozin after receiving reports of 101 cases (73 canagliflozin, 28 dapagliflozin).[71] Four died, and 15 needed dialysis.

The FDA issued the following recommendation on 14th June 2016.

ISSUE: FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

RECOMMENDATION: Health care professionals should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other

medications such as diuretics, blood pressure medicines called angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

There has been no such warning for empagliflozin and in the Empagliflozin Outcomes trial, there was no increase in acute kidney injury.[72] A subsequent paper from the EmpaOutcomes trial by Wanner et al[73] reported that empagliflozin was reno-protective, by reducing progression of nephropathy and also reducing the proportion of patients whose creatinine doubled (1.5% on empagliflozin versus 2.6% in the control group) and the proportion starting dialysis (0.3% versus 0.6%).

There is some evidence that dapagliflozin can be renoprotective in people with stage 3 kidney disease (eGFR 30-59 ml/min) as reflected in improvements in albuminuria and urinary albumin/creatinine ratio.[74] Note however that dapagliflozin is not recommended for people with GFR < 60ml/min, and its glucose lowering effect is reduced in renal impairment.

Fractures

The FDA issued a warning on Sept 10th 2015 on an increased risk of fractures in people taking canagliflozin.[75]

A pooled analysis of nine trials of canagliflozin by Watts and colleagues (J Clin Endocrinol Metab online November 2015) found an increased incidence of fractures of 2.7% amongst 6554 patients randomised to canagliflozin, compared to 1.9% amongst controls, but this excess was driven by only one study, the CANVAS trial (Canagliflozin cardiovascular assessment study). The other 8 trials showed no difference when pooled. The CANVAS patients were older, had a history of cardiovascular disease, poorer renal function and glycaemic control at baseline.

Fractures have also been reported amongst people taking dapagliflozin. Kohan and colleagues[76] randomised 252 people with moderate renal impairment (94% in the range 30 to 59 ml/min) to placebo or dapagliflozin. Eight of 85 (9.4%) people on dapagliflozin 10mg suffered fractures, compared to none on placebo.

A study by Ljunggren [77] of bone mineral density amongst 165 people in a trial of dapagliflozin versus placebo in dual therapy with metformin found no difference in bone density after 50 weeks.

In the pooled analysis by Fioretto and colleagues[40] there was no increase in fractures amongst people taking dapagliflozin.

A recent good quality review by Tang and colleagues[78] found no increase in fracture rates in 30,384 patients taking flozins. Event rates (any fractures) were 1.59% for those taking flozins and 1.56% for control groups, giving an odds ratio of 1.02. Heterogeneity was low at I^2 23%. Odds ratios for the individual drugs compared to placebo were for canagliflozin 1.15 (0.71-1.88), dapagliflozin 0.68 (0.37-1.25) and empagliflozin 0.93 (0.74-1.18).

Cancer

Concerns have been raised about breast and prostate cancer risks in people taking dapagliflozin but recent evidence, as reported in pages 100-101 of the AstraZeneca submission, is reassuring.

Diabetic ketoacidosis

There has been reports of diabetic ketoacidosis (DKA) with all the flozins. However rates are low in absolute terms, with the EMA (2015) reporting 101 cases over about 500,000 patient years of flozins use. The latest communication from the EMA (26/02/2016 EMA) confirms recommendations to minimise ketoacidosis risk) concludes that DKA should be regarded as a rare adverse event of flozin treatment, affecting no more than one in 1,000 patients. It makes recommendations for reducing the occurrence of DKA, including avoiding use of the flozins in people with poor insulin production, increased insulin requirement such as due to illness or alcohol abuse or conditions that lead to dehydration.[79]

Amputations

The EMA has also noted an increase in amputations, mostly of toes, but some of lower limb, amongst people on canagliflozin in the CANVAS trial[80] which is the cardiovascular outcomes trial of canagliflozin. The EMA view is that "*the possibility that canagliflozin increases lower limb amputations is currently not confirmed".* Such events may be the result of volume depletion in patients with vulnerable micro/macrocirculations. No such concern has been raised for dapagliflozin.

3.11 Effect sizes for modelling

ERG approach to NMAs in STAs.
The ERG approach is restricted by the tight time and resource limitations. We do not get access to the manufacturers' NMA models, and do not have time or resources to do our own NMAs. So all we can do is;

- Check what is included and not included in manufacturers' NMAs, and check that the included trials are reasonably similar. Marked heterogeneity would cause concern
- Critique the reported methods of the manufacturers' NMA using text and a checklist

- Consider the results of the manufacturers' NMAs and whether the results seem credible, and compatible with the data from the trials

We now consider some of the rows in the Astra Zeneca Table 38, reproduced on the next page as table 8.

DDP4 inhibitors.

Astrazeneca Table 38 gives HbA1c reduction of 0.79% when a gliptin is added to metformin and SU. This is slightly larger than reported in the Craddy[42] meta-analysis (0.76%) and considerably larger than in the sitagliptin trials (average 0.68%). The weight gain from the NMA is 0.12kg, which is less than in the Craddy meta-analysis (0.52kg) and in the sitagliptin trials (0.33kg). So these NMA estimates appear somewhat favourable to the gliptins, which would disadvantage dapagliflozin.

A review and meta-analysis by the Canadian Agency Drugs and Technologies in Health (CADTH 2010) reported a larger reduction in HbA1c with the gliptins of 0.89%, associated with weight gain of 1.11%. However only one trial of a gliptin was included – Hermansen 2007, which was included in the AstraZeneca NMA.[53]

AstraZeneca Table 38 gives a rise in SBP of 1.85mmHg on gliptins. None of the individual trials that reported SBP had such high estimates. Schernthaner 2013 reports a rise of 0.9mmHg and Liu 2013 reported no change. This would give an average rise of 0.5mmHg.[81]

Dapagliflozin

The HbA1c reduction from the NMA is 0.85%. This is odd, since in the only dapagliflozin trial included (Matthaei 2015) the reduction was 0.70% at 52 weeks. Weight reduction is given as 2.20 kg, compared to 1.9 kg in the trial. SBP reduction is given as 3.13 mmHg, which is considerably more than in the trial wherein there was a reduction of only 1 mmHg at 52 weeks, or 2 mmHg after placebo-adjustment. So the NMA results favour dapagliflozin more than would be expected from the only trial.

The figures for hypoglycaemia from the NMA are puzzling. For all symptomatic hypoglycaemia, a figure of 0.202 is given. This is higher than the 16% reported by 52 weeks in the Matthaei trial, but not by much. A figure for severe hypos of 0.040 (4% a year) is provided, which is odd because no severe hypos were reported by Matthaei and colleagues. It is also odd because it is almost double the frequency reported for intensified insulin. The estimate for severe hypos will disadvantage dapagliflozin.

Table 8 Treatment effects and AE parameters applied in the economic model – AstraZeneca table 38

Variable	Source	Change from baseline *			Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
		HbA1c (%)	Weight (kg)	SBP (mmHg)					
DPP4	NMA add-on to MET + SU for change from baseline & symptomatic hypoglycaemia Schernthaner 2013[41] for AEs except for symptomatic hypoglycaemia	-0.79	+0.12	+1.85	0.029	0.181	0.034	0.021	0.056
Dapagliflozin		-0.85	-2.20	-3.13	0.053	0.202	0.040	0.119	0.040
Empagliflozin 10mg		-0.85	-2.10	-3.30	0.053	0.148	0.040	0.119	0.040
Empagliflozin 25mg		-0.85	-2.00	-3.19	0.053	0.131	0.040	0.119	0.040
Canagliflozin 100mg		-0.867	-1.78	-4.82	0.053	0.208	0.040	0.119	0.040
Canagliflozin 300mg		-1.09	-2.06	-4.16	0.053	0.208	0.040	0.119	0.040
MET + insulin	Monami 2008[82]	-1.1	1.084*	0.00[+]	0.000	0.0108	0.037	0.000	0.000
Intensified insulin	Waugh 2010[83]	-1.11	1.90	0.00[+]	0.000	0.616	0.022	0.000	0.000

*It is not clear where the weight figure comes from since Monami reported only BMI .

Empaglifozin

The figures for HbA1c reduction in Table 38 are 0.85% for both doses of empagliflozin. These figures are larger than in the only trial from which Haering et al (2015) reported reductions of 0.7%. Weight reductions in table 38 are also slightly larger than in the trial – 2.2kg and 2.1 kg, compared to 1.8 and 1.7kg in the trial. SBP reductions are also about 50% higher than in the trial.

Canagliflozin

Astrazeneca Table 38 gives figures for HbA1c reductions of 0.86% on canagliflozin 100mg and 1.09% on 300mg. The two trials included in the AstraZeneca NMA, Ji 2105 and Wilding 2013, gave rather lower reductions, of 0.5% and 0.73% for 100mg, and 0.59% and 0.95% for 300mg. The trial figures for weight loss and SBP reductions in the trials are also less than in Table 38.

Insulin

Two rows are provided for insulin – metformin and insulin and "intensified insulin". The figures for the latter are attributed to Waugh 2010, but this is wrong. The AstraZeneca submission seems to assume that intensified insulin can be an increase in basal insulin by 50%. However once patients are started on insulin, it should be titrated to achieve target control. So the two insulin rows really apply to the same scenario.

One difference from ERG thinking is that when insulin is started in the AstraZeneca base case, it is assumed that all of the oral drugs except metformin are discontinued.

AstraZeneca have clarified the sources of some of their insulin assumptions. The figure of 1.11 reduction in HbA1c comes from the Heine trial of insulin versus exenatide.[84] In this trial, patients were failing to achieve good control on metformin and sulfonylureas, and had a baseline HbA1c of 8.1%, which is comparable to the Matthaei trial of dapagliflozin. For weight gain on starting insulin, AstraZeneca report in the clarifications that they use a figure of 1.6 kg from the PREDICTIVE-BMI trial, but the figure in Table 32 is 1.9kg. This is close to the 1.8 kg seen on glargine in the Heine trial. Other figures from the Heine trial that could have been used include 10% for discontinuations, 6.3% for all hypoglycaemia (events per pt/yr), and 1.5% for severe hypoglycaemia. However it should be noted that patients with a history of severe hypoglycaemia were excluded from the Heine trial so the 1.5% may under-estimate true frequency.

The AstraZeneca submission also draws insulin data from the Monami meta-analysis[82] comparing long-acting insulin analogues with NPH insulin. This assembled data from 14 trials, with a wide range of baseline HbA1c, from 7.1% to 9.6%, mean 8.7%. The mean reduction in HbA1c was 1.1%,

The figure of a reduction of 1.1% in HbA1c after starting insulin, used in the AstraZeneca submission, seems reasonable.

The ERG preference is to assume that basal insulin will be titrated to achieve target, and if that cannot be done, short-acting insulin will be added at mealtimes. Our estimates for the marginal effects of adding meal-time insulins are as used in the appraisal of the flozins in monotherapy, based on the Harmony 6 trial, in which baseline HbA1c was 8.4%;

- HbA1c reduction 0.66%
- Weight effect + 0.8kg
- Non-severe hypos 38%
- Severe hypos 0.7%
- UTIs 6.0%
- SBP no effect (not reported in this trial).

In Table 9, we replace some of the AstraZeneca NMA figures with alternatives.

Other sources.

Mearns and colleagues[85] reviewed trials of different third glucose-lowering drugs added to metformin and sulfonylureas. They concluded that the drugs fell into two groups, with one group (including canagliflozin and pioglitazone) lowering HbA1c by over 1%, and the second group (including dapagliflozin and the DPP-4 inhibitors) lowering it by 0.60-0.70%. They reported that the flozins were the only group of drugs that significantly reduced weight compared to placebo, but this seems surprising when they had trials of liraglutide and exenatide with weight losses of 1.8kg and 2.3kg respectively.

A Canadian meta-analysis (CADHT 2010)[86] of adding third drugs to metformin and sulfonylureas derived estimates for HbA1c reductions of 1.22% and 0.89% for adding basal insulin and gliptins respectively. Weight changes were increases of 0.88 kg on insulin and 1.1 kg on gliptins.

Lee et al[87] reviewed triple therapy trials and carried out a network meta-analysis. They found little difference in HbA1c reductions between the DPP-4 inhibitors and the flozins (mean reduction estimates of 0.69% (0.46 to 0.92) and 0.56% (0.42 to 0.7), but weight loss estimate of 1.79kg on flozins versus no change on gliptins.

Table 9 Treatment effects and AE parameters applied in the economic model: ERG alternative values to AstraZeneca Table 38

Variable	Source	Change from baseline *			Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
		HbA1c (%)	Weight (kg)	SBP (mmHg)					
DPP4	NMA add-on to MET + SU for change from baseline & symptomatic hypoglycaemia Schernthaner 2013 for AEs except for symptomatic hypoglycaemia	-0.76	+0.52	+ 0.5	0.015 (RCTs)	% with any hypos 27% RCTs	1.3% RCTs	0.056 (rcts)	0.021 (RCTs)
Dapagliflozin		-0.70	-1.90	-2.00	0.019	7.3% 0.073	0.0	10.1% 0.101	10.1% 0.101
Empagliflozin 10mg		-0.7	-1.75	-2.2	0.053	0.148	0.0	0.119	0.040
Empagliflozin 25mg		-0.7	-1.75	-2.2	0.053	0.131	0.0	0.119	0.040
Canagliflozin 100mg		-0.62	-1.25	-2.9	0.053	0.208	0.08	0.119	0.040
Canagliflozin 300mg		-0.77	-2.5	-2.5	0.053	0.208	0.05	0.119	0.040
Basal insulin	Waugh 2010	-1.11	1.8	0.00[+]	10%	61%	1.3%	0.000	0.000
Meal-time short-acting insulin added to basal	Monotherapy appraisal	-0.66	+ 0.8	0		38%	0.7%	0	0
Pioglitazone	RCTs	-0.87	+2.2	-0.5	-	11.6	0	0	0

Dapagliflozin figures from Matthaei et al 52 week results

4 COST EFFECTIVENESS

4.1 ERG comment on manufacturer's review of cost-effectiveness evidence

AstraZeneca carried out very broad searches for cost-effectiveness studies on all possible pharmacological interventions for patients inadequately controlled on metformin and sulfonylureas. Studies with mixed populations could be included if 85% or more were inadequately controlled on both drugs. The searches included for studies of drugs little used in the UK. Many of the 40 studies identified came from countries other than the UK and were not considered relevant. 13 studies reported costs per QALYs applicable to the UK but three were of exenatide, not considered to be a relevant comparator. Of the 10 remaining studies, the submission says that nine were sponsored by the manufacturer. However of the 10 in table 34, two were ERG reports, one on liraglutide which is not relevant, and several are SMC or NICE guidances. The submission may have meant that sponsored studies were submitted for these appraisals.

The studies or guidances are not quality assessed and are only briefly summarised in table 34. Only two are immediately relevant to this appraisal, being on dapagliflozin in triple therapy. These are the abstract by Charokopou [88] and the SMC guidance 799/12[45]. The AstraZeneca submission notes that the analysis by Charokopou and colleagues, on behalf of AstraZeneca, is similar to the analysis in the current submission, and it can add little.

4.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 10 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	The scope specifies a wide range of comparators: • Other SGLTs inhibitors • DPP-4 inhibitors • Pioglitazone • GLP-1 agonists • Sulfonylureas • Insulin The scope does not specify what treatment sequence should be assumed at intensification from oral to insulin therapy.	The therapies that are compared are: • Dapagliflozin 10mg • Canagliflozin 100mg • Canagliflozin 300mg • Empagliflozin 10mg • Empagliflozin 25mg • A basket of DPP-4 inhibitors comprising sitagliptin (71%), saxagliptin (10%), vildagliptin (3%), linagliptin (12%) and alogliptin (3%). All the above are in combination with metformin and a sulfonylurea. At intensification to insulin it is assumed that the above treatments are withdrawn and patients only receive insulin and a sulfonylurea. This is not in line with either the recent NICE clinical guideline NG28 or the recent NICE assessment of SGLT2 inhibitors for monotherapy ID756.
Patient group	As per NICE scope. "*Adults with type 2 diabetes that is inadequately controlled on dual therapy with either metformin and a sulfonylurea or metformin and a DPP-4 inhibitor*"	Broadly yes. The patient baseline characteristics are taken from the pivotal dapagliflozin trial, with a sensitivity analysis that uses those

		of the recent NICE clinical guideline NG28. But note that the pivotal dapagliflozin trial included patients with a baseline HBA1c of between 7.0% and 10.5%. As a consequence, some patients were below the NG28 intensification threshold of 7.5%.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	40 years. Given the patient baseline age of 61 years this is effectively a lifetime horizon.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The baseline QoL of 0.87 and the age related decrements are drawn from the Health Survey for England 2003. The QoL decrements for the main diabetes complications are drawn from the UKPDS 68. The QoL decrement for BMI is drawn from Bagust (2005). All these are based upon the EQ-5D. Quality of life values for UTIs and GTIs are drawn from Barry et al (1997) which uses the Index of Well-Being (IWB) administered among 62 American nurses.

Benefit valuation	Time-trade off or standard gamble	The EQ-5D UK social tariff is based upon a time trade-off exercise. The IWB was valued using an undocumented mapping technique.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	The EQ-5D UK social tariff is based upon a representative sample of the UK public. The IWB mapping appears to be based upon expert opinion.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity analyses are presented.

4.2.2 Model structure

By way of background, for much cost effectiveness modelling in T2DM the results of the UKPDS have been used. Until recently the main UKPDS publication relevant to cost effectiveness modelling was the UKPDS68.[89] This outlines a number of equations for estimating the progression of the risk factors of HbA1c, SBP, TC:HDL and smoking status through time. Given the evolution of these risk factors the UKPDS68 also specifies a number of equations that calculate the annual risk of experiencing first "events", these events being the macro-vascular complications of diabetes such as stroke and the micro-vascular complications of diabetes such as blindness. The UKPDS68 also permits the calculation of annual probabilities of death.

The UKPDS68 has recently been partially updated by the UKPDS82.[90] the latter incorporating longer follow-up data of the UKPDS. This provides an alternative more up to date set of equations to estimate

the probability of events and deaths, and also permits the estimation of the probability of some second events: MI, stroke and amputation. These may better reflect current management of diabetes. Updates to the UKPDS 68 risk factor evolution equations are planned but have yet to be published.

The CARDIFF model is a patient level simulation in C++ which attempts to largely replicate the UKPDS model of UKPDS 68 or the UKPDS 82 depending upon user choice. If the more recent UKPDS 82 event equations are applied, the risk factor evolution equations of the UKPDS 68 are retained.

As an individual patient model, a cohort of patients is sampled from an initial patient distribution based largely upon the pivotal trial. Each patient is run through the model once for each comparator treatment sequence under consideration. Patients intensify through three line of therapy:

- DPP-4i/SGLT2 + metformin + sulfonylurea; i.e. triple therapy
- Insulin + metformin
- Intensified insulin + metformin

This leads to the dapagliflozin treatment sequence being compared to five other treatment sequences on a pairwise basis.

Table 11 Treatment sequences compared

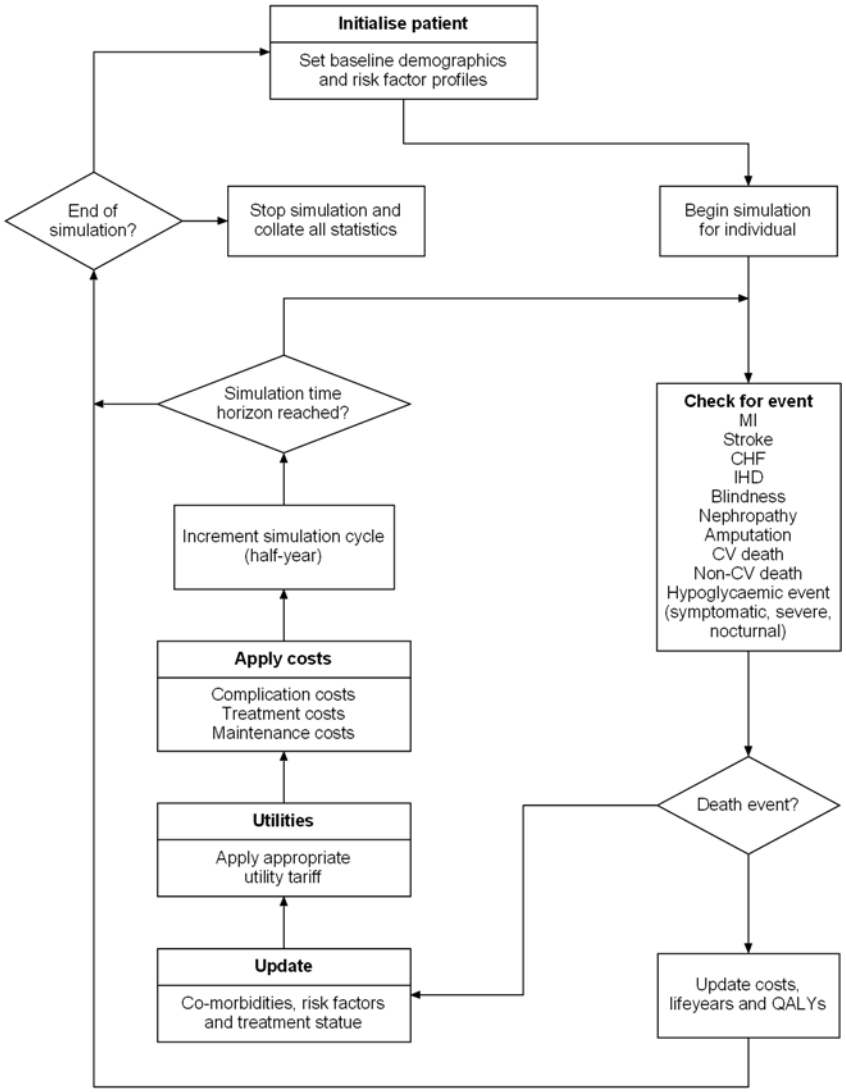
Comparator	1st line	2nd line	3rd line
Dapagliflozin	Dapa + Met + SU	Insulin + Met	Int. insulin + Met
DPP-4i	DPP-4i + Met + SU	Insulin + Met	Int. insulin + Met
Empagliflozin 10mg	Empa10 + Met + SU	Insulin + Met	Int. insulin + Met
Empagliflozin 25mg	Empa25 + Met + SU	Insulin + Met	Int. insulin + Met
Canagliflozin 100mg	Cana100 + Met + SU	Insulin + Met	Int. insulin + Met
Canagliflozin 300mg	Cana300 + Met + SU	Insulin + Met	Int. insulin + Met

The initial triple therapy is associated with a variety of clinical effects, the main ones being upon HbA1c, SBP and weight. It is assumed that there are no effects upon lipids. Adverse events and discontinuations are also modelled. HbA1c is then evolved according to the UKPDS 68 equation 11 until it breaches the NICE intensification threshold of 7.5%. When this happens the patient is modelled as intensifying to insulin, which is also associated with changes to HbA1c, SBP and weight, and the various adverse events. HbA1c is again then evolved according to the UKPDS 68 equation 11 until it breaches 7.5%, at which point the patient intensifies their insulin therapy.

Given the patient intensification timing, SBP and the total cholesterol to HDL cholesterol are evolved according to equations 12 and 13 of the UKPDS 68 taking into account the 1st line, 2nd line and 3rd line treatment effects upon these. Similarly, weight is evolved assuming an annual gain of 0.1kg except during years when a new therapy is started. Both weight gains and weight losses are assumed to be maintained for only one year.

Given the evolution of the risk factors and the patient baseline characteristics, the microvascular and macrovascular complications of diabetes can be modelled and the diabetes related deaths.

Figure 2 Model structure for diabetes complications and deaths



4.2.3 Population

The population characteristics for the base case are largely drawn from the pivotal study, with those for those starting triple therapy of the recent NICE clinical guideline NG28 THIN database being applied as a sensitivity analysis.

Table 12 Baseline values: Patient demographics

	Pivotal study		**THIN database**	
	Value	**s.e.**	**Value**	**s.e.**
Current Age (Yrs)	61.00	0.64	65.40	..
Proportion female	0.51	0.03	0.44	..
Duration diabetes (Years)	9.45	0.43	8.50	..
Height (m)	1.68	0.00	1.68	..
Proportion Afro-Caribbean	0.03	0.00	0.03	..
Proportion Indian	0.03	0.00	0.03	..
Proportion smokers	0.19	0.00	0.19	..

Table 13 Baseline values: Patient modifiable risk factors

	Pivotal study		**THIN database**	
	Value	**s.e.**	**Value**	**s.e.**
HbA1c (%)	8.15	0.06	7.90	..
Total-Cholesterol	211.97	0.21	211.97	..
HDL Cholesterol	46.72	0.06	46.72	..
LDL Cholesterol	93.85	0.00	0.00	..
SBP (mmHg)	135.40	0.09	143.20	..
Weight (kg)	89.35	1.15	86.70	..
eGFR (ml/min/1.73^2)	77.50	0.00	77.50	..
Haemoglobin (g/dl)	14.50	0.00	14.50	..
Albuminuria (mg/l)	47.00	0.00	47.00	..
White Blood Cell Count	6.80	0.00	6.80	..
Heart Rate	72.00	0.00	72.00	..

Table 14 Baseline values: Patient proportions with event clinical history

	Pivotal study		THIN database	
	Value	**s.e.**	**Value**	**s.e.**
AF	0.63%	0.04%	0.63%	..
PVD	0.47%	0.03%	0.47%	..
IHD	9.70%	0.14%	9.70%	..
MI	2.50%	0.08%	2.50%	..
CHF	2.30%	0.07%	2.30%	..
STROKE	1.80%	0.06%	1.80%	..
AMP	0.40%	0.03%	0.40%	..
BLIND	2.20%	0.07%	2.20%	..
ESRD	1.00%	0.05%	1.00%	..

Note that the recent NICE clinical guideline NG28 does provide quite extensive sampling information including a full variance-covariance matrix, but the company sensitivity analysis that uses the THIN data only applies the central values; i.e. the same representative patient is repeatedly run through the model.

After some model exploration, despite the pivotal trial standard errors being within the company model inputs it appears that these are not applied within the company base case modelling.

4.2.4 Interventions and comparators

Dapagliflozin is compared with a pooled DPP-4i comparator and the other SGLT2s, with patients being able to subsequently intensify to insulin and intensified insulin.

Table 15 Comparators and sequences

Comparator	1st line	2nd line	3rd line
Dapagliflozin	Dapa + Met + SU	Insulin + Met	Int. insulin + Met
DPP-4i	DPP-4i + Met + SU	Insulin + Met	Int. insulin + Met
Empagliflozin 10mg	Empa10 + Met + SU	Insulin + Met	Int. insulin + Met
Empagliflozin 25mg	Empa25 + Met + SU	Insulin + Met	Int. insulin + Met
Canagliflozin 100mg	Cana100 + Met + SU	Insulin + Met	Int. insulin + Met
Canagliflozin 300mg	Cana300 + Met + SU	Insulin + Met	Int. insulin + Met

4.2.5 Perspective, time horizon and discounting

The perspective for costs is that of the PHS/PSS while the perspective for benefits is that of the patient. The time horizon is 40 years which is effectively a lifetime horizon. Costs and benefits are discounted at 3.5%.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

The treatment effectiveness estimates for HbA1c, SBP, weight and hypoglycaemia events are drawn from the company NMA preferred analysis: the study endpoints restricted network NMA. The results relative to the reference treatment of the NMA, placebo + MET + SU, were added to the NMA estimate of the absolute change for the reference placebo + MET +SU. The following presents these for HbA1c, SBP and weight. Hypoglycaemia event rates were estimated from odds ratios and their calculation is a little more involved, but they have little impact upon the company final results. They have not been presented below for reasons of space.

Table 16 Treatment effects: changes relative to reference and absolute reference effect

	HbA1c	Weight	SBP
Reference Placebo + MET + SU absolute	-0.150	-0.300	-1.092
Comparator changes relative to reference placebo + MET + SU			
DPP-4i	-0.643	0.420	2.940
Dapa	-0.703	-1.901	-2.038
Empa10	-0.698	-1.803	-2.212
Empa25	-0.699	-1.698	-2.099
Cana100	-0.716	-1.478	-3.731
Cana300	-0.944	-1.759	-3.070
Pioglitazone	-0.875	2.035	2.444

Notable in the above is that while pioglitazone is associated with weight gain and a worsening of blood pressure, the company NMA finds it to be quite effective in terms of HbA1c.

These can be equivalently expressed as changes for dapagliflozin relative to the other comparators in order to permit a direct read across to tables 26, 27 and 28 of the submission.

Table 17 Treatment effects: changes for dapagliflozin relative to comparators

	HbA1c	Weight	SBP
Placebo + MET + SU	-0.703	-1.901	-2.038
DPP-4i	-0.060	-2.321	-4.978
Dapa	..	..	..
Empa10	-0.005	-0.098	0.174
Empa25	-0.005	-0.203	0.061
Cana100	0.013	-0.423	1.693
Cana300	0.241	-0.142	1.032

The above values are, with some minor differences, broadly the same as those reported for the random effects base case of tables 26, 27 and 28. Note that pioglitazone has been dropped from the list of comparators within the economics despite being within the company NMA. At central estimates pioglitazone is estimated to be superior to dapagliflozin in terms of HbA1c, but worse in terms of weight and SBP.

