NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes [ID756]

Committee papers

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Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

This premeeting briefing is a summary of:

- the evidence and views submitted by the company(ies), the consultees and their nominated clinical experts and patient experts and
- the assessment 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 is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical

- NICE clinical guideline (CG) 87 (a partial update of CG66) is currently being updated (publication expected December 2015). The draft clinical guideline recommends repaglinide, pioglitazone, a sulphonylurea or a DPP-4 inhibitor as options for a patient unable to take metformin (taking into account safety concerns, intensification issues, and weight gain):
  - What treatment is currently used in clinical practice for patients unable to use metformin?
  - Are any of these treatments **not** routinely used?
  - Which treatments (if any) are SGLT-2 inhibitors more likely to replace?
- Are the SGLT2 inhibitors similarly effective?

- The higher doses of canagliflozin and empagliflozin were generally found to be more effective than the starting doses. However in the clinical trials, people could start on the larger dose, rather than have to titrate to it if the starting dose was not effective (as required in the marketing authorisations):
  - Would the trial results for people starting on larger doses be seen in clinical practice for the population who titrate to it?
  - To what extent are the higher doses of canagliflozin and empagliflozin used in clinical practice?
- Are the clinical trial results generalisable to UK clinical practice?
  - Some of the evidence for the effectiveness of comparators as monotherapy in the network meta-analysis was taken from trials where it was given in combination with another treatment
  - The scope population was those for whom metformin was not tolerated or was contraindicated, however these were not exclusion criteria in trials.
  - A high proportion of patients are from 'Asian' countries (including Japan, China, Korea, and Malaysia).

Cost

- The scope comparators are repaglinide, pioglitazone, a sulphonylurea or a DPP-4 inhibitor; the SGLT2 inhibitors are also compared with each other:
  - Three models (Assessment Group, Janssen and BI) found that SGLT2 inhibitors were not cost effective compared with pioglitazone because of its substantially cheaper price, and one submission (Janssen) stated that the use of pioglitazone is declining in the UK. Is pioglitazone used in clinical practice?
  - Two models (Janssen, AZ) did not include repaglinide in its base case – is repaglinide used in clinical practice?
  - The NICE draft clinical guideline recommends treatment choice should depend on safety concerns, intensification issues, and weight gain – does this need to be taken into account when deciding the most appropriate comparator?
  - Are the SGLT2 inhibitors similarly cost-effective?
  - Should the cost effectiveness of SGLT2 inhibitors be considered as a class (as presented by Astrazeneca) or as individual treatments?

- In some instances, model results are presented for both starting and intensified doses of canagliflozin and empagliflozin, and the Assessment Group (AG) model presents only results for the higher doses:
  - Which results are the most relevant for interpretation?
  - Janssen (the company for canagliflozin) state that canagliflozin 300 mg monotherapy alone is not used routinely in clinical practice
- In total there are 5 models presented, including several different bespoke diabetes models (OM1, ECHO T2DM, and CARDIFF), with different cost and utility assumptions:
  - Are all models equally appropriate?
  - Which model is the most appropriate for decision making?
- HbA1c drift is an important assumption in all models, determining the initiation of the next treatment. Which assumption is most relevant to use – the linear drift assumption in the Janssen model or the assumptions taken from UKPDS used by all other models?
- The AG cost effectiveness results are highly sensitive to assumptions about weight gain and its effect on utility:
  - Are treatment related weight changes (increases or decreases) permanent or transient in clinical practice?
  - Do weight loses associated with SGLT2 inhibitors have a significant impact on quality of life?
  - What are the most appropriate assumptions about weight changes associated with treatment?

1 Background: clinical need and practice

1.1 Type 2 diabetes is a chronic metabolic disorder where a lack of the hormone insulin or resistance to its action causes elevated blood glucose levels (hyperglycaemia). It is a progressive disease, gradually worsening over time. The UK Prospective Diabetes Survey (UKPDS) estimated an increase in haemoglobin A1c (HbA1c), which identifies average plasma glucose concentration, of around 0.2% per year.

1.2 Approximately 2.7 million people aged 17 and over in England were diagnosed with diagnosed diabetes in 2013, 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 prevalence of type 2 diabetes in England 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.