The treatment effects assumed for the move to insulin and to intensified insulin are stated as being drawn from Monami et al[91] and Waugh et al [83] and are as below.

Discontinuation rates, UTI rates and GTI rates are assumed to be the same for all SGLT2-is. Severe and non-severe hypoglycaemia event rates are estimated from treatment specific total event rate and proportions of events that are severe.

Table 18 Treatment effects: change from baseline

						Hypoglycaemia events					
	HbA1c	Weight		SBP	Discon.	Total	% Sev.	Severe	NSev	UTI	GTI
DPP-4i	-0.790	0.120		1.850	2.9%	0.181	3.4%	0.006	0.175	2.1%	5.6%
Dapa	-0.850	-2.200		-3.130	5.3%	0.202	4.0%	0.008	0.194	11.9%	4.0%
Empa10	-0.850	-2.100		-3.300	5.3%	0.148	4.0%	0.006	0.142	11.9%	4.0%
Empa25	-0.850	-2.000		-3.190	5.3%	0.131	4.0%	0.005	0.126	11.9%	4.0%
Cana100	-0.867	-1.780		-4.820	5.3%	0.208	4.0%	0.008	0.200	11.9%	4.0%
Cana300	-1.090	-2.060		-4.160	5.3%	0.208	4.0%	0.008	0.200	11.9%	4.0%
Insulin	-1.100	1.084		..	..	0.011	3.7%	0.000	0.010		
Int. Ins.	-1.110	1.900		..	..	0.616	2.2%	0.014	0.602		

The extrapolations of HbA1c, SBP and the total cholesterol to HDL cholesterol ratio are based upon equations 11, 12 and 13 of the UKPDS 68. When HbA1c rises above 7.5% it is assumed that triple therapy treatment is withdrawn with patients switching to insulin + metformin. When HbA1c again rises above 7.5% patients intensify their insulin therapy. This yields a sawtooth pattern for HbA1c and SBP given the treatment effectiveness estimates for insulin and intensified insulin. Cholesterol is unaffected throughout due to no treatment effects being applied to it.

The extrapolation of weight assumes that initial changes for the triple therapies are only maintained for one year. This is coupled with an assumption of a +0.1kg per year annual drift as has been applied in a number of other NICE assessments of treatments for type 2 diabetes. The rebound to natural history for weight losses is in line with the recent NICE clinical guideline and MTA of SGLT2-is for monotherapy, but these also assumed that weight gains would be maintained. As a consequence, for weight changes the current assessment may be very slightly conservative for the comparison with the DPP-4is given their central estimate of a weight gain of 0.12kg. The weight gains associated with intensifying to insulin and intensified insulin are assumed to be maintained indefinitely.

The following graphs are for a patient with the central baseline characteristics who has the central clinical effectiveness estimates applied to them[1].

[1] Values taken from the *Biannual_Risk_Factors* worksheet of the submitted model

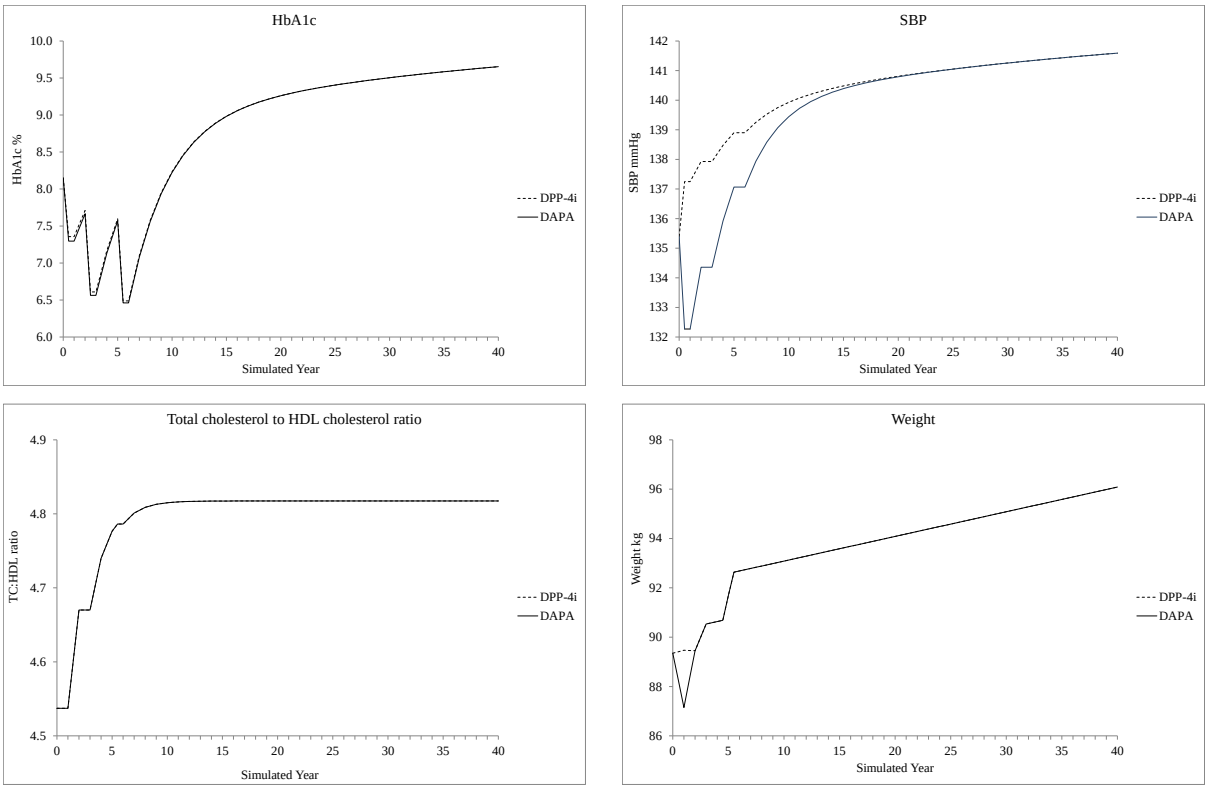


Figure 3 Evolution of HbA1c, SBP, TC:HDL ratio and weight: Dapagliflozin vs DPP-4i

For the base case comparison of dapagliflozin with the composite DPP-4i this results in survival curves that are in effect indistinguishable, though a small survival gain is modelled for dapagliflozin.

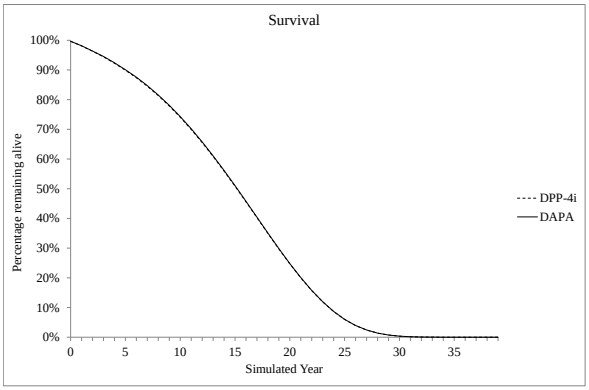


Figure 4: Survival curves: Dapagliflozin vs DPP-4i

4.2.7 Health related quality of life

There are five main elements to the quality of life values of the model.

- The age related quality of life without complications
- The disutility associated with complications

- The disutility associated with UTIs and GTIs
- The disutility associated with hypoglycaemia
- The disutility associated with weight gain

The age related quality of life without complications

Study 5 reported a mean baseline EQ-5D quality of life of 0.85. The company applies a baseline mean of 0.87 for those with no complications as derived from age adjusted Health Survey for England (2003) data. This is further reduced through age adjustment over the remainder of the model.

The disutility associated with complications

The disutility associated with complications is largely derived from the UKPDS 62.[92] As this does not provide a disutility for ESRD the value for this is taken from Currie et al[93]. For those with more than one complication disutilities are assumed to be additive.

Table 19 Company disutility of complications

	Disutility
IHD	-0.090
MI	-0.055
CHF	-0.108
Stroke	-0.164
Blindness	-0.074
Amputation	-0.280
ESRD	-0.263

The disutility associated with UTIs and GTIs

QALY decrements for UTIs and GTIs of 0.00283 are taken from Barry et al.[94] These are as per the company submission to the recent MTA of SGLT2-is for monotherapy, the AG report of which noted that "*For UTIs the average of the values of Barry et al of -0.3732 for pyelonephritis and of -0.2894 for dysuria appears to have been coupled with an assumed duration of around three days to yield a QALY decrement of -0.00283 per UTI. Apparently no values were found for GTIs and as a consequence these had the same disutility applied*".

The disutility associated with hypoglycaemia

The disutility associated with hypoglycaemia is based upon the study of Currie et al[95] an industry sponsored study that developed a model of how the fear of hypoglycaemia and hypoglycaemic event rates determine patients' EQ-5D quality of life scores. This is reviewed in greater detail in the ERG critique below.

The disutility associated with weight gain

The Baghust & Beale[96] coefficient of -0.0061 per BMI point above 25kgm^{-2} is applied. This has been used in a large number of other NICE assessments in T2DM.

It appears that within the modelling this is applied to both weight gains and weight losses associated with treatment. As a consequence, it may be applied to patients with a BMI of less than 25kgm^{-2}. This could slightly benefit dapagliflozin compared to the DPP4-i, but would be of only very marginal benefit for dapagliflozin compared to the other SGLT2-is. Given the mean baseline BMI of 32kgm^{-2} this is likely to be of minimal importance even when patient baseline characteristics are being sampled.

4.2.8 Resources and costs

Direct drug costs

The costs of the SGLT2-is are as below, with the cost of the DPP-4i being taken to be a market share weighted average as outlined below.

Table 20 Direct drug costs

	Cost	Tablets	mg	Dose	Share	Annual
Dapagliflozin	£36.59	28	10	10		£477
Canagliflozin 100	£39.20	30	100	100		£477
Canagliflozin 300	£39.20	30	300	300		£477
Empagliflozin 10	£36.59	28	10	10		£477
Empagliflozin 25	£36.59	28	25	25		£477
Sitagliptin	£33.26	28	100	100	71%	£434
Saxagliptin	£31.60	28	5	5	10%	£412
Vildagliptin	£33.35	56	50	100	3%	£435
Linagliptin	£33.26	28	5	5	12%	£434
Alogliptin	£26.60	28	25	25	3%	£347
DPP-4i						£424
Insulin	£0.0055kg-1 per day for 90kg patient					£181
Intensified insulin	£0.0082kg-1 per day for 90kg patient					£269

Additional annual costs of metformin £25.29 and of sulfonylurea £29.46 are listed in the submission but have not been applied.

Insulin therapy is somewhat less expensive than the initial triple therapies. Intensification to insulin is based upon triple therapy discontinuation rates and the evolution of HbA1c. As a consequence, a treatment with a lower discontinuation rate such as the DPP4-i or a greater initial treatment efficacy upon HbA1c such as canagliflozin 300mg will tend to cause patients to intensify to insulin therapy at a later date. This will tend to increase the direct drug costs in these arms above those of dapagliflozin.

Administration and monitoring costs

A one off cost of renal function testing of £45 for a GP appointment and £2 for the test itself has been applied to dapagliflozin triple therapy.

There is no allowance for self-monitoring of blood glucose (SMBG) or needle use in the insulin regimes. Given the company treatment sequences this may cause the company analyses to be biased against the DPP4-i and canagliflozin 300mg.

Severe hypoglycaemia costs

Severe hypoglycaemia events are costed at £380 based upon Hammer et al.[97]

Adverse event costs

UTIs and GTIs are assumed to cost one GP visit at £45. The company acknowledges that this does not include the associated drug costs of treatment.

Ongoing medical costs and the costs of complications

The costs of having no complications and of having complications are taken from the UKPDS 65[98] rather than the UKPDS 84[99] which provides an updated version of these costs. For those with none of the complications of diabetes that are modelled an annual £465 cost for ongoing medical care is applied. The costs of the complications are as below.

Table 21 Company costs of diabetes complications: UKPDS 65

	1st year		
Event	Fatal	Non-fatal	Subs. Years
Ischaemic Heart Disease	..	£3,346	£1,105
Myocardial Infarction	£1,695	£6,451	£1,062
Congestive Heart Failure	£3,731	£3,731	£1,308
Stroke	£4,977	£3,946	£746
Amputation	£12,847	£12,847	£742
Blindness	..	£1,685	£714
ESRD (including dialysis)	£35,715	£35,715	£35,631

4.2.9 Cost effectiveness results

The company base cases appear to have been run over 5,000 patients. The company model does not permit the presentation of QALYs by source apparently.

Table 22 Company base case results

	Dapa	DPP-4i	Empa10	Empa25	Cana100	Cana300
Cost	£20,417	£20,529	£20,456	£20,410	£20,351	£20,610
net Costs		-£112	-£38	£8	£66	-£192
LYs	11.60	11.57	11.60	11.60	11.61	11.60
net LYs		0.026	0.000	0.000	-0.008	-0.004
QALYs	9.62	9.58	9.61	9.61	9.62	9.61
net QALYs		0.032	0.005	0.006	-0.001	0.003
ICER		Dominant	Dominant	£1,354	Dominated	Dominant

Discussion of the company base case modelling as re-run by the ERG over 25,000 patients is presented in section 5.3.1 below and the reader is referred to this for the detail rather than the following bulleted brief summary. That said, the following brief summary captures the main points of interest. These are:

- The slightly superior clinical effectiveness estimates for dapagliflozin compared to the DPP-4i result in lower complications and costs of complications with these more than offsetting the additional direct treatment costs of dapagliflozin. They also result in QALY gains which are further augmented by the superior weight profile of dapagliflozin, and dominance results.
- Slightly higher costs and worse outcomes for the comparison with canagliflozin 100mg resulting in dapagliflozin being dominated.
- The slightly inferior clinical effectiveness estimates for dapagliflozin compared to canagliflozin 300mg result in higher complications and costs of complications. Their additional costs are more than offset by patients intensifying to insulin more quickly and so discontinuing their relatively expensive oral therapies. The QALY impacts of the complications are more than offset by the weight profile and hypoglycaemia event rates, with the latter possibly being biased by the base case not applying hypoglycaemia event rates to insulin.

The company has further clarified the 0.032 QALY gains for the comparison with the DPP4-i as arising from the following sources:

- A small loss of 0.0004 QALYs, or 1% of the total, due to AEs
- A negligible loss due to hypoglycaemia
- A gain of 0.0041 QALYs, or 13% of the total, due to BMI
- A gain of 0.0283 QALYs, or 88% of the total, due to long term complications, which the ERG takes to also include any survival effects.

It should be borne in mind that the CARDIFF model only allows pairwise comparisons to be made and that the above company presentation combines a number of different model runs. The values may not be entirely comparable and the reliability of the signs of estimates of very small differences is questionable. But a full incremental analysis would suggest that canagliflozin 100mg dominates all other treatments. Given the differences that are being estimated this is quite a strong statement and the general impression is that there is broad equivalence over the clinical effects. Cost differences with the DPP-4i and canagliflozin 300mg may appear to be more reliably estimated, but for the latter these differences may be mainly a function of assuming that patients cease their relatively expensive oral therapies when they intensify to insulin.

The full company PSA results can be found in section 5.11 [page 165] of the company submission. Note that the probabilistic modelling treats the evolution of the risk factors deterministically and so probably underestimates the uncertainty. The company has at clarification supplied the central estimates of the PSA.

Table 23 Central probabilistic estimates: dapagliflozin versus comparators

	Δ Costs	Δ QALYs	ICER
DPP4-i	-£140	0.039	Dominant
Cana100	£58	0.004	£16,612
Cana300	-£104	0.002	Dominant
Empa10	£13	0.005	£2,754
Empa25	£11	0.005	£1,978

There is little to be gleaned from the scatter plots which are broadly centred around the origin and to the eye are symmetric around an upward sloping line through the origin. The pairwise CEACs suggest that the likelihood of dapagliflozin being the most cost effective:

- compared to the DPP-4i dapagliflozin is slightly higher at around 60% for willingness to pay values of up to around £10k per QALY, but then converges to around a 55% likelihood.
- compared to both empagliflozin 10mg and empagliflozin 25mg is virtually equivalence.
- compared to canagliflozin 100mg is initially a likelihood of slightly less than 50% for willingness to pay values of less than £10k per QALY but that this rapidly converges to virtual equivalence.

- compared to canagliflozin 300mg is initially a likelihood of up to 60% for willingness to pay values of less than £10k per QALY but that this rapidly converges to virtual equivalence.

4.2.10 Sensitivity analyses

The company presents a range of scenario analyses for the comparison of dapagliflozin with the DPP-4i.

- SA01: Revising the patient baseline characteristics to be from the THIN database that underlies the recent NICE clinical guideline, from the NMA full network and from the NMA restricted network.
- SA02: Revising the baseline HbA1c to be 7.5% based upon NICE guidelines, 7.9% apparently based upon the THIN database coupled, perhaps oddly, with an additional assumption that dapagliflozin weight loss is maintained for 2 years, and 8.24% taken from an NMA of metformin and sulfonylureas
- SA03: Revising the intensification thresholds for the move from insulin to intensified insulin to 8.0%, and to 8.0% for all intensifications after triple therapy.
- SA04: Using the full NMA network.
- SA05: Using the more recent UKPDS 84 costs of complications.
- SA06: Including costs associated with BMI according to the UK Counterweight Project Team.
- SA07: Applying BMI disutilities of 0.014 and 0.0038 per BMI point.
- SA08: Not including adverse event disutilities.
- SA09: Revising the UTI and GTI decrements to the confidence intervals from Barry et al of 0.0104 QALYs and 0.000657 QALYs.
- SA10: Using the more recent UKPDS 82 event equations.
- SA11: Assuming no discontinuations and that the DPP-4i discontinuation rate is the same as that of dapagliflozin.
- SA12: Assuming no prior history of cardio vascular disease in the patient cohort.
- SA13: Assuming that patients retain their oral therapies when they intensify to insulin therapy.
- SA14: Assume that weight changes are retained indefinitely.

These result in the following.

Table 24 Company scenario analyses: dapagliflozin versus DPP-4i

Scenario	Base value	New value	ΔCosts	ΔQALYs	ICER
Base case	..	..	-£112	0.032	Dominant
SA01: Patient chars	Study 5	THIN data	-£51	0.039	Dominant
		NMA full	-£261	0.089	Dominant
		NMA restricted	-£108	0.028	Dominant
SA02: Baseline HbA1c	8.15%	7.50%	£240	0.020	£12,256
		7.90%	-£51	0.029	Dominant
		8.24%	-£112	0.032	Dominant
SA03: Intens. thresholds	7.5% and 7.5%	7.5% and 8.0%	-£104	0.032	Dominant
		8.0% and 8.0%	£7	0.028	£246
SA04: Network for NMA	Restricted	Full	-£75	0.027	Dominant
SA05: Complication costs	UKPDS 65	UKPDS 84	-£142	0.032	Dominant
SA06: BMI costs	None	UK Counterweight	-£122	0.032	Dominant
SA07: BMI Disutility	-0.0061	-0.0140	-£112	0.037	Dominant
		-0.0038	-£112	0.030	Dominant
SA08: AE disutility	?????	None	-£112	0.032	Dominant
SA09: UTI/GTI QALY	-0.00283	-0.010400	-£112	0.031	Dominant
		-0.000657	-£112	0.032	Dominant
SA10: Event equations	UKPDS 68	UKPDS 82	£71	0.018	£3,914
SA11: Discontinuations	DPP-4i 2.9% and	None	-£104	0.034	Dominant
	Dapa 5.3%	5.3% and 5.3%	-£107	0.033	Dominant
SA12: CV history	Various*	None	-£111	0.031	Dominant
SA13: Orals with insulin	Discontinued	Retained	£431	0.032	Dominant
SA14: Weight change dur.	2 years	Indefinite	-£115	0.035	Dominant
*0.6% AF, 9.7% IHD, 2.5% MI, 2.3% CHF, 1.8% stroke					

The main sensitivities are to whether the baseline HbA1c is likely to be less than that of study 5, whether intensification to insulin occurs later, whether it is more appropriate to use the recent UKPDS 82 event equations and whether patients remain on their oral treatments when intensifying to insulin.

These scenario analyses are not presented for the comparisons with the other SGLT2-is.

4.2.11 Model validation and face validity check

Internal and external validation

Given the black box nature of the C++ of the model there is little that the ERG can present in terms of model validation. Internal validation relates to whether the model replicates the trials that were used to construct it. External validation relates to whether the model replicates trials that were not used in its construction.

McEwan et al[100]present the results of using the CARDIFF model to predict the validation endpoints of 12 pivotal T2DM trials using both the UKPDS 68 equations and the UKPDS 82 equations. The overall R^2 was similar though slightly better for the UKPDS 82 at 0.870 compared to 0.851 for the UKPDS 68. Internal validation suggested mean absolute percentage errors of 44% when the UKPDS 82 was used compared to 40% for the UKPDS 68. But external validation suggested a mean absolute percentage error when the UKPDS 82 was used of 38% compared to 54% for the UKPDS 68.

Validation of the evolution of the risk factors

The evolution of the risk parameters, HbA1c, SBP, the TC:HDL ratio and BMI are modelled in the VBA of the excel front end to the model. The ERG has cross checked the implementation of these and found that the evolutions of HbA1c, SBP, the TC:HDL ratio largely conform to equations 11, 12 and 13 of the UKPDS 68. But equations 11, 12 and 13 of the UKPDS 68 make a distinction between values at diagnosis and, in effect, values at baseline. The company modelling assumes that values at diagnosis will have been equal to those at baseline. This is unlikely to be correct. The THIN data base alluded to by the company in table 37 provides the baseline characteristics that were applied within the recent NICE clinical guideline among those intensifying to triple therapy.

To explore the impact of this discrepancy the value at diagnosis can be set equal to the baseline value of 8.15% as assumed by the company or equal to the 7.69% of the THIN database. Equation 11 of the UKPDS 68 can then be applied for a patient with a 9.45 duration of diabetes, a baseline HbA1c of 8.15% and two hypothetical treatments, one reducing HbA1c by 0.5% and the other by 1.0%.

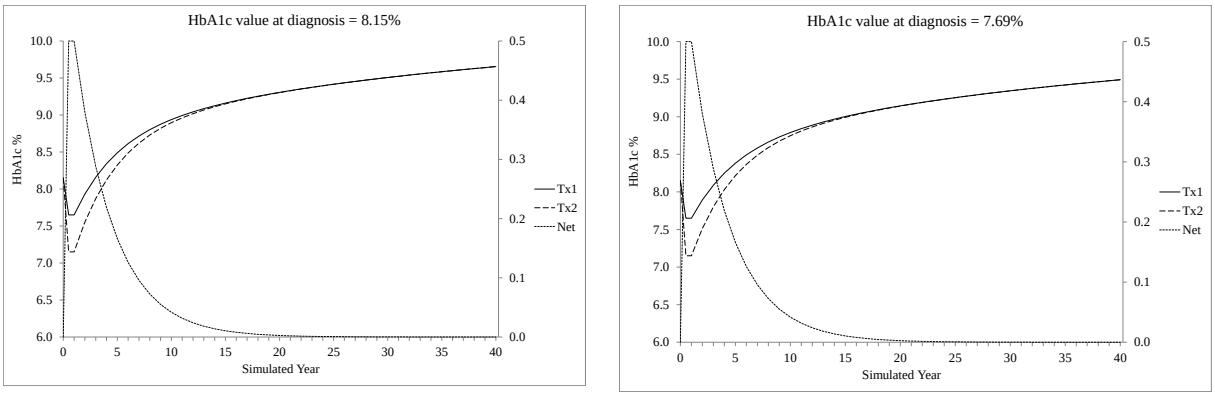


Figure 4 Impact of different HbA1c values at diagnosis on HbA1c evolution

Both arms have a common amount added within equation 11 of the UKPDS 68 of 0.085 * (Value at diagnosis – 7.09). As a consequence the net difference between the two arms is the same whether the value at diagnosis is taken to be 7.69% as per the recent NICE clinical guideline modelling or the baseline value of 8.15% as assumed by the company.

But the amount added to an arm, 0.085 * (Value at diagnosis – 7.09) is affected by whether the value is 7.69% or 8.15%. The 7.69% value causes HbA1c to converge at a lower value over time than the 8.15% value: after 40 years to 9.49% rather than 9.69%. This means that the model will tend to overestimate complication rates and deaths. This error was also identified in the previous STA of dapagliflozin [TA288][101] and it seems surprising for it to recur within the CARDIFF model.

Retaining the company error, an ERG cross check rebuild of the evolutions of the risk factors shows a very good correspondence with those of the company model. Only SBP is marginally out by around 0.5mmHg and as this applies to both arms it is unlikely to have any practical impact upon model results.

The parameters of equations 11, 12 and 13 of the UKPDS 68 have been supplied as lookup value samples to the Mt. Hood challenge participants. Within the company model these elements have not been implemented probabilistically within the PSA analysis.

Barring the error of assuming that the value at baseline is synonymous with the value at diagnosis which was on average 9 years earlier, the evolution of HbA1c, SBP and the TC:HDL ratio corresponds with equations 11, 12 and 13 of the UKPDS 68. But there may be an error in the implementation of switching therapies. At central values, in the DPP4-i arm it appears that patients remain above 7.5% HbA1c for two six month cycles before intensifying while in the dapagliflozin arm it appears that patients remain above 7.5% HbA1c for only one cycle. As a consequence, for the company base case patients in the DPP4-i arm

may tend to remain on the more expensive triple therapy for longer than those in the dapagliflozin arm after having exceeded the HbA1c switching threshold.

The company has confirmed at clarification that intensifications due to breaching the intensification threshold are based upon an annual cycle, despite the six month cycle of the model. This may tend to exaggerate differences in treatment costs that arise from differences in the timing of intensification to insulin.

Face validity

Given:

- The clinical inputs
- The treatment sequences modelled
- The costs of triple therapies compared to insulin

Results are much as would be expected, with the differences in costs largely being the result of differences in the timings of intensifications determining the direct drug costs and there being broad clinical equivalence.

4.3 ERG cross check and critique

4.3.1 Base case results

Due to the C++ of the modelling of complications and death being a black box to the ERG it cannot be rebuilt or cross checked. Re-running the base cases over 25,000 patients and 5,000 model runs results in the following estimates for the pairwise comparisons.

Comparison with DDP-4i

Table 25 Pairwise comparison of dapagliflozin and DPP-4i: Events

Events	DPP-4i		Dapagliflozin		Difference
	Non-Fatal	Fatal	Non-Fatal	Fatal	
Macrovascular					
Ischaemic Heart Disease	8.42%	0.00%	8.35%	0.00%	-0.07%
Myocardial Infarction	10.85%	14.54%	10.72%	14.43%	-0.24%
Congestive Heart Failure	7.84%	0.86%	7.78%	0.85%	-0.07%
Stroke	6.45%	1.87%	6.29%	1.84%	-0.20%
Microvascular					
Blindness	4.71%	0.00%	4.71%	0.00%	0.00%
Nephropathy	2.29%	0.25%	2.21%	0.24%	-0.08%
Amputation	2.88%	0.33%	2.83%	0.33%	-0.05%
Deaths from complications					
Macrovascular		17.27%	0.00%	17.13%	-0.14%
Microvascular		0.58%	0.00%	0.57%	-0.01%

Table 26 Pairwise comparison of dapagliflozin and DPP-4i: Costs

Costs	DPP-4i	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£1,849	£1,843	-£6
Myocardial Infarction	£1,510	£1,489	-£20
Congestive Heart Failure	£923	£915	-£8
Stroke	£618	£601	-£18
Microvascular			
Blindness	£403	£403	£0
Nephropathy	£6,156	£5,982	-£174
Amputation	£376	£368	-£8
Hypoglycaemia	£40	£45	£5
Adverse Events	£8	£16	£8
Treatment	£3,254	£3,350	£96
Indirect Diabetes Costs	£5,383	£5,395	£12
Total	£20,519	£20,406	-£113

Table 27 Pairwise comparison of dapagliflozin and DPP-4i: Cost effectiveness

Cost effectiveness	DPP-4i	Dapa	Difference
Discounted Cost	£20,519	£20,406	-£113
Discounted QALYs	9.586	9.618	0.032
Discounted Life Years	11.576	11.602	0.026
Cost per QALY			Dominant
Cost per Life Year			Dominant

Event rates are slightly higher in the DPP-4i arm resulting in slightly higher deaths from complications and a small survival gain for dapagliflozin. Given the current ERG understanding of the model and 1st order sampling, the reason for the increase in treatment costs is unclear. The higher discontinuation rate for dapagliflozin would be expected to cause patients to move more quickly onto the cheaper insulin regimes. The source may be the slight improvement in survival, but this seems unlikely. The higher treatment costs are more than offset by the reduced costs of complications and in particular the costs of nephropathy. Given the weight loss associated with dapagliflozin compared to the slight weight gain associated with the DPP-4i this further increases the QALY gains from dapagliflozin to 0.032 QALYs resulting in dapagliflozin dominating the DPP-4i.

When compared to the company modelling the mean costs are around £100 higher but this applied to both arms and the net costs are virtually identical, as are the net QALYs.

Comparison with empagliflozin 10mg

The modelling comparing dapagliflozin with empagliflozin 25mg suggests that there are no differences in event rates at the 0.00% level. Costs are also near identical as outlined below.