1.3 If not managed effectively, type 2 diabetes can lead to kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication of type 2 diabetes and is the greatest cause of morbidity and premature death. Life expectancy is reduced by up to 10 years in people with diabetes.

1.4 NICE clinical guideline (CG) 87 (a partial update of CG66) is currently being updated, anticipated publication December 2015. The draft guideline states that standard-release metformin should be the initial drug treatment for people with type 2 diabetes, and if metformin is contraindicated or not tolerated consider one of the following: dipeptidyl peptidase 4 inhibitors (DPP4i), pioglitazone, repaglinide or a sulphonylurea (SU) (draft recommendation 1.6.23). It also states the choice of drug treatment should be based on effectiveness, safety,

tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost) (draft recommendation 1.6.17). The draft full guideline pp.193-201 explains some of the rationale for the recommendations in this area. The Guideline Development Group (GDG) considered whether to recommend a hierarchy for the non-metformin treatments. However, because of the lack of direct evidence, the likely small proportion of eligible patients, and possible issues related to safety, intensifications or weight gain, the GDG concluded it was appropriate to recommend that people with type 2 diabetes could be considered for any of the alternative treatment options as part of their individualised care. If blood glucose is not adequately controlled following monotherapy, dual therapy should be considered followed by either the addition of insulin or triple therapy. NICE has produced individual guidance for canagliflozin (TA315), dapagliflozin (TA288) and empagliflozin (TA336) as combination therapies; this appraisal considers these drugs for monotherapy.

2 The technologies

2.1 Canagliflozin (Invokana, Janssen), dapagliflozin (Forxiga, AstraZeneca) and empagliflozin (Jardiance, Boehringer-Ingelheim and Lilly UK) are all selective sodium glucose-cotransporter 2 (SGLT-2) inhibitors, which block the reabsorption of glucose in the kidneys and promote excretion of excess glucose in the urine. Through this mechanism, canagliflozin, dapagliflozin and empagliflozin may help control glycaemia independently of insulin pathways. They all have marketing authorisations for treating type 2 diabetes mellitus to improve glycaemic control in adults:

- as monotherapy: when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

- 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

They are all administered orally.

Canagliflozin

2.2 The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) of at least 60 ml/minute/1.73 m2 or creatinine clearance (CrCl) of at least 60 ml/minute and need tighter glycaemic control, the dose can be increased to 300 mg once daily. For patients with renal impairment, the summary of product characteristics notes that canagliflozin should not be initiated in patients with an eGFR of less than 60 ml/minute/1.73m2 or CrCl of less than 60 ml/minute. In patients tolerating canagliflozin whose eGFR falls persistently below 60 ml/minute/1.73 m2 or whose CrCl persistently falls below 60 ml/minute, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 ml/minute/1.73 m2 or CrCl is persistently below 45 ml/minute.

2.3 The summary of product characteristics states the following adverse reactions for canagliflozin as the most commonly reported: vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (that is, urinary frequency). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of canagliflozin is £39.20 for 30 100mg or 300mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts.

Dapagliflozin

2.5 The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.

2.6 The summary of product characteristics lists the following adverse reactions for dapagliflozin: urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit. Dapagliflozin is not recommended for use in people with moderate to severe renal impairment (patients with a creatinine clearance rate of less than 60 ml/min or an eGFR of less than 60 ml/min/1.73 m2) because its efficacy is dependent on renal function. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.7 The list price of dapagliflozin is £36.59 for 28 5-mg or 10-mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online September 2015). Dapagliflozin is administered orally as a single dose of 10 mg per day. Costs may vary in different settings because of negotiated procurement discounts.

Empagliflozin

2.8 The recommended starting dose is 10 mg once daily for monotherapy. According to the summary of product characteristics, the dose can be increased to a maximum of 25 mg daily for people who tolerate empagliflozin well and need tighter glycaemic control, if they have an eGFR of 60 ml/min/1.73 m2 or more.

2.9 The summary of product characteristics states the following adverse reactions for empagliflozin: vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (that is, urinary frequency). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.10 The list price of empagliflozin is £36.59 for 28 10-mg or 25-mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online

September 2015). Costs may vary in different settings because of negotiated procurement discounts.