Table 28 Pairwise comparison of dapagliflozin and empagliflozin 25mg: Costs

Costs	Empa10	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£1,843	£1,843	£0
Myocardial Infarction	£1,489	£1,489	£0
Congestive Heart Failure	£914	£915	£0
Stroke	£600	£601	£1
Microvascular			
Blindness	£403	£403	£0
Nephropathy	£5,977	£5,982	£5
Amputation	£367	£368	£0
Hypoglycaemia	£40	£45	£4
Adverse Events	£16	£16	£0
Treatment	£3,399	£3,350	-£49
Indirect Diabetes Costs	£5,395	£5,395	£0
Total	£20,444	£20,406	-£38

Table 29 Pairwise comparison of dapagliflozin and empagliflozin 10mg: Cost effectiveness

Cost effectiveness	Empa10	Dapa	Difference
Discounted Cost	£20,444	£20,406	-£38
Discounted QALYs	9.613	9.618	0.005
Discounted Life Years	11.602	11.602	0.000
Cost per QALY			Dominant
Cost per Life Year			£79,898

The source of the £49 reduction in treatment costs for dapagliflozin is unclear given the inputs of table 38 and empagliflozin 10mg being assumed equivalent to dapagliflozin in terms of both the HbA1c effect and the discontinuation rate. The ERG had thought that the source might be not applying the one off renal function monitoring costs of £47 in the empagliflozin 10mg arm, but it appears that this is not the case if the model is correctly reporting results as these should appear in the indirect diabetes costs. However, the company at clarification has stated that renal monitoring costs were only applied for dapagliflozin, so this may be the source of most of the cost differences.

Empagliflozin 10mg and dapagliflozin are essentially estimated to be little different, with the possible exception of a very slightly superior weight profile for dapagliflozin yielding a very small QALY gain.

When compared to the company modelling the mean costs are similar and the net costs are virtually identical, as are the net QALYs.

Comparison with empagliflozin 25mg

The modelling comparing dapagliflozin with empagliflozin 25mg suggests that there are no differences in event rates at the 0.00% level. Costs are also near identical as outlined below.

Table 30 Pairwise comparison of dapagliflozin and empagliflozin 25mg: Costs

Costs	Empa25	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£1,843	£1,843	£0
Myocardial Infarction	£1,489	£1,489	£0
Congestive Heart Failure	£915	£915	£0
Stroke	£601	£601	£0
Microvascular			
Blindness	£403	£403	£0
Nephropathy	£5,980	£5,982	£2
Amputation	£368	£368	£0
Hypoglycaemia	£39	£45	£6
Adverse Events	£16	£16	£0
Treatment	£3,350	£3,350	£0
Indirect Diabetes Costs	£5,395	£5,395	£0
Total	£20,398	£20,406	£8

Table 31 Pairwise comparison of dapagliflozin and empagliflozin 25mg: Cost effectiveness

Cost effectiveness	Empa25	Dapa	Difference
Discounted Cost	£20,398	£20,406	£8
Discounted QALYs	9.613	9.618	0.006
Discounted Life Years	11.602	11.602	0.000
Cost per QALY			£1,421
Cost per Life Year			£113k

Empagliflozin 25mg and dapagliflozin are essentially estimated to be equivalent, with the possible exception of a very slightly superior weight profile for dapagliflozin yielding a very small QALY gain.

When compared to the company modelling the mean costs are similar and the net costs are virtually identical, as are the net QALYs.

Comparison with Canagliflozin 100mg

Table 32 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Events

Events	Canagliflozin 100		Dapagliflozin		Difference
	Non-Fatal	Fatal	Non-Fatal	Fatal	
Macrovascular					
Ischaemic Heart Disease	8.32%	0.00%	8.35%	0.00%	0.03%
Myocardial Infarction	10.68%	14.39%	10.72%	14.43%	0.08%
Congestive Heart Failure	7.75%	0.85%	7.78%	0.85%	0.02%
Stroke	6.23%	1.83%	6.29%	1.84%	0.06%
Microvascular					
Blindness	4.71%	0.00%	4.71%	0.00%	0.00%
Nephropathy	2.19%	0.24%	2.21%	0.24%	0.02%
Amputation	2.82%	0.33%	2.83%	0.33%	0.01%
Deaths from complications					
Macrovascular		17.08%	0.00%	17.13%	0.05%
Microvascular		0.57%	0.00%	0.57%	0.00%

Table 33 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Costs

Costs	Cana100	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£1,841	£1,843	£2
Myocardial Infarction	£1,483	£1,489	£7
Congestive Heart Failure	£912	£915	£3
Stroke	£595	£601	£6
Microvascular			
Blindness	£404	£403	£0
Nephropathy	£5,928	£5,982	£55
Amputation	£365	£368	£3
Hypoglycaemia	£45	£45	£0
Adverse Events	£16	£16	£0
Treatment	£3,352	£3,350	-£2
Indirect Diabetes Costs	£5,399	£5,395	-£4
Total	£20,339	£20,406	£67

Table 34 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Cost effectiveness

Cost effectiveness	Cana100	Dapa	Difference
Discounted Cost	£20,339	£20,406	£67
Discounted QALYs	9.619	9.618	-0.001
Discounted Life Years	11.610	11.602	-0.008
Cost per QALY			Dominated
Cost per Life Year			Dominated

Due to the slightly worse treatment effects from dapagliflozin upon HbA1c and SBP, canagliflozin 100mg is estimated to result in fewer complications which results in both lower costs and a slightly superior survival. There is a smaller difference in net QALYs than in net life years, which is probably due to dapagliflozin's slightly superior weight profile. Canagliflozin 100mg is estimated to formally dominate dapagliflozin, but the differences in costs and outcomes are slight.

When compared to the company modelling the mean costs are similar and the net costs are virtually identical, as are the net QALYs.

Comparison with Canagliflozin 300mg

Table 35 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Events

Events	Canagliflozin 300		Dapagliflozin		Difference
	Non-Fatal	Fatal	Non-Fatal	Fatal	
Macrovascular					
Ischaemic Heart Disease	8.32%	0.00%	8.35%	0.00%	0.02%
Myocardial Infarction	10.72%	14.34%	10.72%	14.43%	0.09%
Congestive Heart Failure	7.73%	0.85%	7.78%	0.85%	0.05%
Stroke	6.25%	1.82%	6.29%	1.84%	0.05%
Microvascular					
Blindness	4.67%	0.00%	4.71%	0.00%	0.03%
Nephropathy	2.21%	0.24%	2.21%	0.24%	0.01%
Amputation	2.78%	0.32%	2.83%	0.33%	0.06%
Deaths from complications					
Macrovascular		17.01%	0.00%	17.13%	0.12%
Microvascular		0.56%	0.00%	0.57%	0.01%

Table 36 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Costs

Costs	Cana300	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£1,844	£1,843	-£1
Myocardial Infarction	£1,489	£1,489	£0
Congestive Heart Failure	£913	£915	£2
Stroke	£598	£601	£2
Microvascular			
Blindness	£403	£403	£0
Nephropathy	£5,971	£5,982	£11
Amputation	£361	£368	£6
Hypoglycaemia	£66	£45	-£21
Adverse Events	£22	£16	-£6
Treatment	£3,535	£3,350	-£185
Indirect Diabetes Costs	£5,397	£5,395	-£2
Total	£20,599	£20,406	-£193

Table 37 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Cost effectiveness

Cost effectiveness	Cana300	Dapa	Difference
Discounted Cost	£20,599	£20,406	-£193
Discounted QALYs	9.616	9.618	0.003
Discounted Life Years	11.606	11.602	-0.004
Cost per QALY			Dominant
Cost per Life Year			£51,012

Despite canagliflozin 300mg being estimated to be more effective than dapagliflozin in terms of event rates and survival, the small cost savings that result are more than offset by additional costs of hypoglycaemia and in particular treatment. It appears likely that this is the result of canagliflozin 300mg being penalised for its greater impact upon HbA1c, as this causes patients to remain on the expensive triple therapy for longer than in the dapagliflozin arm. Due to the modelling also apparently assuming that there are no hypoglycaemic events associated with insulin this also increases the cost and QALY impacts of hypoglycaemia in the canagliflozin 300mg arm compared to the dapagliflozin arm. When coupled with the very slight additional weight loss from dapagliflozin this causes dapagliflozin to yield an additional 0.003 QALYs compared to canagliflozin 300mg despite having an inferior survival estimate, and so to dominate canagliflozin 300mg.

When compared to the company modelling the mean costs are similar and the net costs are virtually identical, as are the net QALYs.

Probabilistic modelling

The ERG has not re-run the company PSA analyses due to time constraints and only provides a brief summary of the company PSA results in section 5.2.9 above. Note that the probabilistic modelling treats the evolution of the risk factors deterministically and so probably underestimates the uncertainty.

4.3.2 Data Inputs: Submission correspondence with sources cited and the literature

Patient baseline characteristics

The company baseline characteristics cross check with those of the pivotal study with the exceptions of baseline total cholesterol which is given as 176mg/dl at baseline rather than the 212mg/dl of table 37 of the submission which is also the value of the submitted company model. The 212mg/dl appears to be the value at diagnosis of the THIN database, while the THIN database value at baseline or intensification to triple therapy is 169mg/dl.

The scenario analysis of the company that applies the THIN database values of the recent NICE clinical guideline modelling in effect assumes the standard deviation to be zero. The ERG prefers the patient characteristics of the recent NICE clinical guideline modelling. The mean values for these have been largely correctly reported by the company. The main ERG addition is to distinguish between the values at diagnosis and the values at baseline, and to include the standard deviations. Due to the NICE CG not specifying a value for LDL this has been taken to be the same ratio at baseline with HDL as reported for the pivotal trial, with the higher total cholesterol at diagnosis being assumed to be due to higher LDL levels given the constancy of the HDL levels.

Table 38 Patient baseline characteristics: NICE CG

	THIN database	
	Value	**s.d.**
Current Age (Yrs)	65.40	12.3
Proportion female	0.44	..
Duration diabetes (Years)	8.50	..
Height (m)	1.68	0.10
Weight (kg)	86.7	18.1
Proportion Afro-Caribbean	0.03	..
Proportion Indian	0.03	..
Proportion smokers	0.19	..
Risk factors at diagnosis		
HbA1c (%)	7.90	1.90
SBP (mmHg)	143.2	18.0
Total cholesterol (mg/dl)	212	43
HDL (mg/dl)	47	12
LDL (mg/dl)	143	..
Risk factors at baseline		
HbA1c (%)	7.60	1.50
SBP (mmHg)	136.2	15.6
Total cholesterol (mg/dl)	169	38
HDL (mg/dl)	47	12
LDL (mg/dl)	100	..

A complication arises in that the CARDIFF model does not have the facility to associate baseline variables through a variance-covariance matrix. As a consequence, even patients' height and weight cannot be associated but are sampled independently which may give a misleading distribution of patient BMIs.

Patient characteristics can tend to covary: a patient with a poor BMI is more likely to also have a poor SBP. As a consequence, it is likely that both the relatively well and the relatively poorly will be under-represented in the company model when there is sampling of patient characteristics. The company suggests that variance-covariance data is rarely available, but this is a little disingenuous of the company.

The company is aware of the patient sampling of the recent NICE clinical guideline, which provides a variance-covariance matrix for the baseline characteristics required for the UKPDS68 modelling.

But it should be noted that the mean baseline 7.6% HbA1c of the above is less than the 8.15% of the pivotal study as used in the company base case. There may be some concern whether the full HbA1c reductions of the NMA would apply here.

The disutilities associated with complications

The values applied correspond with the UKPDS 62 and those used in the recent NICE MTA of the SGLT2-is for monotherapy.

The disutilities associated with UTIs and GTIs

The recent NICE MTA of SGLT2s for monotherapy [ID756] considered Barry et al[94] as a possible source, but derived quality of life decrements per event of 0.19 for a severe UTI and 0.25 for a mycotic infection from a Janssen TTO study that was conducted among 100 members of the UK general public. These were coupled with a mean 2 week duration as drawn from Nicolle et al[102] to yield decrements of 0.007 QALYs for a UTI and 0.009 QALYs for a GTI. The ERG will apply these values for its base case.

The disutility associated with discontinuation

The company modelling does not apply a disutility for the patient experience leading to discontinuation. The SGLT2-is have roughly double the discontinuation rate of the DPP4-is.

In the NICE T2DM CG[3] treatment discontinuations were assigned a QALY decrement associated with nausea as drawn from Matza et al.[103] The with and without nausea quality of life values of 0.89 and 0.85 were taken to apply yielding a mean decrement of 0.04, which the GDG thought a six week duration would be most reasonable estimate, this yielding a mean QALY decrement of -0.00462. In the context of discontinuation rates of 2.9% and 5.3% this is inconsequential.

Direct drug costs

The BNF outlines that the SGLT2-is with the exceptions of dapagliflozin 25mg and canagliflozin 300mg are available for the same daily price in combination with daily doses of 1.7g or 2.0g of metformin. These require that two tablets be taken daily, presumably to split the metformin dose. The DPP-4is are similarly all available in combination with either daily doses of 1.7g or 2.0g metformin, though sitagliptin and

alogliptin are only available in combination with 2.0g metformin. The study 5 baseline characteristic was a mean daily dose of marginally more than 2g.

Costs of severe hypoglycaemia

The £380 cost per severe hypoglycaemic event is the same as the cost that was applied during the recent NICE CG modelling and similar to the £411 cost that was applied during the recent NICE MTA of SGLT2-is as monotherapy.

Costs of UTIs and GTIs

The £45 cost of UTIs is somewhat lower than the £73 cost of UTIs applied within the recent NICE MTA of SGLT2-is as monotherapy. The £45 cost of GTIs is similar to the £51 cost of GTIs applied within the recent NICE MTA of SGLT2-is as monotherapy. The differences largely arise from the NICE MTA of SGLT2-is as monotherapy assuming that two GP visits would be required for male UTIs, coupled with medication costs being included.

Ongoing medical costs and the costs of complications

It appears that the model assumes that all patients incur the ongoing medical costs of those with no complications and that the costs of the complications are additional to these costs. It is the opinion of the ERG that within both the UKPDS 65 and the updated UKPDS 84 that the ongoing medical costs for those with no complications should not be applied to those with complications.

Given the ERG preference for the UKPDS 82[90] event equations, the ERG also prefers the UKPDS 84[99] for costs as presented in the recent MTA of SGLT2-is for monotherapy. Costs in the UKPDS 84 are differentiated by gender, with age also being a determinant. Based upon patients being 65 years of age and 44% female as per the THIN database this suggests the following mean costs of being complication free and having complications[2], these costs being uprated for inflation by 3%.

[2] Based upon the electronic supplement to the UKPDS 84

Table 39 ERG costs of diabetes complications: UKPDS 84

	Male			Female			
	IP	OP	Total	IP	OP	Total	Mean
No complications	£596	£569	£1,165	£702	£736	£1,438	£1,285
Year of complication							
Fatal MI	£1,765	£569	£2,334	£1,989	£736	£2,725	£2,506
Non fatal MI	£6,824	£1,012	£7,836	£7,075	£1,179	£8,254	£8,020
Fatal stroke	£4,266	£569	£4,835	£4,490	£736	£5,227	£5,007
Non fatal stroke	£7,597	£1,144	£8,742	£8,007	£1,312	£9,319	£8,995
Fatal IHD	£4,099	£569	£4,668	£4,333	£736	£5,069	£4,844
Non-fatal IHD	£10,526	£910	£11,436	£10,877	£1,078	£11,955	£11,665
Heart failure	£3,581	£1,029	£4,610	£3,842	£1,196	£5,039	£4,799
Blindness in one eye	£1,672	£1,864	£3,536	£1,886	£2,032	£3,918	£3,704
Amputation	£10,170	£2,800	£12,970	£10,460	£2,968	£13,427	£13,171
Subs year							
Non fatal MI	£1,436	£712	£2,148	£1,631	£879	£2,510	£2,307
Non fatal stroke	£1,407	£800	£2,206	£1,595	£967	£2,562	£2,363
Non-fatal IHD	£1,511	£694	£2,205	£1,711	£861	£2,572	£2,367
Heart failure	£1,812	£1,023	£2,835	£2,037	£1,190	£3,228	£3,008
Blindness in one eye	£594	£781	£1,374	£706	£948	£1,653	£1,497
Amputation	£2,166	£1,681	£3,847	£2,415	£1,848	£4,263	£4,030

The CARDIFF model structure does not reliably permit the £1,285 cost for those with no complications to be implemented only among those with no history of complications. The revised ERG base case will simply subtract this value from the costs of the complications. But the ERG acknowledges that this is imperfect since for those with multiple complications it will subtract this value at least twice which is incorrect. As a consequence, a sensitivity analysis that does not subtract this amount will also be undertaken.

The UKPDS 84 does not provide a costing for renal disease. In common with the recent NICE CG for diabetes and MTA of SGLT2-is as monotherapy, these have been drawn from Lamping et al[104] and uprated for inflation using a multiplier of 1.75 from the PSSRU index [105] to yield costs of £36,889 for a fatal event and £36,801 for a non-fatal event and subsequent years. These estimates are broadly in line with those of the company.

4.3.3 Data Inputs: Correspondence between written submission and electronic model

The ERG has cross checked the values of tables 37, 38, 40, 41, 42, 43, 44 and 45 against the values applied within the submitted electronic model. In general there is a good correspondence but the ERG notes the following discrepancies:

- The annual therapy costs for DPP4-i and dapagliflozin of £424 and £477 are associated with standard errors of £85 and £95, while the costs of the other treatments are deterministic.
- The disutility of non-severe and severe hypoglycaemia events is set to zero for dapagliflozin and the DPP4-i, but are applied for the other SGLT2-is[3].
- The number of symptomatic hypoglycaemic events for insulin + metformin is set to zero in the model
- The proportion of symptomatic hypoglycaemic events that are severe for insulin + metformin is set to zero in the model.
- The cost of symptomatic hypoglycaemic events of £45 (s.e. £9) and the cost of severe hypoglycaemic events £380 (s.e. £76) are not applied in the model when patients intensify to insulin.
- The ongoing patients OP and IP costs associated with no complications appear to have been assumed to be additional to the costs of complications among patients experiencing or having a history of any complication.
- The ongoing patients OP and IP costs associated with no complications have not been applied within the company UKPDS 84 cost scenario.
- Additional annual costs of metformin £25.29 and of sulfonylurea £29.46 are listed in the submission but have not been added. Since the metformin costs are common to all therapies and minimal differences in survival are modelled, their exclusion is unlikely to affect results much. The exclusion of sulfonylurea costs might affect results slightly.
- In the empagliflozin 10mg arm an annual insulin costs of £0.00082 per kg per day, or around £26 per year for those on triple therapy appears to have been accidentally included.

Company NMA results

[3] This is ambiguous within the model due to the *Advanced_inputs* worksheet having the coefficients of Currie et al (2006) but the *Treatment_profiles* worksheet having placeholders for the disutilities. As a consequence it is unclear what source the C++ uses to calculate these from. Since the model is not set up to report QALYs by source, this cannot be cross checked by the ERG.

The written submission does not outline the absolute clinical effectiveness estimates for changes from baseline for the reference treatment, which apparently in reality is placebo + MET + SU, or for the triple therapies. The submitted model also only contains that company NMA results for the company base case. The alternative possible values are outlined below with the values for HbA1c, weight and SBP being changes from baseline and hypoglycaemia being annual rates.

Table 40 Company absolute changes from baseline: base case analysis

	Random effects model				Fixed effects model			
	HbA1c	Weight	SBP	Hypo	HbA1c	Weight	SBP	Hypo
MET+SU	-0.150	-0.300	-1.092	0.108	-0.150	-0.300	-1.092	0.108
DAPA	-0.854	-2.201	-3.130	0.202	-0.851	-2.195	-3.163	0.202
CANA300	-1.095	-2.059	-4.162	0.208	-1.119	-2.065	-4.148	0.208
CANA100	-0.867	-1.778	-4.823	0.208	-0.883	-1.786	-4.835	0.208
EMPA25	-0.849	-1.998	-3.191	0.131	-0.850	-1.999	-3.187	0.131
EMPA10	-0.849	-2.103	-3.304	0.148	-0.850	-2.100	-3.294	0.148
DPP4	-0.793	0.120	1.848	0.181	-0.790	0.067	1.845	0.181
PIO	-1.025	1.735	1.352	0.152	-1.021	1.670	1.356	0.152

Table 41 Company absolute changes from baseline: 24 week analysis

	Random effects model				Fixed effects model			
	HbA1c	Weight	SBP	Hypo	HbA1c	Weight	SBP	Hypo
MET+SU	-0.125	-0.425	-1.851	0.094	-0.125	-0.425	-1.851	0.094
DAPA	-0.816	-2.495	-5.818	0.303	-0.814	-2.495	-5.845	0.301
CANA300	-0.973	-2.649	-3.873	0.155	-0.990	-2.878	-3.721	0.149
CANA100	-0.783	-2.142	-4.338	0.165	-0.799	-2.250	-4.244	0.159
EMPA25	-0.724	-2.426	-3.944	0.125	-0.725	-2.424	-3.951	0.125
EMPA10	-0.775	-2.198	-4.534	0.151	-0.775	-2.194	-4.551	0.151
DPP4	-0.785	0.083	-4.353	0.182	-0.776	-0.012	-5.110	0.156
PIO	-1.052	1.922	-4.873	0.188	-1.062	1.775	-5.619	0.216

Table 42 Company absolute changes from baseline: 52 week analysis

	Random effects model				Fixed effects model			
	HbA1c	Weight	SBP	Hypo	HbA1c	Weight	SBP	Hypo
MET+SU	0.064	-0.416	0.046	0.132	0.064	-0.416	0.046	0.132
DAPA	-0.630	-2.304	-2.086	0.242	-0.636	-2.315	-2.036	0.240
CANA300	-0.907	n.a.	-3.002	0.286	-0.907	n.a.	-2.946	0.287
CANA100	-0.690	n.a.	-3.780	0.262	-0.687	n.a.	-3.749	0.262
EMPA25	-0.631	-2.415	-2.455	n.a.	-0.637	-2.416	-2.460	n.a.
EMPA10	-0.735	-2.417	-2.856	n.a.	-0.737	-2.416	-2.859	n.a.
DPP4	-0.533	n.a.	3.003	0.264	-0.537	n.a.	3.049	0.267
PIO	-1.073	4.384	n.a.	0.359	-1.065	4.385	n.a.	0.357

Table 43 Company absolute changes from baseline: study endpoints analysis

	Random effects model				Fixed effects model			
	HbA1c	Weight	SBP	Hypo	HbA1c	Weight	SBP	Hypo
MET+SU	-0.071	-0.445	-1.146	0.105	-0.071	-0.445	-1.146	0.105
DAPA	-0.771	-2.378	-3.261	0.198	-0.772	-2.334	-3.229	0.197
CANA300	-0.991	-2.194	-4.690	0.224	-1.040	-2.206	-4.543	0.205
CANA100	-0.770	-1.918	-5.092	0.219	-0.803	-1.930	-5.062	0.204
EMPA25	-0.770	-2.145	-3.232	0.128	-0.771	-2.146	-3.246	0.127
EMPA10	-0.770	-2.241	-3.328	0.145	-0.771	-2.249	-3.343	0.144
DPP4	-0.720	-0.007	0.821	0.202	-0.712	-0.058	1.247	0.180
PIO	-0.987	1.841	0.176	0.039	-1.001	1.790	0.612	0.263

The 52 weeks set of values is generally incomplete. The other values will be used as scenario analyses by the ERG.

4.3.4 ERG commentary on model structure, assumptions and data inputs

Sampling of patient characteristics: 1st and 2nd order uncertainty

During ERG runs of the model it has specified patient distributions with non-zero standard deviations for some of the baseline characteristics and has also specified patient distributions with zero standard deviations for all of the baseline characteristics. For the mean value modelling these result in the same model outputs. In the company deterministic analyses there appears to be no sampling of 1st order uncertainty; i.e. patient heterogeneity. Elements such as gender may be sampled but it appears that the

continuous variables such as HbA1c and weight at baseline are not. (See section 3.8 and appendix 5 for heterogeneity checks.)

This may unduly polarise some of the analyses. For instance, a cohort of 5,000 patients all with a baseline HbA1c of 7.5% will have the same post treatment HbA1c and so will in due course all intensify to insulin at the same time. A comparator treatment with a lesser HbA1c effect would similarly cause all patients to intensify at the same time, but this might be earlier than for the other treatment. Since in the company model insulin is somewhat cheaper than the SGLT2-is, the comparator that intensifies to insulin earlier realises cost savings and these cost savings are realised among all patients. It seems likely that sampling patients' baseline HbA1c would lessen this. The baseline range in the NMA trials ranged from 8.0% to 8.8%.

Further exploration of the company model has found there to be a sub-menu within the "*Probabilistic Sensitivity Analysis*" option. This sub-menu permits it to be specified that only demographics, clinical risk factors and clinical history are sampled. Consequently, it appears that it is possible for the model to sample 1st order uncertainty without having to do so within the context of sampling 2nd order uncertainty. The ERG will explore this as a scenario analysis.

But the sampling of patient characteristics is complicated by the section below on the variance-covariance.

Sampling of patient characteristics: 1st order uncertainty and variance-covariance

The CARDIFF model suggests that patient characteristics should be specified using the mean value and the standard error around this mean value. There is no facility to enter the sample size that these estimates are based upon so it appears that the CARDIFF model cannot derive the standard deviation from the mean and standard error.

Largely following the lead of the recent NICE Clinical Guideline NG 28 on type 2 diabetes, the ERG understanding is that within a patient level model, 1st order uncertainty around patient characteristics should be sampled using the population standard deviation, while 2nd order uncertainty around input parameters such as treatment effectiveness should be sampled using the standard error of the central estimate. It appears that the company modelling has used the standard errors for the sampling of 1st order uncertainty. These standard errors are quite small compared to the central estimates and as a consequence the company modelling can be crudely characterised as roughly simulating a quite similar set of patients

as passing through the model. The scenario analysis of the THIN database also applies standard errors of zero and so does not sample 1st order uncertainty at all. As a consequence, it appears that the company modelling does not adequately explore 1st order uncertainty.

But given the inability of the CARDIFF model to associate patient characteristics through a variance-covariance matrix, there is an argument for simply running a cohort of identical patients with the central estimates for their baseline characteristics through the model.

Choice of UKPDS 68 versus UKPDS 82 event equations

The ERG had been under the impression during the decision problem meeting that the company was going to use the more recent UKPDS 82 event equations. The ERG noted that this might cause problems with model validation given that the C++ of the CARDIFF model that the DSU evaluated during the previous STA of dapagliflozin [TA288] applied the UKPDS 68 event equations as these were the most up to date UKPDS equations then available. The ERG also noted that this might suggest that some validation work should be undertaken to show that the CARDIFF model UKPDS 68 event equations implementation and UKPDS 82 event equations implementation led to ratios of 10 year events being model that were broadly in line with those of Hayes et a[90] as reproduced below. Within this the OM1 model implements the UKPDS 68 equations and the OM2 implements the UKPDS 82 equations.

Table 44 10 year event rates: UKPDS 68 versus UKPDS 82

	50-54 years		60-64 years		70-74 yrs		All ages	
	OM1	OM2	OM1	OM2	OM1	OM2	OM1	OM2
1st MI	14.9	7.5	22.5	10.3	29.6	13.3	21	9.9
2nd MI	n/a	0.9	n/a	1.0	n/a	1.1	n/a	1.0
Ulcer	n/a	1.5	n/a	1.9	n/a	2.2	n/a	1.8
Blindness	2.2	2.2	3.5	3.1	4.9	4.0	3.3	2.9
IHD	8.6	6.9	10.3	8.3	10.5	9.0	9.5	7.8
1st stroke	3.3	3.3	7.9	6.4	14.2	10.7	7.6	6.2
2nd stroke	n/a	0.3	n/a	0.7	n/a	1.5	n/a	0.7
Renal failure	0.9	0.3	1.4	0.6	1.6	0.8	1.3	0.5
1st amputation	1.7	1.3	2.0	1.6	1.7	1.8	1.8	1.5
2nd amputation	n/a	0.4	n/a	0.6	n/a	0.4	n/a	0.4
Heart failure	3.0	2.5	5.9	4.3	9.9	6.4	5.7	4.0
Death	14.5	11.1	32.1	22.3	58.8	43.3	31.6	22.5

As can be seen from the above, the UKPDS 82 event equations suggest a lower incidence of MI events, renal failure and deaths. As a consequence, the company base case UKPDS 68 modelling may over-estimate the patient gains and costs offsets from the reduced complication rate of the more effective treatment.

The scenario analysis of the company also suggests that the company base case changes from dapagliflozin being slightly cost saving to being more costly than the DPP-4i when the UKPDS 82 equations are applied.

The company for the current submission argues that the UKPDS 68 sat of event equations should be preferred due to "*their extensive use and validation compared to the more contemporary UKPDS 82 equations*". In the opinion of the ERG this is not a particularly strong argument and it is likely that much if not all diabetes modelling will switch to the use of the UKPDS 82 equations in preference to the UKPDS 68 equations. It also sits uncomfortably alongside the company having preferred the UKPDS 82 equations in its submission to the recent MTA of SGLT2 for monotherapy. The current submission on page 126 also notes that in validation exercises of CORE and the CARDIFF models "*These publications evaluated both the UKPDS 68 and more contemporary UKPDS 82; the latter were found to provide a better fit to the UKPDS data with slightly improved goodness of fit results recorded against external validation studies*". The company argues that the choice has negligible impact and may indeed be conservative for dapagliflozin.