Table 1 Summary description of technologies

Non-proprietary name	Canagliflozin	Dapagliflozin	Empagliflozin
Proprietary name	Invokana	Forxiga	Jardiance
Company	Janssen	AstraZeneca	• Boehringer-Ingelheim • Lilly UK
Dose	100mg once daily (or 300mg in patients who tolerate 100mg, have an eGFR at least 60 ml/ minute/1.73 m2 or creatinine clearance (CrCl) of at least 60 ml/minute and need tighter glycaemic control).	10 mg once daily	10 mg once daily (or 25 mg for people who tolerate 10 mg, have an eGFR of 60 ml/min/1.73 m2 or more, and need tighter glycaemic control.
Acquisition cost (BNF, accessed online September 2015)	£39.20 for 30 100mg or 300mg tablets	£36.59 for 28 5-mg or 10-mg tablets	£36.59 for 28 10-mg or 25-mg tablets

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of canagliflozin, dapagliflozin and empagliflozin monotherapy within their licensed indications for treating type 2 diabetes.

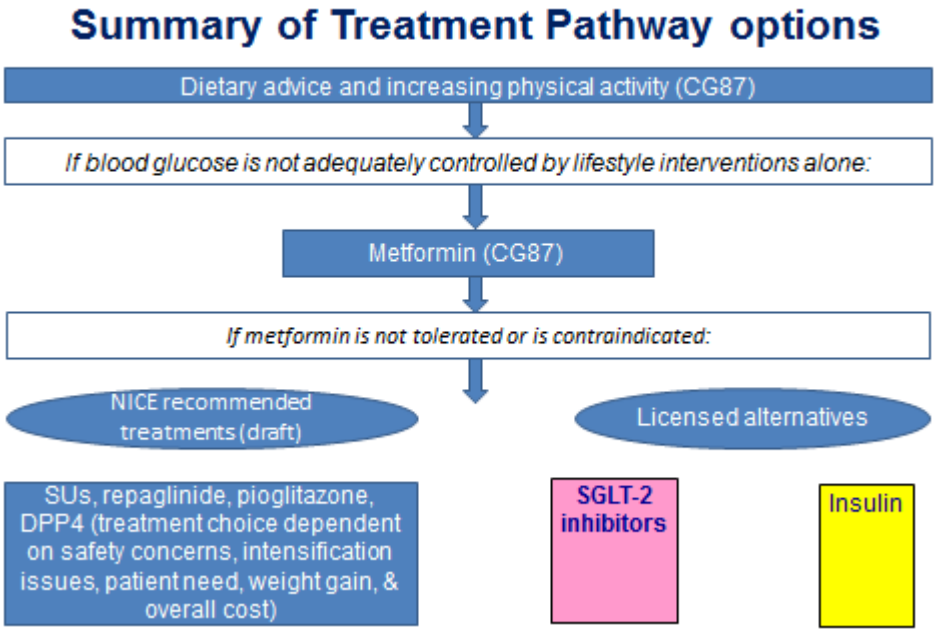
	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**

Population	People with type 2 diabetes for whom metformin is not tolerated or is contraindicated.	Trials of SGLT2 inhibitors and other drugs as monotherapy have not been restricted to patients that have not been able to tolerate metformin. Given the lack of data, it is necessary to assume that the effectiveness of other drugs, and the effect on long-term complications, is no different in those who get gastro-intestinal adverse effects with metformin, than from those who can tolerate it. However some renal function restrictions also apply to other drugs such as the SGLT2 inhibitors.
Intervention	• Canagliflozin monotherapy • Dapagliflozin monotherapy • Empagliflozin monotherapy	• Canagliflozin 100mg and 300mg • Dapagliflozin 10mg • Empagliflozin 10mg and 25mg In cost-effectiveness analyses, the AG did not included starting doses of canagliflozin and empagliflozin. This is because it assumed that people would not intensify to further combination treatment without first titrating the larger doses of the SGLT inhibitors.
Comparators	The following interventions as monotherapy: • Repaglinide • Sulfonylureas • Pioglitazone • DPP-4 inhibitors • The SGLT-2 inhibitors will be compared with each other	The Assessment Report included all comparators from the NICE scope. Janssen did not include repaglinide in its base case but it was included in a sensitivity analysis. Astrazeneca did not consider repaglinide because of a lack of evidence.