The choice of model should perhaps also be conditioned by McEwan et al[90] which appears to suggest a somewhat better external validity when using the UKPDS 82 than when using the UKPDS 68.

In the light of this the ERG prefers to use the UKPDS 82 event equations for the base case, and the UKPDS 68 event equations as a scenario analysis.

Time spent on triple therapy and direct drug costs

The switching profile determined by treatment discontinuation rates, the initial triple therapy HbA1c treatment effect and subsequent sawtooth evolution of HbA1c determines the duration of each line of treatment for each patient. This results in the following proportions of surviving patients being on triple therapy, insulin and intensified insulin during the first 10 years of the model[4].

[4] Calculated in the *T2_Events* worksheet from cells D66:M68 and D71:M73

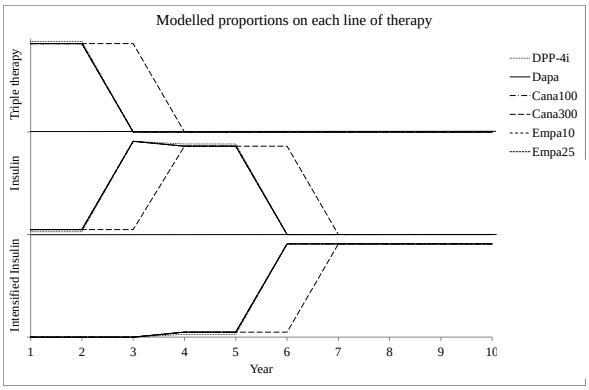


Figure 5 Modelled proportions on each line of therapy

Due to identical discontinuation rates and similar effects upon HbA1c the model simulates virtually identical proportions remaining on each line of therapy for dapagliflozin, canagliflozin 100mg, empagliflozin 10mg and empagliflozin 25mg due to identical initial discontinuation rates and near identical initial effects upon HbA1c. Their lines in the figure above essentially overlie one another. The main distinctions are between these therapies, the DPP-4i and canagliflozin 300mg.

The DPP-4i has a lower initial discontinuation rate of 2.9% compared to 5.3% for the SGLT2-is. As a consequence, a slightly higher proportion remains on the more expensive triple therapy during the first two years of the model. This tends to increase treatment costs in the DPP-4i arm compared to dapagliflozin.

Canagliflozin 300mg is associated with an initial HbA1c reduction of 1.09% compared to 0.85% for dapagliflozin. This causes most patients to remain below 7.5% treatment intensification threshold for an additional year. This tends to increase treatment costs in the canagliflozin 300mg arm compared to dapagliflozin within the company model.

It seems likely that the impact upon therapy costs from treatment switching outweighs the impact upon downstream complication rates. In other words the DPP-4i may be being penalised for its lower discontinuation rate while canagliflozin 300mg may be being penalised for its better treatment effectiveness in terms of HbA1c. But it does not seem reasonable to the ERG to assume that those intensifying to insulin will cease their oral therapies. This was a key difference between the company submissions and the AG modelling during the recent MTA of SGLT2s for monotherapy which the company made a submission to and was intimately involved in. During this MTA the clinical experts stated that patients would not generally cease their DPP-4i/SGLT2s when intensifying to insulin and this

was the preferred assumption of the AC. As a consequence, for the base case the ERG will assume that patients intensify according to the following schedule:

- SU+MET+DPP-4i/SGLT2/Pioglitazone
- Insulin+SU+MET+DPP-4i/SGLT2/Pioglitazone
- Intensified insulin+MET+DPP-4i/SGLT2/Pioglitazone

For the triple therapies this results in direct drug costs of £477 for the SGLT2-is, £424 for the DPP4-i and £21 for pioglitazone and £72 for BNP monitoring in pioglitazone, plus £62.18 for a daily 60mg of modified release gliclazide from the drug tariff and £16.95 for a daily dose of 1700mg metformin. This yields total non-insulin costs for each line of therapy as follows:

Table 45 ERG non-insulin related drug and consumables costs by arm and line of therapy

	Triple	Insulin	Int. Insulin
SGLT2-is	£556	£556	£494
DPP4-i	£503	£503	£441
Pioglitazone	£172	£172	£110

Insulin within the model has to be costed on a cost per kilogram per day. The ERG will assume a daily 0.55IU/kg for basal insulin which equates to a daily cost per kg of £0.00642. For intensification to basal-bolus an additional 0.20IU/kg will be assumed. Given the slightly higher cost of £0.0162 for bolus this equates to a daily cost per kg of £0.00966.

The costs of needles and SMBG also have to be added. These costs have been taken from the recent NICE MTA of SGLT2-is for monotherapy. For basal insulin this adds an additions £32 for needles and £51 for SMBG. The intensification to basal-bolus insulin adds a further £32 for needles and £68 for SMBG.

Duration of weight loss

The company base case estimates suggest that dapagliflozin is associated with not only a weight loss compared to the DPP-4is but also compared to all the SGLT2-is. As a consequence, if weight losses tend to be maintained for longer than one year the company base case may be biased against dapagliflozin on this count. The company cites Del Prato et al[106] as demonstrating that weight loss with dapagliflozin is maintained for up to 4 years. Patients were on dual therapy with metformin and were blinded to treatment to the 4 year follow up point, with around half of the original patients enrolling in the final follow-up

study. Broadly, weight losses of 3.65kg were sustained for dapagliflozin as were weight gains of 0.73 for glipizide.

UKPDS68 values at baseline versus values at diagnosis

As noted in the validation section, when modelling the evolution of the risk factor the UKPDS 68 makes a clear distinction between the values at diagnosis and the values at baseline. The company model as submitted does not make this distinction. But the evolution of the risk factors in the company model appears to be within the VBA to which the ERG has access, rather than the C++ of the model to which the ERG does not have access.

The ERG has revised the VBA of the company model to make the distinction between values at diagnosis and values at baseline, and has derived differences between these of 0.3% for HbA1c, 7.0mmHG for SBP and 0.99 for the total:HDL cholesterol ratio from the recent NICE CG for T2DM. These values when coupled with the ERG revisions to the VBA result in the anticipated changes to what the excel model labels as the Biannual Risk Factor Input: Values used in model. But the model outputs that result are identical whether the values at diagnosis are applied or not.

As a consequence, it appears that the evolution of the risk factor equations implemented within the model cannot be revised by the ERG. The ERG assumption is that the Biannual Risk Factor Input: Values used in model values are not used within the model but are rather a separate modelling exercise at central values the reasons for which are not clear.

Discontinuation rates

The company model base case applies the probabilities of adverse event related discontinuations. This is assumed to be the same for all the SGLT2-is.

At clarification the company has supplied an additional NMA for discontinuations based upon the restricted network study endpoints of its preferred base case. The central values appear to suggest worse discontinuation rates for the other SGLT2-is, but very similar discontinuation rates for dapagliflozin and the DPP4-i. But the odds of discontinuing due to adverse events are somewhat better for dapagliflozin than the other comparators, particularly canagliflozin.

These odds ratios can be compared with the odds ratios implied by table 38 of the submission. That for the DPP-4i is similar to the new company NMA but the other SGLT2-is have been assumed to have the same discontinuation rates as dapagliflozin.

Table 46 Company NMA odds ratios of discontinuation: Random effects

	Odds ratios		
	Any reason	AE related	Table 38
Cana100	1.54 (0.32-7.22)	0.23 (0.02-1.99)	1.00
Cana300	1.67 (0.39-6.74)	0.23 (0.02-1.80)	1.00
Empa10	1.34 (0.27-6.66)	0.77 (0.06-7.43)	1.00
Empa25	1.14 (0.23-5.72)	0.47 (0.04-4.35)	1.00
DPP4-i	1.05 (0.28-3.73)	0.48 (0.05-3.64)	0.53

It may be reasonable to only model discontinuations due to adverse events if other discontinuations are more driven by trial protocol. But given the width of the confidence intervals it may be questionable whether in the deterministic modelling the treatments should be differentiated by discontinuation rates at all.

The model also assumes that those who discontinue move straight onto insulin rather than trying an alternative triple therapy. In the opinion of the ERG it seems likely that another triple therapy would be tried; e.g. those discontinuing due to adverse events within 6 months of trying triple therapy by adding dapagliflozin might try switching to a DPP4-i in order to delay the move to insulin.

In the light of the above, but more particularly the modelling assumption about those discontinuing moving onto insulin leading to possibly perverse model outputs, it may be preferable to not differentiate treatments by discontinuation rates. This is most simply achieved by setting them to zero.

Hypoglycaemia quality of life

Currie et al[95] used two separate 3 month recall surveys among patients with diabetes (n=408 and n=897) undertaken at different time points, though 145 patients responded to both surveys.

The first survey was used to estimate a relationship between a patient's score on the Hypoglycaemic Fear Survey (HFS) and the number of hypoglycaemic events.

Table 47 Currie et al HFS coefficients

	Coefficient (s.e.)
Intercept	11.171 (1.362)
Age	-0.110 (0.019)
Insulin use	2.668 (0.584)
Severe hypo (dichotomous)	5.881 (1.553)
Symptomatic hypos	1.773 (0.230)

The second survey was used to estimate the relationship between the HFS and the EQ-5D quality of life with a coefficient of -0.008 (s.e. 0.001). Since this is a linear relationship with the HFS, the intercept and age coefficients will in some sense cancel out between the arms provided that there are no significant survival differences being modelling, so can be disregarded. But the start of insulin use differs between the arms and will not cancel out between the arms. It appears that this has not been applied within the model. A lesser HbA1c effect causes patients to tend to intensify to insulin more quickly, so this omission may have been slightly detrimental to dapagliflozin when compared to the DPP-4i and slightly beneficial when compared to canagliflozin.

The values of Currie et al come with some major caveats. As Currie et al note regarding the two data sources "*These studies were commissioned by the pharmaceutical industry to inform drug developments around new treatments for diabetes that were found to reduce the frequency of hypoglycaemia*". The paper authorship also includes staff of Novo Nordisk and Sanofi-Aventis.

The values are based on results from two surveys, with a response rate of 31%. The hypoglycaemic episodes were recent events and perhaps therefore fresh in the memory. 45% of respondents were on insulin. Respondents might have been more likely to have been concerned about hypoglycaemia than non-respondents.

Around one third of respondents had T1DM with around two thirds of respondents having T2DM. Quite what covariates were considered and quite how the paper arrived at the final regressions is not explicit. Patient data from the first survey was removed if the patient also responded to the second survey reducing the sample to 57% of the original, though the reasons for this and impacts of doing so are not clear. Similarly, the grouping of complications was also possible subjective.

The 5.881 coefficient for severe hypoglycaemia episodes was also based on whether patients had had any severe hypoglycaemia events during the recall period. If within this group the mean number of severe hypoglycaemic episodes was more than one, it seems likely that the coefficient somewhat overestimates the impact of having one severe hypoglycaemia event within a quarter.

The patient number and demographics reported by Currie et al for the first survey are based upon the full 408 patients of this survey. But for the analysis 175 of these patients were excluded due to also being in the second survey. As a consequence the demographics and events rates that were used when analysing the data subset of the first survey cannot be determined.

For the full 408 patients of the first survey only 2.3% (n=9) reported experiencing at least one severe hypoglycaemic event during the previous 3 months. This was somewhat less than the 8.6% (n=77) proportion who reported experiencing at least one severe hypoglycaemic event during the previous three months in the second survey.

For severe hypoglycaemic event rates, Currie et al state that within the surveys "*very few people >1 event*" and they report a mean rate of "*1.47 events per patient year*". It seems likely that this mean rate was the average across the two surveys. It would have been useful to have known the mean rate for each survey, and for the small subset of the first survey that was actually analysed.

The relationship between having experienced at least one severe hypoglycaemic event in the last three months and the HFS index i.e. the 5.881 coefficient consequently appears to have been based upon at most 9 patients reporting. The restriction of the subset analysed to 57% of the total sample of the first survey suggests that this number is likely to have been somewhat less than 9 patients. This gives rise to the possibility of an outlier patient within this small subset having an unreasonable impact upon results. The construction of the subset was at investigator discretion.

The covariate for whether the patient is taking insulin is not included in the company modelling. Since, with the exception of canagliflozin 300mg, patients tend to intensify to insulin at the same time this will only really affect the comparison of dapagliflozin with canagliflozin 300mg. Company calculations suggest that its introduction causes canagliflozin to no longer be dominated, and rather than being associated with a loss of 0.003 QALYs confers an additional 0.015 QALYs compared to dapagliflozin. While the overall change is small at 0.018 QALYs it should be borne in mind when reviewing both the company and the ERG results.

Self-monitoring of blood glucose (SMBG) and insulin needles

In its clarification response the company asserts that since all treatments with the exception of canagliflozin 300mg intensify to insulin therapy at the same time, including the costs of SMBG would have minimal impact upon results. But this is not the case for the comparison with canagliflozin 300mg which will avoid the costs of SMBG and needles for insulin for one year, and perhaps also the net additional costs of SMBG and needles for intensified insulin compared to insulin.

Pioglitazone costs

The BNF suggests the following costs for pioglitazone from the BNF[5]:

- 15mg 28 tabs £1.17
- 30mg 28 tabs £1.42
- 45mg 28 tabs £1.61

Using the 45mg dose results in a direct drug cost of £20.99.

Note that the prices for pioglitazone in both the drug tariff and eMIMS have increased substantially since the MTA of SGLT2-is for monotherapy. These were in line with the BNF but now appear to have been revised as follows:

- 15mg 28 tabs £13.31
- 30mg 28 tabs £14.48
- 45mg 28 tabs £17.29

Using the 45mg dose results in a direct drug cost of £225. Costs may have been even higher in spring of 2016 which might suggest a short term problem in supply.

The CMU EMIT database outlines costs that are very much more in line with the BNF:

- 15mg 28 tabs £0.88
- 30mg 28 tabs £0.88
- 45mg 28 tabs £2.01

[5] http://www.evidence.nhs.uk/formulary/bnf/current/6-endocrine-system/61-drugs-used-in-diabetes/612-antidiabetic-drugs/6123-other-antidiabetic-drugs/pioglitazone accessed 05 Jul 2016.

The ERG will use the BNF costs for the base case and explore the eMIMS price as a sensitivity analysis. The recent MTA of SGLT2-is included an annual monitoring cost of £72 for BNP monitoring which will also be included.

Minor Issue: Smoking status

The company has clarified that it has not implemented equation 14 of the UKPDS which models the evolution of smoking status. In general, if this is implemented patients tend to cease smoking over time with this extending their survival. The company model assumes that smoking status remains constant over the time horizon of the model. The company has run additional scenario analyses which set the baseline prevalence of smoking to 0% and to 100% for the comparison of dapagliflozin with the DPP4-I, showing that there is minimal impact upon the modelled net costs, net QALYs and ICER.

Minor Issue: Model cycle length

Despite the model having a six month cycle, patients may only intensify therapy at the end of a year. The main point of having a six month cycle would seem to be to permit patients to intensify therapy more promptly. Not permitting this seems to largely obviate the point of the six month cycle. Given the annual estimation of the UKPDS68 relationships there is the concern that applying a six month cycle for no obvious reason may risk error with no gain in model accuracy.

It is possible that discontinuations are modelled as occurring at the end of the first 6 month cycle, which might provide some limited justification for the 6 month cycle.

Minor issue: Weight rebound after 1st line

It appears that weight rebounds after the 1st year in year 2 to only 0.1kg above baseline rather than 0.2kg above baseline. This applies to both arms and is unlikely to have any impact upon results.

4.4 Exploratory and sensitivity analyses undertaken by the ERG

ERG revised clinical model inputs

As previously outlined, the ERG has revised the model inputs for placebo adjusted HbA1c, SBP and weight as below.

Table 48 ERG placebo adjusted HbA1c, SBP and weight

	HbA1c	Weight	SBP
DPP4	-0.760	0.520	0.500
Dapa	-0.700	-1.900	-2.000
Empa10	-0.700	-1.750	-2.200
Empa25	-0.700	-1.750	-2.200
Cana100	-0.620	-1.250	-2.900
Cana300	-0.770	-2.500	-2.500
Pioglitazone	-0.870	2.200	-0.500

The ERG has not had time to formally estimate placebo changes from baseline and as a consequence has adopted the company base case values. The impact of this is explored in a scenario analysis that does not apply the company base case placebo changes from baseline and applies the above values. Coupled with the other ERG inputs these result in the following clinical effectiveness inputs.

Table 49 ERG base case inputs

	HbA1c	Weight	SBP	Discont.	Hypos	S.Hypos	UTI	GTI
DPP4	-0.910	0.220	-0.592	0.015	0.270	1.3%	0.056	0.021
Dapa	-0.850	-2.200	-3.092	0.019	0.073	0.0%	0.101	0.101
Empa10	-0.850	-2.050	-3.292	0.053	0.148	0.0%	0.119	0.040
Empa25	-0.850	-2.050	-3.292	0.053	0.131	0.0%	0.119	0.040
Cana100	-0.770	-1.550	-3.992	0.053	0.208	8.0%	0.119	0.040
Cana300	-0.920	-2.800	-3.592	0.053	0.208	5.0%	0.119	0.040
Pioglitazone	-1.020	1.900	-1.592	0.100	0.116	0.0%	0.000	0.000

The ERG has revised the company model to[6]:

- Apply the ERG clinical effectiveness estimates as outlined above.

[6] Due to the revised NICE process that the company routinely receives a copy of the ERG revised company model, the ERG changes to the model are typically not itemised here. Most changes to the model have been implemented as adding additional sets of user inputs such as costs and selecting these in the user drop downs of the *Simulations* worksheet. Should any of the ERG changes not be transparent the ERG would welcome any clarification questions that the company may have.

- Assume that patients retain their oral SGLT2-is, DPP-4is or pioglitazone when intensifying to insulin.
- Apply metformin and sulfonylurea costs to the triple therapies and insulin, and the metformin costs to intensified insulin.
- Apply self-monitoring of blood glucose costs of £51 for insulin and £119 for intensified insulin, as drawn from the recent NICE STA of SGLT2-is for monotherapy.
- Apply needle costs of £32 for insulin and an additional £32 for intensified insulin, as drawn from the recent NICE STA of SGLT2-is for monotherapy.
- Attempt to apply values at diagnosis within the UKPDS 68 equations 11, 12 and 13[7] though it is unclear whether the ERG changes to the VBA are carried forward to the C++ of the model.
- Apply the UKPDS 82 event equations.
- Apply the THIN database values for patient characteristics complete with standard deviations.
- Apply the hypoglycaemia event rates for insulin+metformin and intensified insulin+metformin.
- Apply the costs of hypoglycaemia events for the insulin containing regimes.
- Subtract the ongoing costs for a patient with no complications from those of the costs of complications. Note that this is imperfect since for patients modelled as having multiple complications the amount will be subtracted more than once. This argues for a sensitivity analysis that turns this off.
- Remove the standard errors from the treatment costs for the DPP-4i and dapagliflozin.
- Apply the UTI and GTI cost and QALY decrement estimates of the NICE MTA of SGLT2-is for monotherapy.

In the light of the company clarification response about how the model runs, the ERG revised base case is run over 5,000 patients and 5,000 runs.

The ERG has also undertaken the following scenario analyses.

- SA01: Revert to the company assumption that SGLT2s and DPP-4is are discontinued when patients intensify to insulin.
- SA02: Not apply the placebo/natural history effect for change from baseline for HbA1c, SBP and weight.
- SA03: Apply the UKPDS 68 event equations.
- SA04: No BMI quality of life impacts.

[7] Implemented within the VBA by subtracting the difference between the baseline value and the value at diagnosis from the *baseValue* variables for HbA1c and SBP and the *baseLine* variable for TC:HDL.

- SA05: Due to the CARDIFF model not applying a variance-covariance structure, setting the standard deviations of the patient characteristics to zero.
- SA06: Apply the Probabilistic Sensitivity Analysis model option but only sampling demographics, clinical risk factors and clinical history.
- SA07: No discontinuations from triple therapies
- SA08: Not subtracting the costs of having no complications from the costs of complications
- SA09: No hypoglycaemia among the triple therapies
- SA10: Higher annual pioglitazone costs of £225
- SA11: Applying the Company NMA results
    - SA11a: Base case random effects
    - SA11b: Base case fixed effects
    - SA11c: Study end points random effects
    - SA11d: Study end points fixed effects
    - SA11c: 24 week random effects
    - SA11d: 24 week fixed effects

Note that the scenario analyses that use the company NMA results assume the same discontinuation, UTI and GTI rates as in the company base case, that the discontinuation rate for pioglitazone is as per the SGLT2-is and that pioglitazone has no UTIs or GTIs. Each set of pairwise scenario analyses are presented alongside the corresponding pairwise base case for ease of reference.

In the following it should be noted that the model interface is quite cumbersome. The model also takes quite a long time to run. The ERG has endeavoured to implement the revised base cases and scenario analyses correctly. But there is no ready means of cross checking this as would be the case with more standard models. For instance, it is probably possible to modify elements within the Excel front end of the model without them automatically feeding through to the C++ model despite there being apparent changes in the excel inputs. In the light of this the ERG encourages the company to cross check both the base cases and the more important scenario analyses and the ERG is open to any questions the company may have concerning the ERG model implementation.

Comparison with DDP-4i

Table 50 Pairwise comparison of dapagliflozin and DPP-4i: Events

Events	DPP-4i	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	12.89%	12.86%	-0.03%
Myocardial Infarction	23.05%	23.03%	-0.02%
Congestive Heart Failure	8.38%	8.37%	-0.01%
Stroke	15.44%	15.36%	-0.08%
Microvascular			
Blindness	6.34%	6.34%	0.00%
Nephropathy	0.25%	0.25%	0.00%
Amputation	5.27%	5.27%	0.00%
Ulcer	3.14%	3.14%	0.00%
Deaths from complications	29.51%	29.48%	-0.03%
Diabetes related	29.12%	29.09%	-0.03%
Other	40.82%	40.88%	0.06%

Table 51 Pairwise comparison of dapagliflozin and DPP-4i: Costs

Costs	DPP-4i	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£2,388	£2,383	-£4
Myocardial Infarction	£1,729	£1,726	-£2
Congestive Heart Failure	£1,049	£1,046	-£3
Stroke	£1,437	£1,426	-£11
Microvascular			
Blindness	£246	£246	£0
Nephropathy	£3,232	£3,233	£1
Amputation	£919	£919	£0
Hypoglycaemia	£50	£35	-£15
Adverse Events	£15	£36	£21
Treatment	£9,779	£10,436	£658
Indirect Diabetes Costs	£15,756	£15,763	£7
Total	£36,598	£37,249	£651

Table 52 Pairwise comparison of dapagliflozin and DPP-4i: Cost effectiveness

Cost effectiveness	DPP-4i	Dapa	Difference
Discounted Cost	£36,598	£37,249	£651
Discounted QALYs	9.927	9.944	0.017
Discounted Life Years	12.225	12.230	0.005
Cost per QALY			£37,997
Cost per Life Year			£119,532

Given the limited differences in clinical effectiveness estimates the results are much as expected. Complication rates are similar between the two treatments but the superior weight profile for dapagliflozin confers some patient benefits. But the benefit from the different weight profiles is limited to one year and patient gains are small at only 0.017 QALYs.

The ERG base case assumes that patients remain on their oral treatments when intensifying to insulin. As a consequence, the higher annual cost of dapagliflozin of £477 compared to £424 for the DPP4-i and net annual cost of £53 persists for the 12 years discounted survival and there is an overall net discounted cost of £615. Given the limited patient benefits this translates into a cost effectiveness of £37,997 per QALY.

Within this it should be borne in mind that not only are weight losses assumed to rebound to natural history after one year, weight gains are as well. The DPP4-i is associated with a small weight gain of 0.22kg. Over the twelve years undiscounted survival if this was maintained it might cause an additional average net gain of 0.006 QALYs which would reduce the cost effectiveness estimate to £28,374 per QALY.

Comparison with empagliflozin 10mg

The modelling comparing dapagliflozin with empagliflozin 25mg suggests that there are minimal differences in event rates, though dapagliflozin is estimated to reduce MI and stroke and most microvascular complications by 0.01%. Costs are also near identical between the arms with some slight savings in treatment costs.

Table 53 Pairwise comparison of dapagliflozin and empagliflozin 10mg: Costs

Costs	Empa10	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£2,383	£2,383	£0
Myocardial Infarction	£1,727	£1,726	-£1
Congestive Heart Failure	£1,047	£1,046	£0
Stroke	£1,427	£1,426	-£1
Microvascular			
Blindness	£246	£246	£0
Nephropathy	£3,232	£3,233	£1
Amputation	£921	£919	-£2
Hypoglycaemia	£35	£35	£0
Adverse Events	£31	£36	£4
Treatment	£10,474	£10,436	-£38
Indirect Diabetes Costs	£15,761	£15,763	£1
Total	£37,284	£37,249	-£35

Table 54 Pairwise comparison of dapagliflozin and empagliflozin 10mg: Cost effectiveness

Cost effectiveness	Empa10	Dapa	Difference
Discounted Cost	£37,284	£37,249	-£35
Discounted QALYs	9.940	9.944	0.004
Discounted Life Years	12.229	12.230	0.001
Cost per QALY			Dominant
Cost per Life Year			Dominant

The slight cost savings coupled with small QALY gains result in dapagliflozin formally dominating empagliflozin, but the two treatments are little different. A QALY difference of 0.004 is inconsequential

Comparison with empagliflozin 25mg

The modelling comparing dapagliflozin with empagliflozin 25mg is much as per the comparison with empagliflozin 10mg, with MI, stroke and most of the microvascular complications being reduced by 0.01%. Costs are also near identical.

Table 55 Pairwise comparison of dapagliflozin and empagliflozin 25mg: Cost effectiveness

Cost effectiveness	Empa25	Dapa	Difference
Discounted Cost	£37,284	£37,249	-£35
Discounted QALYs	9.940	9.944	0.003
Discounted Life Years	12.229	12.230	0.001
Cost per QALY			Dominant
Cost per Life Year			Dominant

Empagliflozin 25mg and dapagliflozin are essentially estimated to be equivalent, with the possible exception of a very slightly superior weight profile for dapagliflozin yielding a very small QALY gain.

Comparison with Canagliflozin 100mg

Table 56 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Events

Events	Cana100	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	12.85%	12.86%	0.01%
Myocardial Infarction	23.07%	23.03%	-0.03%
Congestive Heart Failure	8.38%	8.37%	-0.01%
Stroke	15.36%	15.36%	0.00%
Microvascular			
Blindness	6.36%	6.34%	-0.02%
Nephropathy	0.25%	0.25%	0.00%
Amputation	5.29%	5.27%	-0.02%
Ulcer	3.16%	3.14%	-0.02%
Deaths from complications	29.50%	29.48%	-0.02%
Diabetes related	29.10%	29.09%	-0.01%
Other	40.85%	40.88%	0.03%

Table 57 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Costs

Costs	Cana100	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£2,381	£2,383	£2
Myocardial Infarction	£1,729	£1,726	-£3
Congestive Heart Failure	£1,047	£1,046	-£1
Stroke	£1,425	£1,426	£1
Microvascular			
Blindness	£246	£246	-£1
Nephropathy	£3,231	£3,233	£2
Amputation	£924	£919	-£5
Hypoglycaemia	£123	£35	-£88
Adverse Events	£31	£36	£4
Treatment	£10,473	£10,436	-£37
Indirect Diabetes Costs	£15,761	£15,763	£2
Total	£37,373	£37,249	-£124

There is some reduction in costs of treatment. But the larger cost offset arises from the reduction in severe hypoglycaemia due to it being assumed that no hypoglycaemic events are serious with dapagliflozin. Note that there are still costs for hypoglycaemic events within the dapagliflozin arm as these occur when patients intensify to insulin.

Table 58 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Cost effectiveness

Cost effectiveness	Cana100	Dapa	Difference
Discounted Cost	£37,373	£37,249	-£124
Discounted QALYs	9.926	9.944	0.017
Discounted Life Years	12.229	12.230	0.002
Cost per QALY			Dominant
Cost per Life Year			Dominant

Given the cost savings and slight patient gain of 0.017 QALYs, dapagliflozin is formally estimated to dominate canagliflozin 100mg. But as with all the comparisons between the SGLT2-is the differences are slight.

Comparison with Canagliflozin 300mg

Table 59 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Events

Events	Cana300	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	12.86%	12.86%	0.00%
Myocardial Infarction	23.04%	23.03%	-0.01%
Congestive Heart Failure	8.37%	8.37%	0.00%
Stroke	15.36%	15.36%	0.00%
Microvascular			
Blindness	6.34%	6.34%	0.00%
Nephropathy	0.25%	0.25%	0.00%
Amputation	5.26%	5.27%	0.01%
Ulcer	3.15%	3.14%	0.00%
Deaths from complications	29.47%	29.48%	0.00%
Diabetes related	29.10%	29.09%	-0.01%
Other	40.87%	40.88%	0.00%

In terms of event rates dapagliflozin and canagliflozin 300mg are near identical.