Outcomes	• 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	The outcomes would ideally be the rates of complications of diabetes, but most trials of new diabetes drugs are short term, and rely on modelling changes in HbA1c, blood pressure, weight and lipids to predict longer term outcomes.
Economic evaluation	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.	

3.2 Canagliflozin (TA315), dapagliflozin (TA288) and empagliflozin (TA336) are already recommended by NICE for *combination* therapy. Current licenced *monotherapy* options are outlined below. NICE recommends starting with metformin if diabetes is not controlled by diet and exercise alone, however some people are not able to tolerate metformin (the Assessment Group estimate this is 5-15% of people), or it is

contraindicated. Note CG87 is currently being updated (see section 1.4).



4 Clinical-effectiveness evidence

4.1 The Assessment Group (AG) conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of canagliflozin, dapagliflozin and empagliflozin as monotherapy for treating adults with type 2 diabetes not controlled by diet and exercise alone. The AG noted that the target population as defined in the scope was also people with type 2 diabetes that were unable to take metformin, but as this was not a distinction made in the trials, this could not form part of the search criteria. The AG identified 7 relevant double-blind randomised controlled trials (the AG did not identify any additional trials relevant to the scope that were not identified in the manufacturer's submissions):

Table 2 Summary of trials

Drug	Trial	Location	Treatment groups	Duration
Canagliflozin	CANTATA-M (2013, n=587)	17 countries, including America, Spain and Malaysia	Cana 100 mg/day Cana 300mg/day Placebo (switched to sitagliptin in 26 week extension, double-blind)	26 weeks with 26 week extension
	Inagaki et al. (2014, n=272)	Japan	Cana 100 mg/day Placebo	24 weeks
Dapagliflozin	MB102-013 (Ferrannini et al. 2010 [24 week data] and Bailey et al., 2014 [102 week data], n=591)	85 sites in countries including US and Russia	Dapa 10mg/day am Dapa 10mg/day pm Placebo (switched to low dose metformin in extension, double blind)	24 weeks with 78 week extension
	MB102-054 (Ji et al. 2014, n=265),	40 sites in China, Korea, Taiwan and India	Dapa 10mg/day am Placebo	24 weeks
	D1692C00006 (Kaku et al. 2014, n=175),	Japan	Dapa 10mg/day am Placebo	24 weeks
Empagliflozin	1275.1 (Lewin et al. 2015, n=1363)	22 countries including Malaysia and US	Empa 10mg/day Empa 25 mg/day Linagliptin 5 mg/day	52 weeks (primary outcome reported at 24 weeks)
	1245.20 (Roden et al. 2013, 24 weeks, n=986) 1245.31 (a 76 week extension of 1245.20, Roden et al. 2014, n=615)	9 countries including China, Ireland and the US	Empa 10mg/day Empa 25 mg/day Sitagliptin 100mg/day Placebo	24 weeks (with 76 week extension)

4.3 The Assessment Group stated that the trials were of good quality. It noted that only the 2 empagliflozin trials included active comparators. Some trials included run-in periods for wash-out of previous medication (if required) and to establish a diet and exercise regime. Doses were generally given as outlined in marketing authorisations – where this was not the case, results are not reported.

4.4 The AG stated that most participants in all of the trials had characteristics as follows: had a diabetes duration of less than 5 years, HbA1c was between approximately 7.5% and 8.4% (in the main comparison groups, and between 10.6% and 11.5% in high HbA1c subgroups), body mass index (BMI) was between 25 and 34 kg/m2, 34% to 59% of participants in the main comparison groups were women, and mean age was between 50 and 60 years. The clinical trials also reported subgroups based on baseline HbA1c and weight.

4.5 The primary outcome in all trials was change in HbA1c from baseline to the end of the main intervention period. This was generally 24 to 26 weeks, with 4 trials including extension periods: either up to 52 weeks (canagliflozin trial CANTATA-M and empagliflozin trial 1275.1) or up to 102 weeks (dapagliflozin trial MB102-013 and empagliflozin trial 1245.31). However the AG noted that the extension period of CANTATA-M did not include a comparator, and that in the 76 week extension of trial 1245.31 around 40% of participants dropped out, leading to the use of last observation carried forward (the AG stated this was not a reliable method of analysis because people may not necessarily drop out for random reasons).

For the primary outcome, all treatments reduced HbA1c compared with placebo (placebo (

4.6 Table 3) ($p<0.001$ at 24 or 26 weeks). The reductions for empagliflozin were also higher than those for sitagliptin (statistical significance not presented).

4.7 Secondary outcomes included change in weight, systolic blood pressure, hypoglycaemia, and cholesterol (total cholesterol, high density lipoprotein [HDL] and low density lipoprotein [LDL]). All selective sodium glucose-cotransporter 2 (SGLT2) inhibitors demonstrated a reduction in weight, from 0.97kg more than placebo (dapagliflozin, trial D1692C00006) to 3.9kg more than placebo (canagliflozin 300mg, CATANTA M, $p<0.001$). Compared with placebo, all SGLT2 inhibitors reduced systolic blood pressure, however no results were statistically significant. For hypoglycaemia, the AG stated that given the infrequency of reported hypoglycaemia, the similarities of the outcome between active and placebo arms, and the cut-off level used, it was reasonable to assume that the SGLT2 inhibitors did not cause hypoglycaemia. For cholesterol, not all trials reported all outcomes. Generally, SGLT2 inhibitors led to increases in all types of cholesterol. Please see Table 3 for secondary outcomes for cholesterol.

Table 3 Canagliflozin, dapagliflozin and empagliflozin clinical trial results for primary outcome (HbA1c) and cholesterol levels

	Time (wks)	%ΔHbA1c	ΔTC (mmol/L)	ΔLDL (mmol/L)	ΔHDL (mmol/L)
CANAGLIFLOZIN					
CANTATA-M (Stenlöf 2013)					
100 mg/day	26	-0.77	NR	0	+0.11
300 mg/day	26	-1.03	NR	+0.12	+0.11
placebo	26	+0.14	NR	-0.07	+0.04
Inagaki 2014					
100 mg/day	24	-0.74	NR	+0.15	+0.07
placebo	24	+0.29	NR	-0.01	-0.03
DAPAGLIFLOZIN					
Ferrannini 2010 / Bailey 2014 (Trial MB102-013)					
10 mg/day am	24	-0.89	NR	NR	NR
10 mg/day pm	24	-0.79	NR	NR	NR
placebo	24	-0.23	NR	NR	NR
10 mg/day am	102	-0.61	NR	NR	NR
placebo / metformin	102	-0.17	NR	NR	NR
Ji 2014 (Trial MB102-054)					
10 mg/day	24	-1.11	+0.06	+0.19	+0.30
placebo	24	-0.29	-0.04	-0.03	+0.11
Kaku 2014 (Trial D1692C00006)					
10 mg/day	24	-0.45	+0.01	-0.03	+0.16
placebo	24	-0.06	+0.02	+0.12	+0.07
EMPAGLIFLOZIN					
Lewin 2015 (Trial 1275.1)					
10 mg/day	24	-0.83	+0.2	+0.1	+0.1
25 mg/day	24	-0.95	+0.2	0	+0.1
linagliptin 5 mg/day	24	-0.67	-0.1	-0.1	0
10 mg/day	52	-0.85	NR	NR	NR
25 mg/day	52	-1.01	NR	NR	NR
linagliptin 5 mg/day	52	-0.51	NR	NR	NR
Roden 2013/4 (trial 1245.20)					
10 mg/day	24	-0.66	+0.07	+0.06	+0.11
25 mg/day	24	-0.78	+0.15	+0.11	+0.13
sitagliptin 100 mg/day	24	-0.66	+0.08	+0.03	+0.02
placebo	24	+0.08	+0.05	+0.04	+0.04
Key: Δ: change; L/HDL: low/high density lipoprotein; mmol/L: millimoles per litre; NR: not reported; TC: total cholesterol					

Adverse effects of treatment

4.8 The Assessment Group reviewed outcomes related to adverse effects of treatment in the clinical trials. SGLT2 inhibitors were generally associated

with higher incidence of urinary tract infections and genital tract infections, both of which were more common in females (empagliflozin was not found to be associated with higher UTI, with the AG noting that one possible explanation was that the placebo group had glycosuria because of poor diabetes control). Most UTIs and genital tract infections were mild to moderate in severity and amenable to standard treatment. No evidence of a dose response relationship was found with any treatment.