Table 60 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Costs

Costs	Cana300	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£2,383	£2,383	£1
Myocardial Infarction	£1,729	£1,726	-£3
Congestive Heart Failure	£1,046	£1,046	£0
Stroke	£1,427	£1,426	-£1
Microvascular			
Blindness	£246	£246	£0
Nephropathy	£3,232	£3,233	£1
Amputation	£920	£919	-£1
Hypoglycaemia	£102	£35	-£67
Adverse Events	£40	£36	-£4
Treatment	£10,252	£10,436	£184
Indirect Diabetes Costs	£15,761	£15,763	£1
Total	£37,139	£37,249	£110

The savings for dapagliflozin arising from none of its hypoglycaemia events being serious are not sufficient to offset the higher treatment costs. The better HbA1c profile for canagliflozin 300mg is sufficient to delay intensification to insulin for a reasonable proportion of patients. As a consequence, dapagliflozin is associated with a net additional cost of £110 compared to canagliflozin 300mg.

Table 61 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Cost effectiveness

Cost effectiveness	Cana300	Dapa	Difference
Discounted Cost	£37,139	£37,249	£110
Discounted QALYs	9.935	9.944	0.009
Discounted Life Years	12.229	12.230	0.001
Cost per QALY			£12,875
Cost per Life Year			£115,649

Dapagliflozin is estimated to be associated with an additional 0.009 QALYs, which may be due to the severe hypoglycaemia assumptions. The additional cost of £110 results in a cost effectiveness estimate of £12,875 per QALY.

Comparison with pioglitazone

Table 62 Pairwise comparison of dapagliflozin and pioglitazone: Events

Events	Pio	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	12.88%	12.86%	-0.03%
Myocardial Infarction	23.07%	23.03%	-0.04%
Congestive Heart Failure	8.41%	8.37%	-0.03%
Stroke	15.44%	15.36%	-0.08%
Microvascular			
Blindness	6.36%	6.34%	-0.01%
Nephropathy	0.25%	0.25%	0.00%
Amputation	5.28%	5.27%	-0.01%
Ulcer	3.15%	3.14%	-0.01%
Deaths from complications	29.52%	29.48%	-0.04%
Diabetes related	29.13%	29.09%	-0.04%
Other	40.79%	40.88%	0.08%

In terms of event rates, while not large dapagliflozin is estimated to provide some benefits over pioglitazone.

Table 63 Pairwise comparison of dapagliflozin and pioglitazone: Costs

Costs	Pio	Dapa	Difference
Macrovascular			
Ischaemic Heart Disease	£2,386	£2,383	-£3
Myocardial Infarction	£1,731	£1,726	-£5
Congestive Heart Failure	£1,052	£1,046	-£5
Stroke	£1,436	£1,426	-£10
Microvascular			
Blindness	£246	£246	-£1
Nephropathy	£3,229	£3,233	£4
Amputation	£921	£919	-£2
Hypoglycaemia	£31	£35	£3
Adverse Events	£5	£36	£31
Treatment	£5,624	£10,436	£4,813
Indirect Diabetes Costs	£15,754	£15,763	£8
Total	£32,415	£37,249	£4,834

Despite the superior event profile there are only modest cost offsets. The main difference is as would be expected. Treatment costs for dapagliflozin are considerably higher.

Table 64 Pairwise comparison of dapagliflozin and pioglitazone: Cost effectiveness

Cost effectiveness	Pio	Dapa	Difference
Discounted Cost	£32,415	£37,249	£4,834
Discounted QALYs	9.935	9.944	0.009
Discounted Life Years	12.224	12.230	0.007
Cost per QALY			£558k
Cost per Life Year			£731k

Given the substantially greater treatment costs and limited patient gains of only 0.009 QALYs the cost effectiveness estimate is poor at £558k per QALY.

As for the comparison with the DPP4-i, the weight gain associated with pioglitazone is assumed to persist for only one year. If weight gains were maintained over the patient lifetime the gain of 1.9kg associated with pioglitazone could cause the patient gains from dapagliflozin to increase by 0.050 QALYs to 0.059 QALYs. This would not in itself render it cost effective compared to pioglitazone, but would improve the ICER to £82,145 per QALY.

Scenario analyses

Table 65 Pairwise comparison of dapagliflozin and DPP-4i: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	£651	0.017	£37,997
SA01: Orals discontinued	£143	0.017	£8,351
SA02: Remove placebo/natural history effect	£650	0.017	£38,147
SA03: UKPDS 68 event equations	£495	0.020	£25,329
SA04: No BMI QoL	£651	0.012	£53,642
SA05: No patient heterogeneity sampling	£651	0.017	£37,997
SA06: PSA patient characteristic sampling	£930	0.104	£8,933
SA07: No discontinuations	£647	0.018	£36,818
SA08: Not subtracting no comp costs	£639	0.017	£37,294
SA09: No triple therapy hypoglycaemia	£651	0.010	£68,210
SA10: Pioglitazone £225 per year	n.a.	n.a.	n.a.
SA11a: Company NMA: Base case random effects	£727	0.013	£57,971
SA11b: Company NMA: Base case fixed effects	£726	0.013	£58,038
SA11c: Company NMA: End point random effects	£729	0.011	£67,243
SA11d: Company NMA: End point fixed effects	£728	0.011	£65,369
SA11e: Company NMA: 24 week random effects	£744	-0.002	Dominated
SA11f: Company NMA: 24 week fixed effects	£747	-0.004	Dominated

The company NMA results appear to result in worse cost effectiveness estimates for dapagliflozin compared to the DPP-4i.

If dapagliflozin and the DPP-4i are discontinued when patients intensify to insulin as in SA01 the additional cost from dapagliflozin is experienced for a much shorter period. Net costs fall to £143 and the cost effectiveness improves to £8,351 per QALY. These results are similar to SA10 of the company scenario analysis, though the net treatment costs are higher possibly due to the ERG addition of the costs of consumables to insulin.

The UKPDS 68 event equations suggest more events are avoided with dapagliflozin than the UKPDS 82 event equations. This provides larger cost offsets and the net cost falls to £495 while the patient gains increase to 0.020 QALYs, improving the cost effectiveness estimate to £25,329 per QALY.

Setting the standard deviations of the patient baseline characteristics to zero yields identical results to the base case. This confirms that the base case does not sample 1st order uncertainty; i.e. patient heterogeneity, other than dichotomous variables such as gender.

Applying the probabilistic sensitivity analysis of the model and unchecking all sampling with the exception of the patient baseline characteristics should correctly sample patient heterogeneity. This has quite a large impact upon results. While the net costs increase to £930 the net QALYs increase to 0.104 and the cost effectiveness estimate improves to £8,933 per QALY. This result is mirrored in the parallel sensitivity analyses when comparing dapagliflozin with canagliflozin. There is no intuitive reason for these results and it may be a result of a lack of model convergence since it is still being run with only 5,000 patients and 5,000 model runs. The ERG does not have confidence that it has reliably conducted this scenario analysis and will do further work on it. But time constraints and the amount of time the model takes to run have meant that it has not been possible to do this for the current report.

Table 66 Pairwise comparison of dapagliflozin and empagliflozin 10mg: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	-£35	0.004	Dominant
SA01: Orals discontinued	£10	0.004	£2,721
SA02: Remove placebo/natural history effect	-£35	0.004	Dominant
SA03: UKPDS 68 event equations	-£31	0.005	Dominant
SA04: No BMI QoL	-£35	0.003	Dominant
SA05: No patient heterogeneity sampling	-£35	0.004	Dominant
SA06: PSA patient characteristic sampling	-£45	0.005	Dominant
SA07: No discontinuations	£6	0.002	£3,729
SA08: Not subtracting no comp costs	-£37	0.004	Dominant
SA09: No triple therapy hypoglycaemia	-£36	0.001	Dominant
SA10: Pioglitazone £225 per year	n.a.	n.a.	n.a.
SA11a: Company NMA: Base case random effects	£50	-0.006	Dominated
SA11b: Company NMA: Base case fixed effects	£1	-0.002	Dominated
SA11c: Company NMA: End point random effects	£49	-0.006	Dominated
SA11d: Company NMA: End point fixed effects	£49	-0.006	Dominated
SA11e: Company NMA: 24 week random effects	£44	-0.005	Dominated
SA11f: Company NMA: 24 week fixed effects	£44	-0.005	Dominated

The scenario analysis SA06 of no discontinuations for the triple therapies means that the 1.9% and 5.3% discontinuation rates for dapagliflozin and empagliflozin 10mg respectively are not applied. As a consequence, patients intensify to insulin at the same time and there are no cost offsets for dapagliflozin from more empagliflozin patients discontinuing and intensifying to insulin.

If at intensification to insulin the orals are discontinued the higher discontinuation rate for empagliflozin now benefits its cost profile and SA01 suggests a small net cost for dapagliflozin.

For the scenarios comparing dapagliflozin with empagliflozin 10mg small cost differences and QALY differences are modelled. It seems reasonable to conclude that dapagliflozin and empagliflozin 10mg are much the same across the base case and the scenarios.

Table 67 Pairwise comparison of dapagliflozin and empagliflozin 25mg: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	-£35	0.003	Dominant
SA01: Orals discontinued	£10	0.003	£3,261
SA02: Remove placebo/natural history effect	-£35	0.003	Dominant
SA03: UKPDS 68 event equations	-£31	0.005	Dominant
SA04: No BMI QoL	-£35	0.002	Dominant
SA05: No patient heterogeneity sampling	-£35	0.003	Dominant
SA06: PSA patient characteristic sampling	-£45	0.004	Dominant
SA07: No discontinuations	£6	0.001	£6,409
SA08: Not subtracting no comp costs	-£37	0.003	Dominant
SA09: No triple therapy hypoglycaemia	-£35	0.001	Dominant
SA10: Pioglitazone £225 per year	n.a.	n.a.	n.a.
SA11a: Company NMA: Base case random effects	£50	-0.006	Dominated
SA11b: Company NMA: Base case fixed effects	£0	-0.002	Dominated
SA11c: Company NMA: End point random effects	£48	-0.006	Dominated
SA11d: Company NMA: End point fixed effects	£48	-0.006	Dominated
SA11e: Company NMA: 24 week random effects	£38	-0.003	Dominated
SA11f: Company NMA: 24 week fixed effects	£39	-0.003	Dominated

For the scenarios comparing dapagliflozin with empagliflozin 25mg small cost differences and QALY differences are modelled. It seems reasonable to conclude that dapagliflozin and empagliflozin 25mg are much the same across the base case and the scenarios.

Table 68 Pairwise comparison of dapagliflozin and canagliflozin 100mg: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	-£124	0.017	Dominant
SA01: Orals discontinued	-£79	0.017	Dominant
SA02: Remove placebo/natural history effect	-£123	0.017	Dominant
SA03: UKPDS 68 event equations	-£99	0.020	Dominant
SA04: No BMI QoL	-£124	0.016	Dominant
SA05: No patient heterogeneity sampling	-£124	0.017	Dominant
SA06: PSA patient characteristic sampling	-£184	0.022	Dominant
SA07: No discontinuations	-£88	0.016	Dominant
SA08: Not subtracting no comp costs	-£127	0.017	Dominant
SA09: No triple therapy hypoglycaemia	-£124	0.013	Dominant
SA10: Pioglitazone £225 per year	n.a.	n.a.	n.a.
SA11a: Company NMA: Base case random effects	£57	-0.008	Dominated
SA11b: Company NMA: Base case fixed effects	£7	-0.004	Dominated
SA11c: Company NMA: End point random effects	£55	-0.007	Dominated
SA11d: Company NMA: End point fixed effects	£57	-0.009	Dominated
SA11e: Company NMA: 24 week random effects	£43	-0.004	Dominated
SA11f: Company NMA: 24 week fixed effects	£44	-0.004	Dominated

For the scenarios comparing dapagliflozin with canagliflozin 100mg, the ERG clinical effectiveness estimates suggest moderate cost savings and moderate QALY gains with dapagliflozin dominating canagliflozin. This situation appears to reverse, though might be better described as turning to broad equivalence, when the company NMA estimates are applied. This may be due the ERG estimates suggesting a slightly greater relative impact upon HbA1c for dapagliflozin compared to canagliflozin 100mg.

Table 69 Pairwise comparison of dapagliflozin and canagliflozin 300mg: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	£110	0.009	£12,875
SA01: Orals discontinued	-£224	0.009	Dominant
SA02: Remove placebo/natural history effect	-£86	0.007	Dominant
SA03: UKPDS 68 event equations	£117	0.014	£8,201
SA04: No BMI QoL	£110	0.009	£11,940
SA05: No patient heterogeneity sampling	£110	0.009	£12,875
SA06: PSA patient characteristic sampling	£259	0.079	£3,284
SA07: No discontinuations	£166	0.006	£27,828
SA08: Not subtracting no comp costs	£106	0.009	£12,441
SA09: No triple therapy hypoglycaemia	£110	0.001	£80,301
SA10: Pioglitazone £225 per year	n.a.	n.a.	n.a.
SA11a: Company NMA: Base case random effects	£263	-0.013	Dominated
SA11b: Company NMA: Base case fixed effects	£227	-0.011	Dominated
SA11c: Company NMA: End point random effects	£262	-0.012	Dominated
SA11d: Company NMA: End point fixed effects	£264	-0.014	Dominated
SA11e: Company NMA: 24 week random effects	£248	-0.010	Dominated
SA11f: Company NMA: 24 week fixed effects	£249	-0.010	Dominated

Due to its greater HbA1c effect, canagliflozin 300mg is estimated to delay the intensification to insulin. In the base case this avoids costs. But in the SA01 scenario analysis where orals are discontinued at intensification to insulin this avoids savings and dapagliflozin comes to dominate canagliflozin 300mg.

Removing the placebo/natural history effect from the ERG estimates as in SA02 causes the HbA1c effect of canagliflozin 300mg and dapagliflozin to be reduced by the same absolute 0.150. This is sufficient for those on canagliflozin 300mg to be modelled as intensifying to insulin at the same time as those on dapagliflozin. As a consequence, the cost saving from delaying intensification to insulin disappears and canagliflozin is estimated to be more costly.

SA01 and SA02 underline the importance of the lack of sampling of patient characteristics at baseline to the model outputs. If all patients have a common HbA1c at baseline the central estimate for treatment effects may be little different between two treatments but this difference may be sufficient for one to model all patients as breaching the 7.5% intensification threshold in, say, year 3 while the other models all as breaching it in year 4. Sampling of patient heterogeneity may reduce this artificial polarisation of

patient experiences and model outputs. But the scenario analysis that samples patient heterogeneity, SA05, presents results which as previous discussed for the comparison with the DPP4-i lack face validity. There is no intuitive reason that the ERG can think of for SA05 to increase the net costs or the net QALYs in the manner in which it does.

For the scenario analyses that use the company NMA for pioglitazone, it has been assumed that discontinuation rates and the proportion of hypoglycaemic events that are severe is the same as the flozins.

Table 70 Pairwise comparison of dapagliflozin and pioglitazone: Scenario analyses

Scenario	Δ Cost	Δ QALY	ICER
Base case	£4,834	0.009	£558k
SA01: Orals discontinued	£1,154	0.009	£133k
SA02: Remove placebo/natural history effect	£4,628	0.011	£440k
SA03: UKPDS 68 event equations	£4,160	0.017	£239k
SA04: No BMI QoL	£4,834	0.000	Dominated
SA05: No patient heterogeneity sampling	£4,834	0.009	£558k
SA06: PSA patient characteristic sampling	£4,579	0.037	£123k
SA07: No discontinuations	£4,974	0.003	£1.8mn
SA08: Not subtracting no comp costs	£4,818	0.009	£557k
SA09: No triple therapy hypoglycaemia	£4,834	0.006	£784k
SA10: Pioglitazone £225 per year	£2,341	0.009	£270k
SA11a: Company NMA: Base case random effects	£4,969	0.006	£866k
SA11b: Company NMA: Base case fixed effects	£4,968	0.006	£872k
SA11c: Company NMA: End point random effects	£4,975	-0.003	Dominated
SA11d: Company NMA: End point fixed effects	£4,972	0.008	£613k
SA11e: Company NMA: 24 week random effects	£4,991	-0.006	Dominated
SA11f: Company NMA: 24 week fixed effects	£4,996	-0.007	Dominated

The scenario analyses suggest that net costs are sensitive to whether orals are discontinued when intensifying to insulin, SA01, and the pioglitazone price, SA09. Other than these scenarios, dapagliflozin results in substantial extra costs. The patient gains remain small throughout, and are dependent upon the quality of life impacts of the weight changes.

4.5 Conclusions of the cost effectiveness section

With regards the scope the main omission that can easily be addressed by the company is the comparison with pioglitazone as it is within its NMA.

The company submission may not provide unbiased estimates of the cost effectiveness of dapagliflozin for two main reasons:

Assuming that oral therapies are discontinued when patients intensify to insulin.
Applying the more dated UKPDS 68 event equations rather than the UKPDS 82 event equations.
Whether the more dated UKPDS 65 costs of complications rather than the UKPDS 84 costs should be applied is also an issue.

For the comparison with pioglitazone and to a lesser extent the DPP4-i assuming that weight gains and weight losses only persist for one year may be unduly pessimistic.

Not sampling patient characteristics at baseline may have unduly polarised the treatment cost estimates for the comparison of dapagliflozin and canagliflozin 300mg. But it seems likely it will also have tended to unreasonably equalise them when the differences in HbA1c are not quite as large as is the case with canagliflozin 100mg and perhaps also the DPP-4i.

4.6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The full results of the additional ERG analyses are tabulated and discussed in section 5.4.

The ERG revisions suggest that dapagliflozin results in additional costs of £615 compared to the DPP4-i, due largely to an increase in treatment costs. Patient benefits are muted at 0.017 QALYs resulting in a cost effectiveness estimate of £37,997 per QALY.

If dapagliflozin and the DPP-4i are discontinued when patients intensify to insulin the additional cost from dapagliflozin is experienced for a much shorter period. Net costs fall to £143 and the cost effectiveness improves to £8,351 per QALY. These results are similar to SA10 of the company scenario analysis, though the net treatment costs are higher possibly due to the ERG addition of the costs of consumables to insulin.

The UKPDS 68 event equations suggest more events are avoided with dapagliflozin than the UKPDS 82 event equations. This provides larger cost offsets and the net cost falls to £495 compared to the DPP4-i while the patient gains increase to 0.020 QALYs, improving the cost effectiveness estimate to £25,329 per QALY.

The company NMA results worsen the effectiveness estimates for dapagliflozin compared to the DPP-4i to around £60k per QALY though this rests upon very small QALY differences. More robust may be that the net costs increase to around £725.

The ERG revisions and scenario analyses suggest virtual equivalence between dapagliflozin and empagliflozin.

The ERG revisions suggest cost savings of around £124 from dapagliflozin compared to canagliflozin 100mg, though these are in part a function of assumptions around differing rates of severe hypoglycaemia. In general there are relatively limited differences in costs, with patient effects ranging between a gain of 0.022 QALYs and a loss of 0.009 QALYs. The ERG clinical assumptions suggest the dapagliflozin formally dominates canagliflozin 100mg, while the company NMA results in the context of the other ERG revisions suggest that canagliflozin 100mg formally dominates dapagliflozin. But in the context of a lifetime of diabetes the differences in costs and QALYs are minor.

The ERG revisions cause dapagliflozin to be more expensive than canagliflozin 300mg by £110 for the base case. Gains of 0.009 QALYs are small, but suggest a cost effectiveness of £12,875 per QALY. The cost increase is due to the ERG assuming the oral therapies are retained when intensifying to insulin. If they are not dapagliflozin is cost saving and dominated canagliflozin 300mg. The QALY gains fall to only 0.001 QALYs if triple therapy hypoglycaemia does not apply. The company NMA results in the context of the other ERG revisions suggest that canagliflozin 300mg formally dominates dapagliflozin.

The company did not consider pioglitazone as a comparator within the economics despite it being within the company NMA. The clinical effectiveness estimates suggest very small patient gains will occur from pioglitazone, though these are in the context of weight gains and losses being assumed to persist for only one year. More concretely, dapagliflozin has considerably higher treatment costs. Net cost estimates are £4,834 for the base case, £2,341 if annual pioglitazone annual drug costs are £225 and £1,154 if patients discontinue their oral therapies when intensifying to insulin.

4.7 End of life

End of life does not apply.

4.8 Overall conclusions

The main differences of economic opinion between the company and the ERG are:

- Do patients cease their oral therapies or continue with them when they intensify to insulin?
- Should the event equations of the UKPDS 68 or the UKPDS 82 be applied?
- Should the costs of diabetes and its complications be drawn from the UKPDS 65 or the UKPDS 84?
- Is it necessary to include the values at diagnosis within the UKPDS 68 risk factor evolution equations?
- Should pioglitazone, which is considerably cheaper than the other comparators, be considered?

Other uncertainties include:

- Should there be sampling of 1st order uncertainty given the CARDIFF model structure?
- Should weight gains rebound to natural history after one year, at treatment intensification or never?
- Should weight losses rebound to natural history after one year, at treatment intensification or never?
- Whether the annual cycle for intensification within a model with a six month cycle is reasonable and whether it may have unduly polarised the handling of treatment costs.
- Should the Currie et al insulin coefficient be applied when calculating the QALY decrements from hypoglycaemia and if so what is its likely impact?
- Should treatments be differentiated by discontinuation rates?
- If pioglitazone is a comparator, what annual direct drug cost should be applied?

5 DISCUSSION

5.1 Principal findings

- Dapagliflozin is effective in triple therapy, with a reduction compared to placebo, of 0.70% HbA1c at 52 weeks. Weight loss of 2.7kg occurred with dapagliflozin compared to 0.6kg on placebo. Systolic blood pressure (SBP) fell by 4.0 mmHg on dapagliflozin and by 0.3mmHg on placebo by 24 weeks but much of the reduction was not sustained at 52 weeks.
- The AstraZeneca submission argues that the three flozins licensed for use in triple therapy – canagliflozin and empagliflozin being the other two – are similar in efficacy and adverse effects, and the ERG broadly agrees with this. There are two adverse effect alerts currently issued for canagliflozin but not for dapagliflozin, amputations and fractures. There has been a warning about acute kidney injury with canagliflozin and dapagliflozin but not with empagliflozin.
- Compared to the DPP-4 inhibitors, the main advantage of dapagliflozin is weight loss. The DPP-4 inhibitors do not cause weight gain or weight loss.
- The AstraZeneca submission ignores pioglitazone as a comparator which the ERG consider to be a major weakness in the submission.

5.2 Strengths and limitations

The use of dapagliflozin in triple therapy was considered in a previous STA but NICE considered that the evidence was insufficient to recommend it. It should be noted that AstraZeneca (and Bristol-Myers Squibb) had not initially submitted evidence on use in triple therapy to that STA in 2012, but were asked by NICE to submit an addendum covering it.

We now have the results of the RCT of dapagliflozin in triple therapy with metformin and sulfonylureas.

The limitations in the AstraZeneca submission include;

- The omission of pioglitazone as a comparator
- The omission of data from the relevant subgroups of the Weber,Cefalu and Leiter trials
- Inconsistencies between data from the Matthaei trial and the NMA
- The trial data on canagliflozin 300mg are based on patients randomised to that dose from the start, whereas according to the licence, patients should be started on 100mg and only switched to 300mg if the effect was insufficient. The results in patients following that sequence may not be as large as in the trial.

The ERG and AstraZeneca had different views on continuation of oral drugs after insulin is started, with the company assuming that only metformin was continued, whereas the ERG assumed that insulin would be an addition not a replacement.

The average age in the Matthaei trial of dapagliflozin in triple therapy was 61. The Astrazeneca submission applied their NMA results to a population resembling those in the trial, but also to a population drawn from the THIN database, with a mean age of 65. However, data from other trials of dapagliflozin, as reported in the pooled analysis by Fioretto and colleagues (2016), showed that dapagliflozin appeared to be more effective in the over 65s, especially as regards HbA1c and blood pressure. So applying the Matthaei results to an older population may underestimate their effects.

5.3 Issues

Are there effectiveness differences amongst the flozins?

A recent systematic review and network meta-analysis by Zaccardi and colleagues from Leicester[107] concluded that canagliflozin 300mg was slightly more effective than dapagliflozin. This study was technically well done, but the ERG has two reservations. Firstly, as previously noted, patients randomised to canagliflozin 300mg may do better than those following the licence sequence of 100mg increasing to 300mg if response is inadequate. Secondly, the analysis does not seem to have adjusted for baseline HbA1c. Of the 38 trials, the three with the lowest baseline HbA1c were all of dapagliflozin, including the Kaku trial with baseline HbA1c 7.5%. Patients with lower baseline HbA1c tend to have lower reductions in trials.

Clinical inertia and the NICE guideline on type 2 diabetes.

If the NICE guideline (NG28)[3] is followed, people with type 2 diabetes will have their glycaemic control regularly monitored, and treatment will be promptly intensified once HbA1c exceeds 7.5% (unless a decision is made not to do so in individualised care). Past appraisals of drugs for type 2 diabetes have noted that many patients do not have prompt intensification. Khunti and colleagues[108] noted that in patients taking two oral agents, who had HbA1c of 7.5% or over, time to intensification by adding a third drug was over 7 years. It remains to be seen whether the 2015 Guideline will reduce clinical inertia. One implication is that if intensification does occur after HbA1c exceeds 7.5%, the reduction in HbA1c will be less than seen in the trials, in most of which HbA1c at baseline was over 8%.

In clinical effectiveness trials, the primary outcome is usually change in HbA1c, with a reduction of 0.5% being seen as clinically significant. However if baseline HbA1c is, say, 8.2% (as in Matthaei 2015 [34]), then even an average reduction of 0.7% will mean that many patients will not achieve the target.

Non-pharmacological interventions

These include intensive lifestyle interventions, bariatric surgery and very low calorie diets, but none were include in the NICE scope.

Update on intensive glycaemic control

Doubt was cast on the value of tight glycaemic control when the ACCORD trial reported a 20% higher cardiovascular mortality in patients randomised to intensive control. The reasons for this have yet to be explained, but the increased risk was seen mostly in patients in the intensive control group but who were poorly controlled. The longer-term follow up of ACCORD,[109] known as ACCORDION, has recently reported and shows no difference in the patients who entered the long-term follow-up (who were of course survivors of the early years) The ACCORD Group also provide a meta-analysis of the ACCORD, UKPDS, VADT and ADVANCE trial showing an odds ratio between intensive and standard care (albeit differently defined) of 0.98 (0.92- 1.04). The message from this is that aiming at tighter control to prevent the microvascular complications of diabetes such as retinopathy, does not increase cardiovascular risk.

Pioglitazone

Triple therapy was considered in the previous STAs of empagliflozin and canagliflozin, but pioglitazone received less attention than in this report. In the ERG report from Southampton, it was noted that pioglitazone "had black triangle status" and that the MHRA had concerns about bladder cancer. The SHTAC ERG also reported that they had received clinical advice that pioglitazone was little used. The SHTAC ERG therefore concluded that pioglitazone was not a relevant comparator.

The searches to support the empagliflozin STA were carried out in early 2014, before the recent large population-based studies of pioglitazone and bladder cancer[13, 16] were published. The IRIS trial in 2016 has provided further reassurance.[17] The NICE empagliflozin guidance (section 4.2) stated "The clinical specialists noted that use of thiazolidinediones is decreasing because of safety concerns, particularly increased risk of bladder cancer."[110]

Research needs

As in previous diabetes STAs and MTAs, many of the differences in lifetime costs and QALYs are too small to be reliable. A QALY difference of 0.001 means about 8 hours.

Asche et al[111] critique 15 studies of the cost-effectiveness of GLP-1 analogues and DPP4 inhibitors in type diabetes, and conclude that the models make unjustified assumptions about the effects of small changes in variables including HbA1c, SBP and weight, on long-term outcomes. These small changes are typically observed in short-term trials but may be assumed to be maintained for many years. The changes are often too small to be regarded as clinically important.

Asche et al recommend that;

"modellers should immediately remove the basic assumption that small clinically inconsequential changes in A1c SBP, lipids and weight result in major clinical improvements in patients."

As recommended in a previous Assessment Group report, we think it would be very useful in NICE would define a clinically meaningful QALY difference. A QALY difference of 0.1 would equate to 36 days. If we are modelling over an average 20 years of expected life (most modelling is done over a 40 year time span), those 36 days represent 0.005% of the lifespan. Any difference of 0.1 or fewer QALYs could be regarded as no difference. Perhaps 0.1 QALY is too small and 0.2 or 0.3 would be better, over a mean expected lifespan of 20 years. The meaningful difference could be expressed as a proportion of expected life expectancy.

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APPENDICES

Appendix 1 Risk of bias assessment

Risk of bias item	Matthaei 2015		Weber 2015	
	Assessment	Support	Assessment	Support
Random sequence generation	Low risk	"Patients on metformin and sulfonylurea were randomized 1:1 via an interactive response system (web or voice based; Perceptive Services Limited)"	Low risk	"Randomisation was done by interactive voice response system."
Allocation concealment	Low risk	As above	Low risk	"Randomisation codes were kept centrally at a Bristol-Myers Squibb facility in Lawrenceville, NJ, USA."
Groups comparable at baseline	Low risk	"The treatment groups were generally balanced with respect to demographics and diabetes-related baseline characteristics, with a higher proportion of women in the dapagliflozin treatment arm."	Low risk	"Baseline demographics and disease characteristics were generally well balanced between treatment groups and additional anti-hypertensive subgroups, although history of cardiovascular diseases differed slightly between additional antihypertensive drug subgroups."
Blinding of participants and personnel	Low risk	"matched placebo (identical in size, color, smell, taste, packaging, and labeling)"	Low risk	"Investigators and patients were masked to treatment allocation throughout the treatment period, after which the data were unmasked for reporting purposes. Masking was done through the identical appearance of the tablets, pill bottles, and labels."
Blinding of outcome assessment	Low risk	According to clinicaltrials.gov, participants, caregivers, investigators, and outcome assessors were blinded	Low risk	As above
Incomplete outcome data	Low risk	Withdrawals and losses to follow-up described and similar between groups, <20% non-completers (7.3% in each group); intention-to-treat analysis; full analysis set included all participants who took at least one dose of study drug and had a nonmissing baseline value and at least one or more postbaseline value for at least one of the outcomes	Low risk	Withdrawals and losses to follow-up described, slightly lower in dapagliflozin group, <20% non-completers (6.2 to 9.8%); intention-to-treat analysis; full analysis set included all participants who took at least one dose of study drug and had at least one baseline value and at least one postbaseline value
Selective reporting	Low risk	All outcomes reported as specified on clinicaltrials.gov	Low risk	All outcomes reported as specified on clinicaltrials.gov

Study power	Unclear risk	Power analysis not reported	Low risk	80% power to detect a difference of 4 mmHg systolic blood pressure (change from baseline) and 94% power to detect a 0.4% difference of HbA1c (change from baseline) with 204 patients per group, assuming 5% discontinuation (achieved)
Other bias	Low risk	None identified	Low risk	None identified
Overall	**8/9 low risk**		**9/9 low risk**	

Appendix 2 Review of statistical methods for NMA of dapagliflozin in triple therapy regimens

The company submission undertook a network meta-analysis (NMA), which was critically appraised by the ERG using a standard approach. The NMA was of RCTs comparing triple therapy combinations of dapagliflozin with MET and SU in adults with type 2 diabetes mellitus poorly controlled on MET and SU. It did not include any evidence on triple therapy for patients poorly controlled on dual therapy with MET plus DPP4-i as it judged that the comparators for which evidence was identified were outside the scope of the appraisal (i.e. acarbose) or were part of a disconnected network (i.e. exenatide). The NMAs included classes of drugs within the same networks rather than considering only individual drugs separately. It focused on the continuous outcomes of the difference in the mean change in HbA1c, weight and SBP and the binomial outcome of subjects with any hypoglycaemia using the odds ratio. Fixed-effect and random-effects models were estimated, although the AstraZeneca submission identified that the likelihood of heterogeneity meant that random-effects models were the *a priori* model of choice. Given differences in the time points at which the studies assessed outcomes, NMAs examined the outcomes at three different time points (i.e. 24 weeks, 52 weeks and study endpoint) and for a base case restricted network (i.e. a network incorporating only DPP4-is and SGLT2-is comparators only – regardless of duration). The AstraZeneca submission stated that planned sensitivity analyses would investigate the effects of study quality, sub-group data, study design, heterogeneity and missing data on outcomes and meta-regression would assess the effects of baseline HbA1c.

The evidence networks were presented through network diagrams, highlighting both the classes and individual drugs included. Although these clearly identified the studies that were included in the different networks, the diagrams were presented for the restricted base case NMAs and sensitivity analyses only. Evidence networks for the studies included for the 24 weeks, 52 weeks and study endpoint NMAs are not presented or the differences in included studies presented. The models used a Bayesian approach through Markov Chain Monte Carlo (MCMC) simulation in WinBUGS, adapting standard code recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU). The AstraZeneca submission stated that vague priors were used for unknown parameters. No details are provided in the submission regarding the distributions or link functions used in the models, but it appears from the WinBUGS code (Appendix 9) that Normal likelihoods were used for the continuous outcomes and binomial likelihoods with logit link functions were used for the binomial endpoints. Clarification from AstraZeneca (Clarification A11, p18-19) indicated that sensitivity analyses were performed on prior distributions using different 'uninformative priors' (changing range from 0-5 to 0-10) and informative priors (using lognormal priors). These increased uncertainty but had limited effect on the point estimates.

The AstraZeneca submission reports that all the models were estimated using three chains starting from different initial values of select unknown parameters. Models used a burn-in period of at least 20,000 iterations and at least 100,000 iterations to update the model. It states that convergence was assessed through history plots of the chains for the relevant parameters (overlapping histories indicating convergence) and Brooks-Gelman-Rubin statistics (ratio of between and within-chain variability equals 1) (plots were provided in clarification A12 and the accompanying appendix). Accuracy of the posterior estimates was assessed using the Monte-Carlo error (error of < 5% of sample standard deviation for each parameter considered acceptable). An assessment of autocorrelation was undertaken (clarification A12, p19-20), affecting the comparison between dapagliflozin plus metformin plus sulfonylurea with basal insulin plus metformin plus sulfonylurea. Appropriate measures were taken to limit the effects of autocorrelation and it was thought to have a limited effect on convergence.

Clinical and statistical heterogeneity was assessed through summarising possible sources and for pairwise comparisons using the I^2, tau and Cochran's Q statistics respectively. Meta-regression was also used to explore the possible causes of heterogeneity, appearing to focus on the effects of baseline HbA1c on the outcomes of mean change in body weight and hypoglycaemia. Although baseline HbA1c was the only covariate considered, other characteristics were identified in the AstraZeneca submission as differing between the studies and it may have been beneficial to assess their influence (e.g. study duration, participant characteristics). Clarification by AstraZeneca stated that the evidence base was insufficient to support meta-regression including these covariates (clarification A14, p20-21). Inconsistency between direct and indirect evidence was evaluated where possible, through calculation of the inconsistency factor (using R software). Given the limited evidence base, there were limited closed loops from which to assess consistency. Sensitivity analyses were planned and presented providing an assessment of the effects of study quality, sub-groups, heterogeneity and missing data (cross-over studies were also identified for analysis a priori, however none were identified). Model fit was assessed using the Deviance Information Criterion (DIC), with models with a DIC at least 3 points lower than their comparator signifying an improved fit. The mean total residual deviance was also used to select the preferred model, with models selected based on those with a mean total residual deviance that was closest to the number of fitted data points. Assessment of the measures of model fit were confined in the submission to comparisons between fixed-effect and random-effects models for each outcomes measure for the base case restricted NMA, without a similar comparison with models for the different time points or from the sensitivity analysis and the meta-regression. Subsequent clarification (A13, p20) showed that sensitivity analyses for the outcomes of bodyweight, SBP and hypoglucaemia showed improved model fit compared with the basecase models, however the effects on model outcomes were limited. For HbA1c, sensitivity analyses had limited effect.

The AstraZeneca submission states that it took the decision to group the different treatments into their respective drug classes (apart from SGLT2-is) rather than assessing all of the treatments individually. Although this is based on an assumption that some, if not all, the treatments are similar (i.e. non-inferior), it does lead to concerns regarding the NMA. The 'lumping' of evidence can affect consistency, lead to heterogeneity, difficulties in interpreting results and potential conflict between direct and indirect evidence. It would have been more appropriate if the NMA had considered the individual treatments separately as well as the class effect.

Although the assessment of study outcomes is described, with these differing from intention to treat, modified intention to treat, last observation carried forward and per protocol, limited information is provided regarding the potential effects on the NMA. Limited data are provided on the baseline characteristics of the participants in the studies included in the NMA and the possible effects on the NMA. With studies differing on participant age (mean 55 to 62 years), sex (37.5% to 64.1 % male), average HbA1c (mean 8.0 to 8.8) and duration of diabetes (mean 7.3 to 10.9 years), it may have been beneficial to incorporate these in NMAs using meta-regression (where data allowed). Although the AstraZeneca submission recognises that heterogeneity may affect the NMA, it only investigates the effects of baseline HbA1c through meta-regression (due to sparse evidence). The network diagrams highlight that many of the links between the different treatment combinations are based on one study only, raising the issue of the possible effects of sparse evidence (i.e. wide credible intervals and global measures of fit having limited discriminatory powers). Sparse evidence and random-effects models may result in wider credible intervals, which may influence interpretation of the outcome of the NMA. Such issues can be assessed through increasing the evidence from an expanded network, examining the influence of vague and informative priors and through additional sensitivity analyses.

In summary, the AstraZeneca submission outlines many of the aspects of the methods used in its NMAs, but some uncertainty remains regarding some areas. Not all networks are clearly presented, meaning it is unclear the extent of the evidence that underpins the analyses. The NMA provides limited details regarding its approach to sensitivity analyses concerning elements of the modelling process (e.g. prior distributions, link functions and priors for parameters). Although the submission does not provide an assessment of autocorrelation, diagnostic plots regarding model convergence or measures of model fit, these were presented as clarifications by AstraZeneca and provided limited concerns. The occurrence of heterogeneity was assessed through summary measures and sensitivity analyses, though only the effects of baseline levels of HbA1c were assessed through meta-regression. Other possible causes of heterogeneity were identified in the AstraZeneca submission, but these were not examined due to limited data. Limitations in the evidence base may mean that the NMA is affected by sparse data, which can

influence the credible intervals and measures of fit. This may have been part of the rationale for presenting a NMA that included classes of treatments with individual treatments, rather than treatment classes and individual treatments separately. Such lumping may have led to concerns regarding consistency, heterogeneity, interpretation of results and potential conflict between the direct and indirect evidence. Although these possible shortcomings may influence the outcome of the NMAs, the nature and extent of the effect remains uncertain.

Appendix 3 Quality assessment of trials included in NMA

The AstraZeneca submission presented a quality assessment using criteria recommended by NICE for the RCTs included in the restricted network (Table 21 p. 72) and expanded network (Appendix 3.1). This is summarised in Table 71 together with the ERG's judgement. The ERG quality assessment agrees with most of the company assessment, although there were some differences as noted in the comments in Table 71.

Three studies (in italics in Table 71) were excluded due to poor quality in sensitivity analysis (Appendix 14.1). Poor quality was defined as an open label study design (p.71) or trials that were not double-blinded (p. 76); one of these trials (Nogueira 2014) was excluded from the ERG's preferred network. The ERG notes that blinding in Nogueira 2014 was judged as unclear rather than high risk of bias. However, the Nogueira 2014 publication does not mention blinding at all, unlike the other trials in the AstraZeneca restricted network, which were described as double-blind but were judged as unclear risk of bias due to limited additional details (such as blinding procedures and who was blinded). The ERG therefore considers it appropriate for the company to exclude Nogueira 2014 in the sensitivity analysis on this basis. Nevertheless, it may be questioned whether there is sufficient justification for using absence of blinding as the definition of poor quality in otherwise well-conducted trials.

Table 71 Company and ERG assessment of quality of trials

Trial	Judgement	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Selective reporting	ITT analysis
Haering 2015	**AZ:**	Low	Low	Low	Unclear	Low	Low	Low
	ERG:	Low	Low	Low	Unclear	Low	Low	Low
Hermansen et al., 2007	**AZ:**	Low	Low	Low	Unclear	Low	Unclear	Low
	ERG:	Low	Low	Low	Unclear	Low	Unclear	Low
Hong et al., 2015	**AZ:**	*Low*	*Unclear*	*Low*	*High*	*Low*	*Low*	*Unclear*
	ERG:	*Low*	*Unclear*	*Low*	*High*	*Unclear*	*Low*	*High*
	Comment: Numbers withdrawing described and similar between groups, but no reasons given, assessed as an unclear risk of bias. Analysis was per protocol, assessed as a high risk of bias.							
Ji et al.,	**AZ:**	Low	Low	Low	Unclear	Low	Low	Low

Trial	Judgement	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Selective reporting	ITT analysis
2015	**ERG:**	Low	Unclear	Low	Unclear	Low	Low	Low
Liu et al., 2013	***AZ:***	*Low*	*Low*	*Low*	*High*	*Low*	*Low*	*Low*
	ERG:	*Low*	*Low*	*Unclear*	*High*	*Low*	*Unclear*	*Low*
	Comment: Cholesterol and triglycerides significantly different between groups at baseline, possibly owing to chance, assessed as unclear risk of bias Aspartate aminotransferase (AST) stated as an outcome but no results reported, assessed as an unclear risk of bias							
Lukashevich 2014	**AZ**	Unclear	Unclear	Low	Unclear	Low	Low	Low
	ERG:	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low
	Comment: Numbers withdrawals with reasons reported, some imbalance between groups, assessed as unclear risk of bias No clinical trials record to assess selective reporting of outcomes, assessed as unclear risk of bias							
Matthaei et al., 2015	**AZ:**	Low	Low	Low	Low	Low	Low	Low
	ERG:	Low	Low	Unclear	Low	Low	Low	Low
	Comment: proportion of women significantly different between groups, assessed as unclear risk of bias							
Moses et al., 2014	**AZ:**	Low	Low	Low	Unclear	Low	Low	Low
	ERG:	Low	Low	Low	Unclear	Low	Low	Low
NCT01590771	**AZ:**	Unclear	Unclear	Low	Low	Low	Low	Low
	ERG:	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
	Comment: Numbers withdrawals with reasons reported, some imbalance between groups, assessed as unclear risk of bias Described as double blind but no details reported, assessed as unclear risk of bias No details of analysis reported, assessed as unclear if ITT analysis							
Nogueira et al., 2014[a]	***AZ:***	*Unclear*	*Unclear*	*Low*	*Unclear*	*Unclear*	*Unclear*	*Unclear*
	ERG:	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Unclear*
	Comment: LDL-cholesterol significantly different at baseline between groups, therefore unclear risk of bias							
Owens et al., 2011	**AZ:**	Unclear	Unclear	Low	Unclear	Low	High	Low
	ERG:	Unclear	Unclear	Low	Unclear	Low	Low	Low
	Comment: Results for all outcomes are reported in the clinical trial registry (https://clinicaltrials.gov/ct2/show/study/NCT00602472?sect=Xj0156)							
Round et al., 2013 /	**AZ:**	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
	ERG:	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Trial	Judgement	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Selective reporting	ITT analysis
Moses 2016	**ERG full paper**	Unclear	Unclear	Low	Low	Low	Low	Low
	Comment: Differences between CS and ERG assessment of quality based on Round et al 2013 abstracts are: no details of baseline characteristics reported in study abstracts, assessed as unclear; and withdrawals for total group only reported, assessed as unclear as not reported by study arm and reasons not provided. ERG identified the full publication for this study (Moses 2016) and have assessed this to enable a view on the study's risk of bias to be considered							
Scherntha ner et al., 2013	**AZ:**	Low	Low	Low	Low	Low	Low	Unclear
	ERG:	Low	Low	Low	Low	Unclear	Low	Low
	Comment: number and reasons for withdrawals reported, some imbalance between groups, assessed as unclear risk of bias Study used modified ITT analysis, assessed as low risk of bias.							
Wilding et al., 2013	**AZ:**	Low	Low	Low	Low	Low	Low	Low
	ERG:	Low	Low	Unclear	Low	Unclear	Low	Low
Comment: proportions of males and females at baseline differed between groups, assessed as unclear risk of bias. Number and reasons for withdrawals reported, some imbalance between groups, assessed as unclear risk of bias								
Additional trials[b]:								
Charpentier et al., 2009	**AZ:**	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
	ERG:	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Comment: HOMA-IR differed between groups at baseline, assessed as unclear risk of bias Number and reasons for withdrawals provided, some imbalance between groups, assessed as unclear risk of bias.								
Home et al., 2015	**AZ:**	Low	Low	Low	Unclear	Low	Low	Low
	ERG:	Low	Low	Unclear	Unclear	Unclear	Low	Low
Comment: baseline characteristics appear unbalanced for male/female and race categories, assessed as unclear risk of bias Numbers and reasons for withdrawals provided, some Imbalance between groups, assessed as unclear risk of bias.								

[a] Excluded from ERG's preferred network. [b] Included in ERG's preferred network.

Appendix 4 Clarification questions on NMA

ERG question	AstraZeneca answer (sometimes abbreviated)
Given the centrality of lipids in the UKPDS 68 and the UKPDS 82, why were lipids not included in the NMA?	No answer
Given both the gender imbalance in study 5 and that the economic modelling requires the patient BMI, why was BMI not considered within the NMA?	Change from baseline in BMI was rarely reported by the studies included in the systematic review. Only one study in the restricted NMA reported BMI change.
Why were discontinuation rates not included in the NMA?	New analyses have been carried out and presented in the clarification responses.
The NMAs incorporate evidence from drug classes and individual drugs in the same network. Was any assessment undertaken to look at these separately (i.e. classes in a NMA and individual drugs in another NMA)? If so, please could the results be provided?	The comparison of dapagliflozin and the DPP4is used a pooled analysis and no evaluation against individual drugs within this class was undertaken. A network meta-analysis (Craddy 2014, provided) of the DPP4is as a triple therapy with metformin and sulfonylureas concluded that there were no statistically significant differences amongst sitagliptin, linagliptin and vildagliptin.
The AZ submission does not discuss whether a sensitivity analysis was undertaken on the different elements in the NMA models, specifically whether prior distributions, link functions and priors for parameters were examined. Please could any sensitivity analysis be outlined and the effects on the outcomes presented?	Sensitivity analyses were performed on the prior distributions in two ways. Analyses were performed to compare different ”uninformative” priors and to assess the effect of using informative priors. The effect of uninformative priors was assessed by changing the breadth of uniform distributions (changing the range from 0-5 to 0-10). The assessment of informative priors involved the use of lognormal priors, as recommended by Turner et al. In both of these scenarios, the effect estimates were similar, but the uncertainty of the posterior estimates was increased. As a result, it was judged that the model was sensitive to avoidable uncertainty introduced by unrealistically broad priors, but was robust to different shaped priors. Based on this analysis, we selected fixed effects models as more suitable over uninformative priors random effects model. For HbA1c CFB, body weight CFB and SBP CFB, REM model was selected on the basis of low DIC and total residual deviance.
The AZ submission does not present any diagnostic plots or summary measures regarding model convergence (i.e. history plots, Brooks-Gelman-Rubin plots/statistics, Monte-Carlo error). Also, no mention is made of whether	In addition to visual inspection of chains for mixing, Brooks-Gelman-Rubin plots were produced (and provided with clarification responses). Autocorrelation was present in the model, primarily when comparing dapagliflozin

autocorrelation was assessed and if it was a concern. Please could comment be provided regarding whether these were undertaken, whether they were considered appropriate and, where possible, provide clearer details?	plus metformin plus sulfonylurea with basal insulin plus metformin plus sulfonylurea. However the autocorrelation observed declined consistently across lags and did not appear to cause problems with convergence. We did re-run the analyses with a larger thin value, but it did not improve the convergence rate or alter the results.
Measures assessing model fit are provided for decisions regarding the use of a fixed-effect or random-effects model, however these are not provided for any other models (e.g. meta-regression or sensitivity analyses). Could these be provided?	Measures of model-fit for fixed and random effects models for all sensitivity analyses were provided with the clarification responses.
The NMAs synthesize relatively sparse evidence. Were the effects of the sparse evidence base assessed and were other approaches considered to overcome any subsequent problems?	The restricted network (base case) included only 14 studies. However we also performed analyses using the expanded network, which included all relevant data from broad literature searches. The majority of results from the expanded network were in line with those from the restricted network.
The AZ submission presents meta-regression for HbA1c only, despite noting that other factors are likely to cause heterogeneity. Were other factors included in a meta-regression analysis? If so, please could the outcomes be provided?	There was a challenge in this analysis in that the evidence network overall was comparatively sparse. We attempted to balance the need to account for observed heterogeneity against the need to avoid over-fitting or adding avoidable uncertainty to the model. We did this by investigating, for each likely covariate, whether there as a correlation between the covariate and the dependent variable and, if so, whether there was sufficient information available to incorporate that covariate into the full statistical model. Feasibility was checked for meta-regression for baseline BMI and disease duration. Meta regression for BMI and disease duration was not feasible. One of the major assumptions of meta-regression is that there should be a correlation between a dependent variable and explanatory variable. To check the correlation, scatter plots were drawn. The plots indicate lack of correlation between dependent and independent variable as the pattern is fairly random. In addition, the value of R2 indicates poor goodness of fit for the regression equations. Hence it was concluded that the baseline BMI and disease duration have no

	significant effect on the outcomes and no meta-regressions were performed. Scatter plots were provided with the clarification responses.

Appendix 5 Baseline characteristics of trials in restricted NMA

Baseline characteristics of the trials included in the AstraZeneca restricted NMA, and the ERG additional trials, can be seen in Table 72. Data on HbA1c and age were taken from Table 18 and checked against the trial publications; where the data differ this is indicated. Mean HbA1c at baseline was similar and ranged from 8.0% to 8.8%. There was notable heterogeneity in mean weight at baseline, which ranged from 67.4 kg to 92.8 kg among the 13 trials reporting it. Similarly, BMI ranged from 25.7 kg/m^2 to 33.1 kg/m^2. Where reported, the proportion of white participants ranged from 22.6% to 95.4%, again showing notable heterogeneity. Mean ages were similar and ranged between 54.9 to 61 years.

Table 72 Baseline characteristics of trials in restricted NMA

Trial	HbA1c Mean (SD)	Weight Mean (SD)	BMI Mean (SD)	SBP Mean (SD)	Ethnicity % (or Country)	Age, Mean (SD)
Haering 2015	8.1 (0.8)	76.9 (18.0)	28.2 (5.3)	128.9 (14.1)	W: 39.3 B: 2.0 A: 57.2 O: 1.5	57.1
Hermansen et al., 2007	8.3	87.0	31.0	-	W: 68.1 B: 5.2 A: 12.7 O: 14.0	57.2
Hong et al., 2015	8.5 [8.6][b]	68.2	25.7	129.8	(S. Korea)	61.7 [59.3][b]
Ji et al., 2015	8.0	69.1	25.7	129.5	(China, Malasia, Vietnam)	57.3 [56.2][b]
Lukashevich 2014	8.8 (0.9)	-	28.0 (4.5)	-	W: 22.6 A: 73.0 O: 4.4	55.1
Liu et al., 2013	8.41	67.4	26.2	128.0	(Taiwan)	59.1
Matthaei et al., 2015	8.15	89.4	32.0	135.5	W: 95.4	61
Moses et al., 2014	8.3	81.4	29.3	-	White: 45.1 Asian: 54.9	57

NCT01590771	8.6 (1.0)	-	-		(China)	57.0 (9.4)
Nogueira et al., 2014	8.05	71.3	27.0	135.8	(Brazil)	56.8
Owens et al., 2011	8.15	76.6 (16.8)	28.3 (4.7)	-	W: 46.6 B: 0.8 A: 51.7 O: 0.9	58.1 (9.8)
Round et al., 2013 / Moses 2016	8.4	77.1	29.2	-	W: 43.8 A: 55.9 O: 0.2	54.9
Schernthaner et al., 2013	8.1 (0.9)	88.3 (23.2)	31.6 (6.9)	130.7	W: 64.2 B: 11.7 A: 17.5 O: 6.6	56.7 (9.5)
Wilding et al., 2013	8.1 (0.9)	92.8 (22.4)	33.1 (6.5)	130.4	W: 82.5 B: 5.5 A: 0.9 O: 11.1	56.8 (9.3)
ERG additional trials:						
Charpentier et al., 2009	8.15	-	29.15	137.8	(France) W: 85.8[a]	59.7
Home et al., 2015	8.3	90.5	32.0	-	W: 72.2 B: 8.7 A: 13.8 O: 5.4	55.7

[a] 'Caucasian'. [b] Different data in trial publication than in CS Table 18. SDs presented where reported. Means for total study population estimated by ERG if not presented in publication. W, White; Black/African American; A, Asian; O, Other.

Appendix 6 Lipid changes

Trial	Changes on drug, mmol					Changes on placebo or other drug, mmol				
	Total cholesterol	**LDL-C**	**HDL-C**	**L/H ratio**	**TGs**	**TC**	**LDL-C**	**HDL-C**	**L/H ratio**	**TGs**
Haering 2015 24 weeks 72 weeks	10mg: 0.08 (0.04) 25mg: 0.20 (0.05) 10mg: 0.16 (SD 0.05) 25mg: 0.19 (SD 0.05)	10mg: 0.04 (0.04) 25mg: 0.10 (0.04) 10mg: 0.09 (SD 0.04) 25mg: 0.10 (SD 0.04)	10mg: 0.05 (0.01) 25mg: 0.05 (0.01) 10mg: 0.06 (SD 0.01) 25mg: 0.04 (SD 0.01)	10mg: 0.01 (SD 0.04) 25mg: 0.02 (SD 0.04)	10mg: 0.03 (0.09) 25mg: 0.17 (0.09) 10mg: 0.01 (0.08) 25mg: 0.12 (SD 0.08)	0.03 (0.04) 0.07 (SD 0.05)	0.02 (0.04) 0.06 (SD 0.04)	−0.02 (0.01) -0.02 (SD 0.01)	0.10 (SD 0.04)	0.08 (0.09) 0.10 (SD 0.08)
Hong 2015 24 weeks	-	-0.3 (95% CI -0.7, 0.0)	-0.1 (95% CI -0.1, 0.0)		-0.9 (95% CI -1.9, -0.1)	-	-0.3 (95% CI -0.6, 0.0)	-0.1 (95% CI -0.2, 0.0)	-	-1.0 (95% CI -1.8, -0.1)
Ji 2015 18 weeks	-	100mg: 0.23 (SE 0.07) 300mg: 0.24 (SE0.07)	100mg: 0.11 (SE 0.03) 300mg: 0.14 (SE 0.03)	100mg: 0.01 (SE 0.06) 300mg: −0.03 (SE 0.06)	100mg: −0.17 (SE 0.16) 300mg: −0.18 (SE 0.16)	-	0.00 (SE 0.07)	0.06 (SE 0.03)	−0.09 (SE 0.06)	0.25 (SE 0.16)
Liu 2013[a] 24 weeks	0.26 (SE 0.1)	0.17 (SE 0.1)	0.16 (SE 0.03)	-	-0.27 (SE 0.1)	0.02 (SE 0.1)	-0.03 (SE 0.1)	0.03 (SE 0.03)	-	0.07 (SE 0.1)
Matthaei 2015[a,b]	Wk 24: 0.17 (95% CI 0.01, 0.32) Wk 52: 0.1 (SD 1.2)	Wk 24: 0.14 (95% CI0.01, 0.28) Wk 52: 0.1 (SD	Wk 24: 0.05 (95% CI 0.02, 0.09) Wk 52: 0.1 (SD	Wk 24: 0.00 (95% CI 0.00, 0.01) Wk	Wk 24: -0.14 (95% CI-0.33, 0.05) Wk	Wk 24: -0.13 (95% CI-0.28, 0.03) Wk	Wk 24: -0.15 (95% CI-0.28, -0.01)	Wk 24: 0.00 (95% CI-0.04, 0.03) Wk 52: 0.00	Wk 24: 0.00 (95% CI -0.01, 0.0) Wk	Wk 24: 0.04 (95% CI-0.15, 0.24) Wk

Trial	Changes on drug, mmol					Changes on placebo or other drug, mmol				
	Total cholesterol	**LDL-C**	**HDL-C**	**L/H ratio**	**TGs**	**TC**	**LDL-C**	**HDL-C**	**L/H ratio**	**TGs**
		1.0)	0.4)	52: -0.1 (SD 0.9)	52: -0.1 (SD 1.5)	52: 0.00 (SD 1.0)	Wk 52: 0.00 (SD 0.8)	(SD 0.3)	52: -0.1 (SD 0.9)	52: 0.1 (SD 1.1)
Moses 2014	-	-	-	-	-	-	-	-	-	-
Moses 2016 (Round 2013) % Change from baseline[c]	2.6 (95% CI -0.2, 5.3)	6.7 (95% CI 2.9, 10.5)	1.0 (95% CI -1.3, 3.3)	-	-9.8 (95% CI -16.0, -3.6)	1.3 (95% CI -1.5, 4.2)	2.2 (95% CI -1.7, 6.2)	2.6 (95% CI 0.3, 5.0)	-	-5.4 (95% CI -11.4, 0.6)
Schernthaner 2013	-	0.16 (SE 0.04)	0.07 (SE0.01)	0.01 (SE 0.04)	0.03 (SE 0.06)	-	0.01 (SE 0.04)	-0.01 (SE0.01)	0.03 (SE 0.04)	0.06 (SE 0.06)
Wilding 2013	-	100mg: –0.02 (SE 0.06) 300mg: 0.11 (SE 0.06)	100mg: 0.06 (SE 0.02) 300mg: 0.06 (SE 0.02)	100mg: –0.14 (SE 0.05) 300mg: –0.04 (SE 0.05)	100mg: 0.02 (SE 0.09) 300mg: –0.07 (SE 0.09)	-	0.00 (SE 0.06)	0.02 (SE 0.02)	–0.03 (SE 0.05)	0.12 (SE 0.09)

[a]converted from mg/dl by ERG. [b]change from baseline calculated by ERG for week 52 using a correlation of 0.5 for calculation of SD. [c]end data not reported. '-' = not reported

	Total cholesterol	LDL-C	HDL-C	L/H ratio	TGs	TC	LDL-C	HDL-C	L/H ratio	TGs
Hermansen et al., 2007[a]	-	-	-	-	-	-	-	-	-	-
NCT01590771	-	-	-	-	-	-	-	-	-	-
Owens et al., 2011 24 weeks[b]	0.05 (SD 0.3)	0.13 (SD 0.6)	0 (SD 0.2)	-	0.01 (SD 1.6)	0.05 (SD 0.4)	0.13 (SD 0.6)	0.03 (SD 0.2)	-	-0.14 (SD 2.1)

[a]reported in the narrative only that no differences. [b]converted from mg/dl by ERG. '-' = not reported.