4.9 The companies reported that canagliflozin, dapagliflozin and empagliflozin were well tolerated. The AG noted that rates of discontinuation across the studies ranged from 7% to 20% with rates balanced across groups. It noted that in Inagaki et al., the rate of discontinuation was 7% in the canagliflozin group, and 20% in the placebo group.

4.10 The AG noted that the European Medicines Agency (EMA) had recently announced a review of the risk of diabetic ketoacidosis for people treated with SGLT2 inhibitors, because 101 cases worldwide had been recorded. The EMA stated that in some cases the level of blood glucose was much lower than is usually seen in diabetic ketoacidosis, and expressed concern that this might lead to delays in diagnosis. The AG noted that Janssen (the company for canagliflozin) reported a low incidence of diabetic ketoacidosis in their trials (0.5 per 1,000 patients years on canagliflozin 100mg daily, 0.8 on canagliflozin 300mg daily, and 0.2 per 1,000 years on placebo (Erondu et al. 2015). Further, although Astrazeneca and Boehringer Ingelheim have not yet reported data for this outcome, an enquiry for a commentary in Diabetes Care suggested rates for these drugs of under 0.1%, although no time period is given.

Meta-analysis

4.11 As there was no direct evidence to compare the SGLT2 inhibitors with all of the comparators in the scope, all companies and the Assessment Group conducted network meta-analyses comparing SGLT2 inhibitors with dipeptidyl peptidase 4 inhibitors (DPP4s), sulphonylureas (SUs), pioglitazone and repaglinide for treating people with type 2 diabetes not

controlled by diet and exercise and alone. As noted in the clinical effectiveness section, metformin contraindication or tolerance was not used in eligibility criteria for trials, therefore it was not used as a search parameter for trials for the network meta-analysis. Not all network meta-analyses included repaglinide, with submissions noting a lack of evidence and infrequency of use in clinical practice.

4.12 All companies and the AG presented network meta-analysis results for outcomes including:

- Mean change in HbA1c
- Mean change in weight or body mass index (BMI)
- Mean change in SBP
- Hypoglycaemia incidence

Canagliflozin network meta-analysis

4.13 Janssen presented outcomes for the following interventions in its network meta-analyses: SGLT2 inhibitors (canagliflozin 100mg and 300mg; dapagliflozin 5mg and 10mg; empagliflozin 10mg and 25mg), DPP4 inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin); pioglitazone (15mg, 30mg and 45mg); SUs (glibenclamide, gliclazide, glimepiride, glipizide). Repaglinide was included only as a sensitivity analysis. The company presented both fixed effects and random effects models.

4.14 The company conducted analyses at 26 weeks (plus or minus 4 weeks) to match the assessment times in its trials and it identified 42 trials for its base case. Trials reporting results at 16 to 21 weeks and 31 to 36 weeks, trials published in conference abstracts only, and trials assessing repaglinide were included in sensitivity analyses. The company also conducted sensitivity analyses excluding non-double-blinded trials.

4.15 The company presented its results for both doses of canagliflozin. Table 4 below shows outcomes for the 100mg dose compared with all comparators. Results for the outcomes mean change in weight (18 trials), systolic blood pressure (8 trials) and hypoglycaemic events (17 trials) are

also presented in Table 4. Not all analyses included all comparators. As there were no SU trials for weight data, the company included SUs in a separate network meta-analysis based on BMI, using 6 trials. For the outcome mean change in systolic blood pressure from baseline, the company noted that the low number of trials included led to broad credibility intervals. For the outcome hypoglycaemic events, the company noted that several treatment arms reported no events at 26 weeks and most studies reported less than 10% of patients who had at least 1 hypoglycaemic episode. Therefore there were a small number of events, which led to uncertain and unreliable results.