Appendix 7 Sulphonylureas used in trials in NMA

Trial	SU	Comments
Haering 2015	Not stated	Not reported in pdfs, supplements or NCT record
Hermansen et al., 2007	Glimepiride	
Hong et al., 2015	Glimepiride, n/N (%) Total sample: 289/344 (84.0) [Vildagliptin 151/172 (87.8); SU dose increasing 138/172 (80.2)] Gliclazide, n/N (%) Total sample 55/344 (16.0) [Vlidagliptin 21/172 (12.2); SU dose increasing 34/172 (19.8)]	Also reports mean doses at baseline if required (supplementary table 1)
Ji et al., 2015	Not stated	Not reported in pdf, supplement or NCT record
Lukashevich 2014	Glimepiride	
Liu et al., 2013	Glimepiride, n/N (%) Total sample 109/120 (91) [pioglitazone 55/60 (92); sitagliptin 54/60 (90)] Glicazide, n/N (%) Total sample 11/120 (9) [pioglitazone 5/60 (8); sitagliptin 6/60 (10)]	Also reports mean doses at baseline if required (Table 1)
Matthaei et al., 2015	Glicazide, n/N (%) Total group 92/218 (42.2%) [Placebo 51/109 (46.8%); dapagliflozin 41/109 (37.6%)] Glimepiride, n/N (%) Total group 98/218 (45%) [placebo 46/109 (42.2%); dapagliflozin 52/109 (47.7%)] Glyburide, n/N (%) Total group 28/218 (12.8%) [placebo 12/109 (11%); dapagliflozin 16/109	From reporting of subgroup data for hypoglycaemia in the 52 week publication

<table>
<tr><td></td><td>(14.7%)]</td><td></td></tr>
<tr><td>Moses et al., 2014</td><td>Not stated</td><td>Not reported in pdf, no supplement or NCT record identified to check</td></tr>
<tr><td>NCT01590771</td><td>Gliclazide or Glimepiride</td><td>No further details</td></tr>
<tr><td>Nogueira et al., 2014</td><td>Glyburide 100%</td><td>Reports mean doses at baseline if required.</td></tr>
<tr><td>Owens et al., 2011</td><td>Not stated</td><td>Not reported in pdf or NCT record</td></tr>
<tr><td>Round et al., 2013 / Moses 2016</td><td>Glimepiride, n/N (%)
Total group 252/422 (59.7)
[sitagliptin 126/210 (60); placebo 126/212 (59.4)]

Gliclazide, n/N (%)
Total group 170/422 (40.3)
[sitagliptin 84/210 (40.0); placebo 86/212 (40.6)]</td><td></td></tr>
<tr><td>Schernthaner et al., 2013</td><td><table><tr><th></th><th>Sita, n=378</th><th>Cana n=377</th><th>Total group n=755</th></tr><tr><td>Glipizide</td><td>40 (11)</td><td>47 (12)</td><td>87 (12)</td></tr><tr><td>Glipizide extended release</td><td>18 (5)</td><td>16 (4)</td><td>34 (5)</td></tr><tr><td>Glyburide /glibenclamide</td><td>133 (35)</td><td>128 (34)</td><td>261 (35)</td></tr><tr><td>Glimepiride</td><td>106 (28)</td><td>121 (32)</td><td>227 (30)</td></tr><tr><td>Gliclazide</td><td>30 (8)</td><td>26 (7)</td><td>56 (7)</td></tr><tr><td>Gliclazide modified release</td><td>50 (13)</td><td>37 (10)</td><td>87 (12)</td></tr><tr><td>Glyburide micronized</td><td>0</td><td>2 (1)</td><td>2 (<1)</td></tr><tr><td>Tolazamide</td><td>1 (<1)</td><td>0</td><td>1 (<1)</td></tr></table></td><td>From supplement table</td></tr>
<tr><td>Wilding et al.,</td><td>Not explicitly stated</td><td>Not reported in pdf or NCT record. Pdf lists possible SU</td></tr>
</table>

2013		doses eligible, but no details of whether these were all used: Glipizide, Glyburide, Glimepiride, Gliclazide, Glicazide modified release, Glipizide extended release
ERG additional trials:		
Charpentier et al., 2009	Glibenclamide, n (%) Total group 105/296 (35.5%) Glimepiride, n (%) Total group 97/296 (32.8%) Gliclazide, n (%) Total group 91/296 (30.7%) Glipizide, n (%) Total group 2/296 (0.7%) Carbutamide, n (%) Total group 1/296 (0.3%)	Total number presented from the safety population was 296, elsewhere text states that 284 were on SU at baseline.
Home et al., 2015	Glimepiride 100%	

The highlighted appendix is academic in confidence

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]

AstraZeneca: Factual Inaccuracy Check of ERG Report 28th July 2016

Summary

1. **There are no meaningful differences in safety, efficacy or cost-effectiveness between dapagliflozin and the other SGLT2s (canagliflozin and empagliflozin) used in triple therapy regimens.**
    - The ERG agrees that dapagliflozin is similar in efficacy and safety to canagliflozin and empagliflozin in line with the findings from other NICE appraisals of the SGLT2s (empagliflozin STA; and SGLT2 monotherapy MTA).
    - Using the ERG revised model, dapagliflozin was found to be cost-effective versus both empagliflozin and canagliflozin.
    - All three SGLT2s are exactly the same daily cost in the UK.
    - Further, canagliflozin and empagliflozin have received positive NICE recommendations for use in a triple therapy regimen based on similar economic results as those presented in this appraisal for dapagliflozin.
    - For these reasons, this appraisal presents a pragmatic case for dapagliflozin to be recommended as an option for treating type 2 diabetes in combination with MET + SU as part of a triple therapy regimen.

2. **Dapagliflozin is cost-effective versus DPP4s (on a background of MET + SU)**
    - The economic model has a 40-year (i.e. lifetime) time period with patients moving onto insulin after either dapagliflozin + MET + SU or DPP4s + MET + SU fail. With regard to the economic modelling, the ERG group queries whether or not patients would retain their oral treatments (SGLT2s & DPP4s) when intensifying to insulin.
    - We have gained clinical opinion from 5 clinicians in July 2016 demonstrating varied clinical practice. SGLT2s and DPP4s may be retained or discontinued dependent on various factors; and tailored to meet individual patient needs. Key to this decision is that patients will only retain their oral treatments where there is clinical benefit from the orals. (Please see appendix 1 for further information.)

    ERG – only two clinicians quoted in Appendix 1

    - Using the ERG model, two clinically realistic scenarios demonstrate cost-effectiveness of dapagliflozin versus DPP4s:
        1. Orals discontinued when intensifying to insulin & weight effect (including weight loss benefit with dapagliflozin) is lost after 1 year since dapagliflozin initiation: ICER = £8,351/QALY
        2. Orals continued when intensifying to insulin & weight effect (including weight loss benefit with dapagliflozin) is not lost after 1 year since dapagliflozin initiation: ICER = £6,914/QALY
    - The ERG base case reflects continuation of orals; and no clinical benefit (i.e. weight loss benefit of dapagliflozin lost after 1 year since dapagliflozin initiation) (ICER of £37,997). This is not a clinically realistic scenario, because

in the event of no clinical benefit, the physician would stop the oral treatments.

ERG comments. The statement immediately above does not make sense. Dapagliflozin reduces hyperglycaemia and blood pressure as well as weight, so it is wrong to say that there is "no clinical benefit" if the weight loss benefit is assumed to be lost by one year. That assumption was used by AstraZeneca in their submission (see page 123). The ERG report regarded the assumption as conservative and pessimistic and this is an area where the EG and AstraZeneca agree. However the amount of weight loss is modest (absolute 3%, placebo-adjusted 2.4%) and would not be expected to have a major effect. A meta-analysis of weight loss studies in type 2 diabetes by Franz et al concluded that weight loss of >5% was required to have beneficial effects on HbA1c, lipids and blood pressure. (J Acad Nut Diet 2015/115/1447-1463)

If a drug was having no clinical benefit, no one would continue it. However when HbA1c rises above 7.5% in patients taking oral agents such as dapagliflozin, it does not mean that dapagliflozin is having no glucose-lowering effect – without it, HbA1c would have risen rather more.

3. We do not consider pioglitazone to be a comparator to dapagliflozin in the population of this appraisal (patients failing on MET + SU) for the following reasons:

a) There is low use of pioglitazone in the population specific to this appraisal:
   - Specifically regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy IMS data (Patient Data, IMS Information Solutions UK Ltd, May 2016) show that 5% of patients are prescribed pioglitazone plus MET plus SU versus 61% being prescribed DPP4s + MET + SU; and 19% prescribed SGLT2s plus MET plus SU. The remaining patients were prescribed various triple therapy regimens (please see appendix 2 for further information).
   - The equivalent IMS data in December 2015 also showed that 5% of patients are prescribed pioglitazone plus MET plus SU indicating that there has been no significant change in the level of prescribing of pioglitazone in this specific population in the six months following the publication of the NICE guideline in December 2015.

b) Pioglitazone was not considered a comparator for the empagliflozin STA in 2014. The rationale for this decision remains.
   - For the empagliflozin STA, the Southampton ERG concluded that pioglitazone was not a relevant comparator referring to MHRA concerns about bladder cancer; and clinical advice that pioglitazone was little used.

   ERG comments. The Southampton ERG report was completed in December 2013 and was on canagliflozin. The evidence base on pioglitazone and bladder cancer is much stronger now.

   - Bladder cancer risk remains in the pioglitazone SPC after the EMA Phamacovigilance Risk Assessment Committee (PRAC) ruling in April 2016 considering the most up to date data.

ERG Comments
The PRAC document reports two observational studies on bladder cancer risk but does not give references, so we do not know whether they include the most up-to date studies. Note that if these refer to the Azoulay 2012 and Tuccori 2016 studies, it should be noted that these were not independent studies, but were by the same group using the same database for patients starting anti-diabetic drugs 1988 - 2009 and 2000-2013. So there is considerable overlap with 2000-2009 patients in both studies.
There is a comment from the EMA that;

"As a result of this variation the Product information has been updated to reflect the fact that although some epidemiological studies have suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, not all of them have identified a statistically significant increased risk."

The date of the evidence review by EMA is not given, nor which studies were included. The most recent studies were by Levin et al 2015 and Lewis et al 2015, and Kernan 2016. See ERG report for details.

- We have gained clinical opinion from five clinicians in July 2016, who state that pioglitazone is rarely used. (please see appendix 1 for more information).

ERG comments. Appendix 1 has comments from only two clinicians, one anonymous. Competing interests are not reported.

Issue 1 The data presented on pioglitazone use in the UK in the ERG report is for all diabetes patients. It is not specific to the population of this appraisal.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20 – table 1 – Prescriptions for selected diabetes drugs, England, 2015. The data presented on pioglitazone use in the UK is for all diabetes patients. It is not specific to the population of this appraisal (Adults with type 2 diabetes, who are inadequately controlled on dual therapy with MET with a SU.)	IMS data in the population specific to this appraisal should be presented rather than table 1 giving data for all diabetes patients. Specifically regarding patients who were previously prescribed metformin and sulfonylurea (the relevant population of this appraisal), and are currently prescribed triple therapy IMS data (Patient Data, IMS Information Solutions UK Ltd, May 2016) shows low use of pioglitazone + met + SU (5%) versus 61% for DPP4s + met + SU; and 19% for SGLT2s + met + SU (May 2016). The remaining patients were prescribed various triple therapy regimens (please see appendix 2 for more information). The equivalent IMS data in December 2015 also showed that 5% of patients are prescribed pioglitazone plus MET plus SU indicating that there has been no significant	It is important to consider data on real world use of treatments in the population specific to this appraisal to demonstrate the most appropriate comparators to dapagliflozin + MET + SU. Data in the population specific to this appraisal supports the comparators proposed in the submission dossier: the DPP4 class; and the other SGLT2s (canagliflozin and empagliflozin). It does not support pioglitazone as a comparator as there is low use of pioglitazone in this specific population.	The low use may be because of past concern about bladder cancer. The ERG view is that recent evidence is reassuring on bladder cancer. Note that there is also low use of the individual SGLT2 inhibitors, so the same argument could apply to them

	change in the level of prescribing of pioglitazone in this specific population in the six months following the publication of the NICE guideline in December 2015. Please see appendix 2 for more detail.		

Issue 2 The information presented on the risk-benefit profile of pioglitazone is misleading as the data has not been collated in a systematic way.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20- 21 – Bladder cancer section There is no evidence that the data on this topic has been collated in a systematic way. Further, some of the trials cited (such as the IRIS trial with 94% of patients not having diabetes) are not in the correct population. The conclusion that recent evidence on pioglitazone and bladder cancer is largely reassuring does not align with the recent EMA Phamacovigilance Risk	The statement on page 21, which does not align with the recent PRAC ruling should be removed: “In summary, recent evidence on pioglitazone and bladder cancer has been largely reassuring”. The conclusion of the recent PRAC ruling should be added in its place to clarify that bladder cancer risk remains in the pioglitazone SPC.	The current information is inaccurate; and misleading; and does not align with the recent EMA PRAC ruling on bladder cancer risk.	As noted above, the PRAC document does not provide references. It mentions “two observational studies”. There are more than that now. The April PRAC document may be recent, but the evidence base may be out of date. ERGs in STA do not have the time to do systematic reviews, but the searches for studies of pioglitazone and bladder cancer were broad, and identified recent very large population base studies plus recent correspondence in the BMJ which provided other sources of evidence, and which discussed confounding factors in diabetes and bladder cancer, notably that

Assessment Committee (PRAC) ruling in April 2016. After considering the most up to date data on this matter and the totality of the evidence, “the PRAC concluded that the evidence is insufficient to substantially alter the existing product information warnings or implemented risk minimisation strategy”. The bladder cancer risk remains in the pioglitazone SPC (May 2016).			people with type 2 diabetes appear to be at increased risk of bladder cancer, and that people treated with pioglitazone may be at higher risk before such treatment.
Page 20-23 Benefits of pioglitazone beyond glycaemic control including cardiovascular risk reduction; and the effect on non-alcoholic fatty liver disease are described yet do not align with the information regarding these topics in the pioglitazone SPC.	The information below from the pioglitazone SPC should be added to this section: The pioglitazone SPC does not refer to effects of pioglitazone in improving NAFLD. The SPC rather states “Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease”. The pioglitazone SPC does not refer to CV risk reduction. The pioglitazone SPC rather states: “The PROACTIVE study failed regarding its primary CV-	The current information is not aligned with the pioglitazone SPC.	See the ERG report, page 23, for the NICE view on pioglitazone and NAFLD.

	outcomes composite endpoint; and the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed."		

Issue 3 Economic modelling: The ERG base case includes continuation of oral therapies when escalating to insulin in the absence of clinical benefit, which is clinically unrealistic.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, 17, 122 Page 12-15, 96, 124 The ERG revised base case includes the continuation of oral therapy costs when escalating to insulin; however, it employs the assumption regarding the persistence of weight effects by which	The ERG base case should be revised to present a more clinically appropriate scenario. Suggested alternatives: • Orals discontinued when intensifying to insulin where no costs or benefits of orals are accrued in the model • Orals continued when intensifying to insulin where costs	Recently published type 2 diabetes NICE guidance states that at insulin initiation, the continued need for other blood glucose lowering therapies should be reviewed [1]. We agree with the ERG that the evaluation of dapagliflozin compared to DPP-4 inhibitors is likely to be "unduly pessimistic" (ERG report page 14), as a result of the assumption that weight changes associated with triple therapy persist for one year and then rebound to natural history. On Page 96 of the ERG report, it states "that is does not seem reasonable to assume those intensifying to insulin will cease their oral therapies". This is consistent with the recent SGLT2 inhibitor monotherapy MTA, in which retaining oral treatment when intensifying therapy was a Committee-preferred assumption [3]. However, combined with a further MTA committee and ERG preferred assumption regarding	No factual error. Note that the NICE guidance does not say oral agents should be stopped. No revision required. These are points to be debated. The ERG report contains scenario analyses that address these points. But the model does contain ongoing benefits from oral therapies. It may rather be unrealistic in scenario SA01 where they are

<table>
<tr>
<td>dapagliflozin weight loss is lost after 1 year since dapagliflozin initiation, which it refers to as “overly pessimistic” (ERG report page 14).

This is not a clinically realistic scenario, because in the event of no clinical benefit, the physician would stop the oral treatments.</td>
<td>and benefits of orals are accrued in the model</td>
<td>the immediate rebound of weight loss this would result in the continued use of an SGLT-2 inhibitor being associated solely with additional cost and no clinical benefit (the ERG assumes that HbA1c target can be achieved with insulin initiation via insulin dose titration (Page 53) and no maintenance of any weight loss benefit). The persistence of an oral therapy providing no clinical benefit is inconsistent with the current NICE guidance for insulin initiations.

In the original assessment of dapagliflozin (TA288) for all indications, the Committee-preferred scenario was gradual convergence of differences in weight between treatment groups at the time of escalation [2]; this scenario was also associated with the cessation of dapagliflozin at escalation. The ICER comparing dapagliflozin with a DPP4i with the cessation of dapagliflozin at escalation (£8,351) is as presented in the ERG report (Table 65, page 115); however, this is based on the pessimistic assumption that weight changes are lost after one year since dapagliflozin initiation.

Emerging evidence from routine clinical practice has shown continued weight loss in patients receiving dapagliflozin in both the triple oral therapy setting and as an add-on to insulin (CPRD analysis – see Appendix 4). Consequently, a logical assumption (considering guidance from NICE) is that the persistence of an SGLT2 within the management of T2DM at insulin initiation would be associated with at least some clinical benefit.

The table below presents results of analysis conducted using the ERG model and ERG base case data and assumptions, with the following exception: after one year, weight changes associated with triple therapy are not lost and natural history progression is modelled.

Cost-effectiveness estimates are similar to those of ERG SA01.

<table>
<tr><th rowspan="2">Comparator</th><th rowspan="2">Analysis</th><th colspan="3">Dapagliflozin versus comparator</th></tr>
<tr><th>ΔCost</th><th>ΔQALY</th><th>ICER</th></tr>
<tr><td>DPP-4i</td><td>ERG base case</td><td>£651</td><td>0.017</td><td>£37,997</td></tr>
</table>
</td>
<td>discontinued to assume no rebound upon their withdrawal.

The ERG would highlight that it cannot change the CARDIFF model structure.

The ERG disagrees with the comment about “persistence of an oral therapy with no clinical benefit”. If triple therapy with dapagliflozin was insufficient and insulin was started, continuing dapagliflozin would mean that a lower insulin dose was required, that hypos would be less of a risk, that the weight gain with insulin would be less, and that SBP would be lower.</td>
</tr>
</table>

<table>
<tr>
<td></td>
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<td>
<table>
<tr><td></td><td>ERG SA01: Orals discontinued</td><td>£143</td><td>0.017</td><td>£8,351</td></tr>
<tr><td></td><td>Orals continued; weight effect not lost after 1 year</td><td>£589</td><td>0.085</td><td>£6,914</td></tr>
<tr><td rowspan="3">Empagliflozin 10mg</td><td>ERG base case</td><td>-£35</td><td>0.004</td><td>Dominant</td></tr>
<tr><td>ERG SA01: Orals discontinued</td><td>£10</td><td>0.004</td><td>£2,721</td></tr>
<tr><td>Orals continued; weight effect not lost after 1 year</td><td>£9</td><td>0.008</td><td>£1,209</td></tr>
<tr><td rowspan="3">Empagliflozin 25mg</td><td>ERG base case</td><td>-£35</td><td>0.003</td><td>Dominant</td></tr>
<tr><td>ERG SA01: Orals discontinued</td><td>£10</td><td>0.003</td><td>£3,261</td></tr>
<tr><td>Orals continued; weight effect not lost after 1 year</td><td>-£9</td><td>0.007</td><td>£1,317</td></tr>
<tr><td rowspan="3">Canagliflozin 100mg</td><td>ERG base case</td><td>-£124</td><td>0.017</td><td>Dominant</td></tr>
<tr><td>ERG SA01: Orals discontinued</td><td>-£79</td><td>0.017</td><td>Dominant</td></tr>
<tr><td>Orals continued; weight effect not lost after 1 year</td><td>-£92</td><td>0.036</td><td>Dominant</td></tr>
<tr><td rowspan="3">Canagliflozin 300mg</td><td>ERG base case</td><td>£110</td><td>0.009</td><td>£12,875</td></tr>
<tr><td>ERG SA01: Orals discontinued</td><td>-£224</td><td>0.009</td><td>Dominant</td></tr>
<tr><td>Orals continued; weight effect not lost after 1 year</td><td>£167</td><td>-0.009</td><td>Dominated</td></tr>
</table>
</td>
<td>Note that the cost and QALY differences in this table are trivial in the context of a life-time model.

For example, differences in lifetime cost of £9 and QALYs of 0.007 should be regarded as showing no difference.</td>
</tr>
<tr>
<td>Page 96

The ERG selectively cite previous evaluations to support their approach; however there is no consistent precedent.</td>
<td>Selective citation of previous evaluations should be removed; all relevant evaluations should be discussed (e.g. TA288) in the context of modelled effects of treatment and rationale for continuation of therapies at intensification.</td>
<td colspan="2">Please refer to discussion of TA288 above.</td>
<td>No factual error.

No revision required.

The company appears to be equally selective. The ERG has mainly based its opinions on the recent NICE clinical guidelines, and the MTA of SGLT2s for monotherapy which was similarly informed by the recent NICE clinical guidelines. To the ERG</td>
</tr>
</table>

			these seem to be reasonable sources.

Issue 4 Potential errors in ERG-derived clinical efficacy profiles in the ERG-revised economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG responses
Page 53-54 Unknown sources/derivation of clinical efficacy applied within ERG-revised base case. The values used lack face validity	Full description should be provided of the sources and methods utilised by the ERG to derive the clinical efficacy profiles used in the revised base case. The clinical efficacy profiles should be revised if they cannot be justified.	On page 53 of the ERG report, the following is stated: "In Table 9, we replace some of the AstraZeneca NMA figures with alternatives." The source and derivation of these values are unclear. We are concerned that the ERG-revised base case ICER comparing dapagliflozin to a DPP4 (£37,997 per QALY) appears to be based on incorrectly applied HbA1c reductions; in particular the DPP4i arm of the ERG-revised base case exhibits greater efficacy compared to dapagliflozin (Table 9, page 54)). This is inconsistent with the NMA data and results presented in the submission. It is expected that the methods and results for an amended NMA would be clearly reported.	The sources of most of the ERG alternative figures in Table 8 are given in the preceding pages and are taken mainly from trials included in the AstraZeneca NMA. We should have made that clearer. For example, the HbA1c lowering effect of canagliflozin are averages of the Ji and Wilding trials. The DPP4i effect in Table 9 is slightly less than in AstraZeneca table 38, and as explained on page 50, is taken from the Craddy meta-analysis. The figure of 0.7% for dapagliflozin is taken from the Matthaei trial. No amended NMA was carried out. In STAs, the ERG is not resourced to do its own NMAs.

Issue 5 Choice of risk equations in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	
Page 95 The ERG-revised base case utilises the UKPDS 82 event equations without proper consideration of the uncertainty introduced by their use without robust data describing the additional risk factors utilised in these equations.	The additional uncertainty associated with the use of the UKPDS 82 event equations should be addressed.	The manufacturer submission supplied analysis using the UKPDS 68 equations in the base case, with UKPDS 82 equations used in scenario analysis. Since the previous assessment of dapagliflozin (TA288) applied the UKPDS 68 equations, this submission allows for a direct comparison with the previous assessment. The ERG assert that "much if not all diabetes modelling will switch to the use of the UKPDS 82 equations in preference to the UKPDS 68 equations". The ERG cites published validation analysis to support this (in terms of slightly improved external validation results obtained when using the UKPDS 82 equations). However, the same published analysis also discusses how the additional risk factors required for the UKPDS 82 equations are highly influential (in terms of predicted risk) and their baseline values are not routinely reported and their time dependent trajectories not well characterised (albuminuria, eGFR, heart rate, LDL cholesterol and white blood cell count). In this light, the wholesale switch to using UKPDS 82 by the diabetes modelling community assumed by the ERG is reliant upon a significantly better understanding of the dynamic profile of these risk factors, in particular renal function. It should be noted that no such baseline data were available for use in the current evaluation,	No factual error. No revision required. It should also be borne in mind that the company submission to the recent MTA of SGLT2s for monotherapy used the CARDIFF model and the UKPDS 82 equations. The company appears to be cherry picking when to use the UKPDS 68 and when to use the UKPDS 82. The company is correct to highlight the lack of evolution equations for the UKPDS82 specific risk factors. But given that there are no treatment specific effects upon these risk factors their evolution would be the same between the arms, much as for the TC:HDL ratio in the company and the ERG modelling. So there is little reason to think that the net effects between treatments would be particularly affected, just as with the TC:HDL ratio. The ERG has provided a scenario analysis that uses the UKPDS 68 equations.

		and use of the UKPDS 82 equations relied on assumptions of no natural progression of these risk factors over time. It is inappropriate to ignore the considerable uncertainty associated with the use of the UKPDS 82 equations within this context.	

Issue 6 ERG report disregards company's revised analysis submitted during ERG clarification stage

Description of problem	Description of proposed amendment	Justification for amendment	
Throughout ERG report The ERG report seems to disregard the revised results submitted at the clarification state	References to issues that were addressed at this stage should be removed from the ERG report/revised to acknowledge their resolution.	It is not appropriate to disregard further information provided to the ERG at the clarification stage.	No factual error. No revision required. It may be appropriate to note "The company submitted revised company analyses at clarifications correcting some of modelling issues identified in section 4.3.3 of the ERG report and the company states that the model outputs were not much affected by these changes. These company changes and new model runs were not requested at clarification, the ERG did not receive the corresponding electronic model and the ERG has not cross checked these revised analyses." In the opinion of the ERG it is not reasonable for the company to take the opportunity at clarification to submit a set of revised analyses and demand that the ERG parse and cross check these. The ERG painstakingly and time consumingly cross checks the electronic

			model that the company submits. For this to then be obviated by the company choosing to correct various errors in their submission and revise their model more than half way through the ERG STA timetable thereby requiring the ERG to undertake another full cross check of an electronic model with the company revised analyses (which was not submitted by the company at clarification in any case) seems unreasonable to the ERG.

Issue 7 Potential errors in economic modelling results presented by ERG

Description of problem	Description of proposed amendment	Justification for amendment	
Page 115 onwards Potential error in SA11	Revise results	The results presented for SA11 could not be replicated using the ERG model and ERG-revised base case data and assumption. For example, Dapagliflozin versus DPP-4i was associated with an ICER of £40,734 rather than ~£60k, as reported in the ERG report.	The company is correct in the ICER it identifies, and also that there is a general problem with the SA11 ICERs in the ERG report. The ERG has re-run all the SA11 scenario analyses and attaches these as an appendix.

Issue 8 Sampling baseline characteristics in the economic modelling

Description of problem	Description of proposed amendment	Justification for amendment	
Page 86; it is stated that "The company suggests that variance-covariance	Remove/revise section	We stand by the original statement in the clarification queries response that the rationale for independent sampling of baseline	No factual error.

data is rarely available, but this is a little disingenuous of the company. The company is aware of the patient sampling of the recent NICE clinical guideline, which provides a variance-covariance matrix for the baseline characteristics required for the UKPDS68 modelling."		characteristics within the Cardiff Model is based on the limited availability of variance-covariance data within the modelled population (the manufacturer's base case). Though a variance-covariance matrix is available in NG28 its application to different populations may not be appropriate; further, the additional risk factors required for the UKPDS 82 equations are not reported and would therefore require additional assumption to be applied.	No revision required. The company is correct to note that the full set of inputs for the UKPDS 82 does not have a variance-covariance matrix within the NICE clinical guideline. But the NICE clinical guideline does provide a variance covariance matrix for the large majority of the inputs to the UKPDS 82 and it is specific to those starting triple therapy. The ERG is also explicit in it being a full variance-covariance matrix for the baseline characteristics required for the UKPDS68 modelling.

Issue 9 Use of baseline characteristics as proxy for "at diagnosis" values in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	
Page 76 and 85; discussion of values at diagnosis within the UKPDS 68 equations	Revise section	The use of baseline characteristics as a proxy for values at diagnosis is an acknowledged limitation of the model; one that commonly applies to T2DM models. This approach was developed as instructed by the previous ERG as part of TA288 [2]. It is uncommon that baseline and at diagnosis data is available; indeed this data was not available for the population modelled in the manufacturer's base case.	No factual error No revision required Values at diagnosis and at baseline for the NICE clinical guideline patient characteristics data is also available.

		The impact of this limitation should not be overstated.	
Page 98	Revise section	The ERG were unable to make the change they wished due to a misunderstanding of the way in which the model works; this issue was not raised at the clarification stage.	No factual error No revision required

Issue 10 Other factual inaccuracies regarding the cost-effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	
Page 12; misleading statement made "there is no ready cross check of whether these are the values being used within the model"	Remove statement	Loaded values can be viewed in the "Used profile" sections of the hidden input worksheets; the ERG modified these worksheets to conduct their analysis.	No factual error No revision required It is correct that the used profile sections can be examined. But this only applies to costs, quality of life and baseline characteristics. There does not appear to be any corollary of this for the treatment effect inputs to the model as far as the ERG can see which is obviously key to the modelling.
Page 14 and 15; it is stated that "The costs of metformin and sulfonylurea are omitted from the model." Application of Met+SU is stated as a change made by the ERG	Remove statement	This is factually inaccurate; this was addressed in the revised model and results provided to the ERG at clarification stage (query C9) showed negligible differences in incremental results.	No factual error No revision required See previous response regarding cross checking of revised models submitted at clarification.

Page 24, annual drug costs for some drugs presented in figure 1 are inconsistent with those presented elsewhere in the ERG report (e.g. table 20, page 69; and the text within page 108)	Edit figure 1 so as to be consistent with the costs presented elsewhere	Ensure consistency	The costs in text in page 108 are for all DPP4is and all flozins, as per table 20.
Page 62; misleading discussion of application of standard errors	Revise/remove statement	Statement is misleading. The manufacturer's base case is based on a mean values analysis. Standard errors are utilised within PSA only. This was discussed at ERG clarification stage.	No factual error No revision required The statements on page 62 are correct and consistent with the company response.
Page 68; misleading discussion of disutility associated with weight gain	Revise/remove statement	The following is stated: "It appears that within the modelling this is applied to both weight gains and weight losses associated with treatment. As a consequence, it may be applied to patients with a BMI of less than 25kgm-2. This could slightly benefit dapagliflozin compared to the DPP4-i, but would be of only very marginal benefit for dapagliflozin compared to the other SGLT2-is." As discussed at the clarification stage modelled BMI is always above 25 kg/m^2. Baseline BMI far exceeds 25.	No factual error No revision required It is not clear to the ERG that with sampling the BMI will always be above 25 kg/m^2.
Page 69; it is stated that "Additional annual costs of metformin £25.29 and of sulfonylurea £29.46 are listed in the submission but have not been applied."	Remove statement	This omission was rectified at the clarification stage (query C9). The ERG were provided with revised results and a revised model containing these costs which showed showed negligible differences in incremental results.	No factual error No revision required See previous response regarding cross checking of revised models submitted at clarification.

Page 70; it is state that “The company base cases appear to have been run over 5,000 patients.”	Revise statement	The manufacturer’s base case is based on a cohort of 5,000 patients simulated 5,000 times, as stated in the submission. (Please see response to clarification query C1).	No factual error No revision required But the company has clarified that each patient cohort is run through the model 5,000 times. It may be reasonable to amend this to read “The company base cases appear to have been run over 5,000 patients with each cohort being run through the model 5,000 times”.
Page 76; it is stated that “But there may be an error in the implementation of switching therapies.”	Remove statement/revise section	This statement is factually inaccurate and the section is misleading. As described in the response to ERG clarifications (Question B5) there is no error in the model but as suggested the model only allows switches in therapies to occur at the end of each year. All therapies are subject to the same structural assumption within the model. This approach is common within T2DM models, with most models operating over annual cycles.	No factual error No revision required Within the context of a model with a six month cycle (or indeed an annual cycle) in the opinion of the ERG it is an error for patients to not switch therapy during the cycle after which their HbA1c is modelled as rising above the switching value. This still strikes the ERG as an error, unless the company is arguing that patients only ever intensify therapy on the calendar anniversary of starting therapy.
Page 84; it is stated that “Due to the modelling also apparently assuming that there are no hypoglycaemic events associated with insulin”	Revise section	This statement is factually inaccurate; the revised company analysis included the hypoglycaemic events associated with insulin at clarification stage, which showed negligible differences in incremental results. Please see response to clarification query B2.	No factual error No revision required See previous response regarding cross checking of revised models submitted at clarification.
Page 90; the following points are	Remove/revise	These points were all addressed in the revised model submitted to the ERG. at clarification	No factual error

factually inaccurate/misleading • The annual therapy costs for DPP4-i and dapagliflozin of £424 and £477 are associated with standard errors of £85 and £95, while the costs of the other treatments are deterministic. • The number of symptomatic hypoglycaemic events for insulin + metformin is set to zero in the model • The proportion of symptomatic hypoglycaemic events that are severe for insulin + metformin is set to zero in the model. • The cost of symptomatic hypoglycaemic events of £45 (s.e. £9) and the cost of severe hypoglycaemic events £380 (s.e. £76) are not applied in the model when patients intensify to insulin. • Additional annual costs of metformin £25.29 and of sulfonylurea £29.46 are listed in the submission but have not been added. Since the metformin costs are common to all therapies and minimal differences in		stage, which showed negligible differences in incremental results. Furthermore, any values entered for standard errors associated with treatment costs would have no impact on the analysis undertaken since sampling of treatment costs was not conducted. Please see the responses to clarification queries C1, C9 and B2.	No revision required See previous response regarding cross checking of revised models submitted at clarification. It is not clear to the ERG that sampling of treatment costs was not undertaken within any company analyses and the ERG would ask the company to cross check this point for the PSA analyses that were submitted. The company response also does not appear to address the last bullet. The ERG does not understand the relevance of the responses to clarification queries C1, C9 and B2 for this point which may means that the ERG has not understood the company points.

survival are modelled, their exclusion is unlikely to affect results much. The exclusion of sulfonylurea costs might affect results slightly. • In the empagliflozin 10mg arm an annual insulin costs of £0.00082 per kg per day, or around £26 per year for those on triple therapy appears to have been accidentally included.			
Page 93; it is stated that "It appears that the company modelling has used the standard errors for the sampling of 1st order uncertainty"	Remove/revise section	This statement is factually inaccurate, as discussed at the clarification stage (query C1). Standard errors are utilised in PSA only, to model uncertainty around the model inputs (i.e. not to model 1st order uncertainty).	No factual error No revision required When sampling 1st order uncertainty – which the ERG assumes was sampled during the company PSA analyses - it appear that standard errors rather than standard deviations have been used.
Page 97; incorrect cost in Table 45	Revise	Table suggests inconsistent application of SU costs across arms	No factual error No revision required SU is assumed to be discontinued when intensifying insulin therapy. The differences in costs between the 3rd and 4th column is £62 for all therapies.
Page 97; discussion of duration of weight loss	Revise	It is unclear that the ERG have retained the company's base case approach	No factual error No revision required Section 5.4 is explicit in the changes the

			ERG has made to the company model.
Page 105; SA05	Remove/revise description of analysis and interpretation of subsequent results	The manufacturer and ERG-revised base cases both employed mean values analysis in which patient characteristics were not sampled. SA05, run using mean values analysis, would by definition have no impact on modelled results. This was clarified at the clarification stage.	No factual error No revision required In the opinion of the ERG and as per the ERG discussion this provides a cross check that patient heterogeneity is not sampled in the base case.

Issue 11 Dapagliflozin data included in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG felt that data from other trials (by Weber et al, Leiter et al, Cefalu et al) could have been used in the NMA. It should be clarified that the populations; and sub-groups of these trials were not considered appropriate for inclusion in the NMA.	The rationale for exclusion of these studies from the NMA should be added to the ERG report: <u>Cefalu and Leiter studies</u> We have presented the sub-group data (patients taking MET + SU at baseline) for the Cefalu & Leiter studies (studies 18 & 19) in Appendix 20 of the NICE submission (see table 52 in appendices). As Studies 18 and 19 only included patients with cardiovascular disease, these studies are not directly representative of the target patient population receiving triple oral therapy considered for this submission, which is the reason why these data were not included in the NMA and were provided as supportive evidence only. <u>Weber study</u> The Weber 2016 trial mentioned is not relevant to the decision problem of this appraisal as it includes a broad	It should be clear that these trials were considered by AstraZeneca; and deemed inappropriate for inclusion in the NMA.	The AstraZeneca explanation for omitting the Cefalu and Leiter trials from the NMA is that these two trials were in people with cardiovascular disease. But in the single trial used for dapagliflozin in the NMA, Matthaei 2015, 86% of recruits had a prior history of cardiovascular disease (Matthaei 2015a, table 1). So the difference in CVD prevalence is slight. Furthermore, there is no reason why the presence of CVD should have a major effect on lowering of HbA1c. In Matthaei, HbA1c was reduced by 0.7%. In the two omitted trials, HbA1c was reduced by 0.5%, with overlapping CIs.

	population uncontrolled on oral antihyperglycaemic drugs, insulin, or both rather than a specific population failing on MET + SU at baseline as specified in the scope of this appraisal. Further, the Weber paper presents sub-group data based on type of anti-hypertensive medication rather than type of OAD medication		Weber As we said in the ERG report (page 34), we note that the published subgroup data were by type of BP lowering drugs, but nevertheless the study data could have been analysed by OAD medication subgroup to provide data for the AstraZeneca submission. So overall, the analysis could have used data from a much larger group of patients.

Issue 12 It should be clarified that the main outputs of the NMA are compatible with the dapagliflozin trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG
One of the limitations of the Astrazeneca submission was cited as inconsistencies between data from the Matthaei trial and the NMA (section 5.2, pg 125, ERG report). The NMA results are correct; and compatible with the results of the Matthaei trial.	The main outputs of the NMA are compatible with the results of the Matthaei trial as explained below; and in appendix 3. This should be clarified in the ERG report. <u>Relative vs absolute values from the NMA:</u> <u>Relative values</u> The relative values from the NMA were derived using used Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS. Code for the NMA was based on that recommended by the	The methods and NMA results should be described clearly in the ERG report.	As noted earlier, the ERG did not carry out any NMA.

National Institute for Health and Clinical Excellence (NICE) Decision Support Unit (NICE 2013). See page 76 in the initial dossier for further information of the methods to obtain the relative values.

The relative values from the NMA are presented in tables 26-29 in the initial submission dossier.

Absolute values

To provide economic model inputs on the absolute scale for each NMA outcome (i.e. absolute change in HbA1c, weight and SBP, and the absolute probability of hypoglycemia), the relative effect outputs from the NMA were combined with an estimate for the absolute change in the reference treatment – in this analysis, placebo plus MET plus SU. The weighted average results of the placebo arms (provided in the Excel sheet attached) were used as anchor values for each outcome and combined additively to the relative effect estimates for each agent (for hypoglycemia, this was done on the natural log scale).

The below table compares the change from baseline results from Matthaei 2015 with the absolute values derived using weighted average of placebo treatment arms for each outcome.

Table 1: Dapa CFB results from Matthaei vs CFB results from NMA (52 weeks)

Outcome	Dapagliflozin	Dapagliflozin

	results from Matthaei 2015 (52 weeks)	results from NMA used in model input sheet (52 weeks)
CFB HbA1c (%)	-0.8	-0.85
CFB Body weight (kg)	-2.9	-2.2
CFB SBP (mmHg)	-1.0	-3.16
Any hypoglycaemia (%)	15.6	20

As the relative values are combined with the 'weighted average of placebo treatment arms from all trials included in the NMA', the absolute values are unlikely to match the absolute values from the single dapagliflozin Matthaei trial.

Change in HbA1c: The NMA results provide dapagliflozin versus placebo relative reduction in HbA1c levels as 0.70% (table 26, pg 81 in the submission). This value is aligned with the placebo

	corrected HbA1c values at 52 weeks reported in dapagliflozin CSR (-0.74%* vs -0.72%$ in the dossier figure 9 pg 56). Weighted average of placebo treatment arms included in the NMA (-0.15%) was calculated and added to the relative results (-0.7%) to derive the absolute change in baseline values for dapagliflozin (-0.85%). The absolute change from baseline HbA1c value reported in Matthei 2015 is -0.8% (table 15, page55 of the dossier) which is similar to the calculated results in the model input sheet (-0.85%). <u>Change in Body Weight:</u> The NMA results provide dapagliflozin versus placebo relative reduction in body weight as 1.9 kg (Table 27, page 84 in submission). This value is aligned with the placebo corrected body weight values at 52 weeks reported in dapagliflozin CSR (-1.98 kg* vs -2.18 kg$ in dossier figure 10 page 56). Weighted average of placebo treatment arms included in the NMA (-0.3 kg) was calculated and added to the relative results (-1.9 kg) to derive the absolute change in baseline values for dapagliflozin (-2.20 kg). The absolute change from baseline body weight reported in Matthei 2015 is -2.9 kg which is similar to the calculated results in the model input sheet. <u>Change in SBP:</u> The NMA results provide dapagliflozin versus placebo relative reduction in SBP as 2.038 mmHg (table 28 page 87 in the dossier). This value is aligned with the placebo corrected SBP		

	values at 52 weeks in dapagliflozin CSR (-2.2 mmHg). Weighted average of placebo treatment arms included in the NMA (-1.092 mmHg) was calculated and added to the relative results (-2.038 mmHg) to derive the absolute change in baseline values for dapagliflozin. The placebo values varied across the placebo controlled studies leading to a weighted average -1.092 mmHg. This resulted in higher absolute values for dapagliflozin for SBP as compared to Matthaei 2015 publication (-1.0 mmHg). This is due to the placebo effect in Matthaei of a slight worsening effect of SBP with placebo (1.1 mmHg) versus the pooled placebo effect from the NMA showing a slight improvement in SBP (-1.092 mmHg). <u>Any hypoglycaemia:</u> The NMA provides dapagliflozin versus placebo odds ratio of 2.09 signifying that the odds of occurrence of any hypoglycaemia event with dapagliflozin are two times more than placebo. This is aligned with the odds ratio calculated from Matthaei 2015 (OR=2.04 calculated using reported proportion of any hypoglycaemia i.e. 15.6% with dapagliflozin versus 8.3% with placebo). Weighted average of placebo treatment arms of studies included in the NMA (10.8%) was calculated and added to the relative results to derive the absolute values for dapagliflozin. The average probability calculated from placebo treatment arms of studies included in the NMA (0.108) impacts the % of any hypoglycaemia observed with dapagliflozin (0.202). The odds ratio remains the same (twice as compared to placebo) but the calculated probability of any hypoglycaemia with dapagliflozin is slightly higher as compared to the		

results in the dapagliflozin trial.

Table 2 highlights similar dapagliflozin vs place + Met + SU relative results obtained from NMA and as observed in Matthaei 2015.

Please also see appendix 3.

Severe hypoglycaemia: The model inputs were derived from the head to head canagliflozin versus sitagliptin trial; and not from the NMA as data was not reported for this outcome in the dapagliflozin trial (Scherthaner 2013).

Table 2: Comparison of dapa vs Pbo relative values from NMA and Matthaei (52 weeks)

Outcome	Dapa vs Pbo +Met + SU (NMA results, 52weeks)	Dapa vs Pbo +Met+ SU (pbo corrected results from CSR,52 weeks)
CFB HbA1c (%)	-0.7	-0.74
CFB Body weight (kg)	-1.9	-1.98
CFB SBP (mmHg)	-2.04	-2.2
Any hypoglycaemia	2.09 (Odds Ratio)	15.6% for dapa 8.3% for pbo+Met + SU

	(%)				

Issue 13 There is a factual inaccuracy regarding adverse effect alerts for amputations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report refers to the adverse effect alert for amputations issued for canagliflozin, but not for dapagliflozin. (page 17; and page 49).	The EMA update of 8 July 2016 should be included: "The scope of the review, which initially only covered canagliflozin, has been extended to include the other medicines in the same class, dapagliflozin and empagliflozin. This is because the potential risk being evaluated for canagliflozin may be relevant for the other medicines in this class."	To ensure regulatory information is up to date and accurate	Noted. This came in very late in the production of the ERG report and was missed. But we think it's a bit harsh of EMA since we have seen no reports or alerts of dapagliflozin and amputations.

Appendix 1: Clinical opinion: Quotations obtained in July 2016

We spoke to five clinicians and asked them the following questions. In summary, in response to question 1, clinicians stated that pioglitazone is rarely used; and in response to question 2, we heard that there is varied clinical practice. SGLT2s and DPP4s may be retained or discontinued when intensifying to insulin dependent on various factors; and tailored to meet individual patient needs. Key to this decision is that patients will only retain their oral treatments where there is clinical benefit from the orals.

We were able to gain the following written quotations from two clinicians within the time period allocated for factual accuracy check of ERG report.

1. **Regarding the most appropriate comparators for 'dapagliflozin + MET + SU' in patients failing on MET + SU**

AstraZeneca has compared dapagliflozin+MET+SU versus 1. DPP4 + MET + SU; and 2. the other SGLT2s+MET+SU (canagliflozin and empagliflozin). The independent technical group has queried whether pioglitazone+MET+SU should also be a comparator.

Our question for you:
Based on clinical practice, in addition to the two comparators above, do you consider that pioglitazone+MET+SU should also be a comparator to dapagliflozin+MET+SU in the population failing on MET + SU?
Please give a reason for your answer, if possible.

"Although pioglitazone is included in the current NICE guidelines (NG 28) as an option for triple therapy when glycaemic control is inadequate on metformin plus a sulphonylurea, in my experience this is rarely used in clinical practice (probably less than 5% of the time in this situation). It would be much more common to consider a DPP-IV inhibitor or an SGLT2 inhibitor (and in very obese patients with a BMI>35 kg / m2, an injectable GLP-1 RA). The reasons for this are partly related to the known contraindications for TZD use (eg heart failure, bladder cancer, microscopic haematuria), but also because of concerns over fracture risk, particularly in post-menopausal women. More importantly, patients do not like the weight gain and fluid retention that are very common adverse effects with pioglitazone; fluid retention may also unmask previously undiagnosed heart failure with normal ejection fraction that is common in people with type 2 diabetes. When offered the alternatives of a DPP-IV inhibitor, pioglitazone, or an SGLT2 inhibitor (which have very similar effects on glycaemic control), and assuming no contraindication to any of the drugs, with a full explanation of benefits and common adverse effects patients tend to choose either a DPP-IV

inhibitor (weight neutral, few adverse effects) or an SGLT2 inhibitor (weight loss but a risk of genital tract infection). " (John Wilding, Professor of Medicine & Honorary Consultant Physician, Obesity and Endocrinology Research, Theme Lead for Metabolism and Nutrition Institute of Ageing & Chronic Disease, University Hospital Aintree)

"In my opinion using Pio + MET + SU would be an inappropriate comparator nowadays as Pioglitazone is not commonly used within my area as local clinicians are concerned about the many potential side effects when using Pioglitazone. Most clinicians contemplating intensification of medication have usually already changed Pioglitazone to a DDPVi before considering the next step before an injectable therapy." (Anonymous)

2. **Regarding the economic modelling:**
A component of the economic modelling compares dapagliflozin + MET + SU versus DPP4s + MET + SU in a population failing on MET + SU.

The modelling has a 40-year (i.e. lifetime) time period.

Patients move onto insulin after either dapagliflozin + MET + SU or DPP4s + MET + SU fail.

Our question for you (to ensure the model represents clinical practice):
Would any patients retain their oral treatments (including dapagliflozin or DPP4s) when intensifying to insulin?
If yes – please can you estimate roughly what proportion of patients would retain their oral treatments (including dapagliflozin or DPP4s) when intensifying to insulin?

"In my current practice it really depends what insulin regimen is being used, for example:

If using a basal only insulin then I would continue using Metformin and an SU but stop the DPPVi or SGLT2i. I would consider reintroducing either drug if the insulin dose reaches 40+ units or if overweight

If using a twice daily biphasic insulin then I would continue using the Metformin but reduce the SU by 50% with the aim of stopping it as the insulin dose is titrated upwards. The DPPVi or SGLT2i would be stopped initially but I would consider reintroducing it if the insulin dose reaches >1 unit/kg or if patient is overweight.

The main aim of any new regimen is to keep it as simple as possible.” (Anonymous)

Appendix 2: IMS data: Triple therapy regimens in patients who were previously prescribed metformin and sulfonyurea

December 2015 data

IMS data Patient Data, IMS Information Solutions UK Ltd, December 2015 show that 31,968 patients who were previously prescribed metformin and sulfonylurea are currently prescribed triple therapy (the relevant population of this appraisal). The numbers of patients and corresponding percentages for each triple regimen is shown in Table 3.

Table 3: Triple therapy regimens in patients who were previously prescribed metformin and sulfonylurea (December 2015)

Triple therapy	**31,968**	
met+SU+DPP	19,665	62%
met+SU+SGLT2	4,567	14%
met+SU+ins	3,775	12%
met+SU+GLP	1,957	6%
SU+met+TZD	1,631	5%
Other triple	140	0%
met+TZD+DPP	93	0%
met+TZD+SGLT2	47	0%
met+DPP+SGLT2	47	0%

May 2016 data

IMS data Patient Data, IMS Information Solutions UK Ltd, May 2016 show that 30,010 patients who were previously prescribed metformin and sulfonylurea are currently prescribed triple therapy (the relevant population of this appraisal). The numbers of patients and corresponding percentages for each triple regimen is shown in Table 2.

Table *2*: Triple therapy regimens in patients who were previously prescribed metformin and sulfonylurea (May 2016)

Triple therapy	30,010	
met+SU+DPP	18,174	61%
met+SU+SGLT2	5,592	19%
met+SU+ins	2,843	9%
SU+met+TZD	1,491	5%
met+SU+GLP	1,445	5%
other triple	606	2%
met+DPP+SGLT2	186	1%
met+TZD+DPP	140	0%
met+TZD+SGLT2	47	0%
SU+DPP4+ins	47	0%

Appendix 3: Tables showing the correlation of NMA results with those of the dapagliflozin key Matthaei 2015 trial

Table 4: NMA results and comparison with CSR/publication

Outcome	NMA results (DAPA+Met+SU vs Met +SU)	CSR (Placebo-corrected adjusted mean)	Absolute values from Matthaei 2015		Relative values calculated from absolute values reported in Matthaei
			DAPA	Placebo	
HbA1c	-0.7	-0.74	-0.8	-0.1	-0.7
Body weight	-1.9	-1.98	-2.9	-1	-1.9
SBP	-2.04	-2.2	-1	1.1	-2.1
Hypoglycaemia N (%)	2.08 (OR)	NR	17 (15.6)	9 (8.3)	1.88

Table 5: NMA results and comparison with model input sheet

Outcome	NMA results (DAPA+Met+SU vs Met +SU)	Absolute change from baseline (model input sheet) for dapagliflozin	Reference treatment value (model input sheet)	Calculated relative values (Dapa-Reference treatment)
HbA1c	-0.7	-0.85	-0.15	-0.7
Body weight	-1.9	-2.2	-0.300	-1.9
SBP	-2.04	-3.16	-1.092	-2.038
Hypoglycaemia	2.08 (OR)	0.202	0.108	1.87

Appendix 4: CPRD data

[redacted]

[redacted]

[redacted]

[redacted]

References

1. National Institue for Health and Care Excellence. NG28: Type 2 diabetes in adults: management. 2015. Available from: http://www.nice.org.uk/guidance/ng28. [Accessed 7 December 2015].
2. National Institue for Health and Care Excellence. TA288: Dapagliflozin in combination therapy for treating type 2 diabete. 2013. Available from: https://www.nice.org.uk/guidance/ta288. [Accessed July 2016].
3. National Institue for Health and Care Excellence. TA390: Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. 2016. Available from: https://www.nice.org.uk/guidance/ta390. [Accessed July 2016].
4. IMS data Patient Data, IMS Information Solutions UK Ltd, May 2016
5. IMS data Patient Data, IMS Information Solutions UK Ltd, May 2016

ERG erratum appendix: SA11 re-run in the light of the company error check.

The Company highlighted that SA11a for the comparison with the DPP-4i was incorrect and suggested that SA11 was in general incorrect. The ERG has re-run these scenario analyses trying to be careful to cross check the input values to these. As highlighted in the ERG report this is not a simple matter with the CARDIFF model. It appears likely that the company has re-run these not just SA11a for the comparison with the DPP-4i. It might help the STA and committee if any discrepancies between these and the ERG model runs as below could be highlighted, perhaps before the first committee meeting.

Table 01: Pairwise comparison of dapagliflozin and DPP-4i: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	£651	0.017	£37,997	£651	0.017	£37,997
SA11a: Company NMA: Base case random effects	£727	0.013	£57,971	£677	0.017	£40,735
SA11b: Company NMA: Base case fixed effects	£726	0.013	£58,038	£677	0.017	£40,792
SA11c: Company NMA: End point random effects	£729	0.011	£67,243	£681	0.015	£45,499
SA11d: Company NMA: End point fixed effects	£728	0.011	£65,369	£680	0.015	£44,371
SA11e: Company NMA: 24 week random effects	£744	-0.002	Dominated	£694	0.003	£242k
SA11f: Company NMA: 24 week fixed effects	£747	-0.004	Dominated	£697	0.000	£27mn

Table 02: Pairwise comparison of dapagliflozin and empagliflozin 10mg: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	-£35	0.004	Dominant	-£35	0.004	Dominant
SA11a: Company NMA: Base case random effects	£50	-0.006	Dominated	£0	-0.002	Dominated
SA11b: Company NMA: Base case fixed effects	£1	-0.002	Dominated	£0	-0.002	Dominated
SA11c: Company NMA: End point random effects	£49	-0.006	Dominated	£0	-0.002	Dominated
SA11d: Company NMA: End point fixed effects	£49	-0.006	Dominated	£0	-0.002	Dominated
SA11e: Company NMA: 24 week random effects	£44	-0.005	Dominated	-£6	0.000	£18,870
SA11f: Company NMA: 24 week fixed effects	£44	-0.005	Dominated	-£6	0.000	£22,603

Table 03: Pairwise comparison of dapagliflozin and empagliflozin 25mg: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	-£35	0.003	Dominant	-£35	0.003	Dominant
SA11a: Company NMA: Base case random effects	£50	-0.006	Dominated	£0	-0.002	Dominated
SA11b: Company NMA: Base case fixed effects	£0	-0.002	Dominated	£0	-0.002	Dominated
SA11c: Company NMA: End point random effects	£48	-0.006	Dominated	£0	-0.002	£246 SW
SA11d: Company NMA: End point fixed effects	£48	-0.006	Dominated	£0	-0.002	Dominated
SA11e: Company NMA: 24 week random effects	£38	-0.003	Dominated	-£11	0.001	Dominant
SA11f: Company NMA: 24 week fixed effects	£39	-0.003	Dominated	-£11	0.001	Dominant

Table 04: Pairwise comparison of dapagliflozin and canagliflozin 100mg: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	-£124	0.017	Dominant	-£124	0.017	Dominant
SA11a: Company NMA: Base case random effects	£57	-0.008	Dominated	£7	-0.004	Dominated
SA11b: Company NMA: Base case fixed effects	£7	-0.004	Dominated	£7	-0.004	Dominated
SA11c: Company NMA: End point random effects	£55	-0.007	Dominated	£7	-0.003	Dominated
SA11d: Company NMA: End point fixed effects	£57	-0.009	Dominated	£9	-0.005	Dominated
SA11e: Company NMA: 24 week random effects	£43	-0.004	Dominated	-£6	0.001	Dominant
SA11f: Company NMA: 24 week fixed effects	£44	-0.004	Dominated	-£6	0.000	Dominant

Table 05: Pairwise comparison of dapagliflozin and canagliflozin 300mg: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	£110	0.009	£12,875	£110	0.009	£12,875
SA11a: Company NMA: Base case random effects	£263	-0.013	Dominated	£213	-0.009	Dominated
SA11b: Company NMA: Base case fixed effects	£227	-0.011	Dominated	£213	-0.009	Dominated
SA11c: Company NMA: End point random effects	£262	-0.012	Dominated	£213	-0.008	Dominated
SA11d: Company NMA: End point fixed effects	£264	-0.014	Dominated	£216	-0.010	Dominated
SA11e: Company NMA: 24 week random effects	£248	-0.010	Dominated	£198	-0.005	Dominated
SA11f: Company NMA: 24 week fixed effects	£249	-0.010	Dominated	£198	-0.006	Dominated

Table 06: Pairwise comparison of dapagliflozin and pioglitazone: Scenario analyses

	ERG report incorrect SA11			Re-run SA11 in light of error check		
Scenario	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	£4,834	0.009	£558k	£4,834	0.009	£558k
SA11a: Company NMA: Base case random effects	£4,969	0.006	£866k	£4,918	0.010	£501k
SA11b: Company NMA: Base case fixed effects	£4,968	0.006	£872k	£4,918	0.010	£503k
SA11c: Company NMA: End point random effects	£4,975	-0.003	Dominated	£4,926	0.011	£454k
SA11d: Company NMA: End point fixed effects	£4,972	0.008	£613k	£4,924	0.012	£400k
SA11e: Company NMA: 24 week random effects	£4,991	-0.006	Dominated	£4,941	-0.002	Dominated
SA11f: Company NMA: 24 week fixed effects	£4,996	-0.007	Dominated	£4,946	-0.003	Dominated