Table 4: Janssen network meta-analysis, mean difference from baseline in HbA1c, weight, and systolic blood pressure, and odds ratio for more than 1 hypoglycaemic event. Canagliflozin 100mg compared with comparator, point estimate with 95% credible interval

	HbA1c	Weight change	SBP	≥1 event hypoglycaemic
Placebo	-0.97 (-1.22 ; -0.72)	-2.40 (-2.88; -1.92)	-3.72 (-5.86; -1.55)	1.69 (0.69; 4.48)
Canagliflozin 300	0.23 (-0.09 ; 0.56)	1.00 (0.47; 1.54)	1.69 (-0.44; 3.83)	1.30 (0.45; 3.99)
Dapagliflozin 5	-0.38 (-0.69 ; -0.06)	-1.09 (-1.73; -0.45)	-0.82 (-3.68; 2.07)	2.65 (0.51; 15.52)
Dapagliflozin 10	-0.33 (-0.65 ; 0.00)	-0.74 (-1.40; -0.09)	-0.50 (-3.43; 2.48)	1.16 (0.24; 5.67)
Glibenclamide	-0.02 (-0.42 ; 0.39)	NR	NR	NR
Glimepiride	-0.02 (-0.76 ; 0.74)	NR	NR	NR
Glipizide	0.39 (-0.64 ; 1.42)	NR	NR	NR
Gliclazide	-0.38 (-0.89 ; 0.12)	NR	NR	NR
Linagliptin 5	-0.38 (-0.67 ; -0.09)	-2.54 (-3.29; -1.79)	NR	1.56 (0.29; 7.87)
Pioglitazone 15	-0.26 (-0.58 ; 0.06)	-4.69 (-5.59; -3.80)	NR	3.62 (0.75; 17.15)
Pioglitazone 30	-0.19 (-0.51 ; 0.12)	-4.81 (-5.67; -3.98)	NR	3.45 (0.73; 16.34)
Pioglitazone 45	-0.05 (-0.34 ; 0.25)	-6.17 (-6.94; -5.39)	-4.60 (-8.17; -1.03)	3.72 (0.86; 16.22)
Saxagliptin 5	-0.47 (-0.78 ; -0.15)	-2.79 (-3.89; -1.70)	-5.92 (-10.57; -1.28)	2.33 (0.50; 11.74)
Sitagliptin 100	-0.25 (-0.54 ; 0.05)	-3.24 (-3.83; -2.65)	-4.52 (-6.69; -2.33)	2.80 (0.65; 12.32)
Vildagliptin 100	-0.49 (-0.86 ; -0.12)	-3.51 (-4.37; -2.68)	NR	NR
Empagliflozin 10	-0.23 (-0.58 ; 0.11)	-0.68 (-1.32; -0.05)	-1.11 (-3.37; 1.15)	NR
Empagliflozin 25	-0.12 (-0.46 ; 0.22)	-0.52 (-1.16; 0.11)	-0.31 (-2.60; 1.98)	NR
Key: NR: not reported; SBP: systolic blood pressure				

4.16 The company noted there was heterogeneity in the network meta-analysis because some trials were not double blinded, and some trials included patients with higher diabetes duration at baseline.

4.17 The company conducted sensitivity analyses, adding repaglinide, and including an additional trial for its canagliflozin data. It stated most sensitivity analyses had minor impacts on the results.

4.18 The Assessment Group stated there was a lack of trials in some parts of the evidence base, which led to increased uncertainty in the results.

Dapagliflozin network meta-analysis

4.19 Astrazeneca presented outcomes for interventions as classes of treatment, rather than for specific drugs. The company stated this approach was relatively common in meta-analyses of antidiabetic agents because of the large number of drugs and similar levels of effectiveness within most drug classes. Classes of drug considered were SGLT2 inhibitors, DPP4s, SUs, and pioglitazone. The company only included trials reporting data at 24 weeks (plus or minus 6 weeks). 32 trials were identified for inclusion.

4.20 The company stated their choice of model for the network meta-analysis was usually random effects, but fixed effect was also used, depending on which was best fitting for the outcome (determined by the value of the deviance information criterion). The company conducted sensitivity analyses using the alternative model to that presented in the base case (fixed or random effects); adjustment of HbA1c using a meta-regression; and exclusion of 9 trials including only patients described as “Asian”.

4.21 Results for the network meta-analysis were as follows:

Table 5: Astrazeneca network meta-analysis results for mean change from baseline HbA1c, weight, systolic blood pressure, and odds ratio for hypoglycaemia. SGLT2 inhibitor compared with comparator

	HbA1c %	Weight	SBP	Hypo
Placebo	-0.78* (-0.98, -0.59)	-2.06* (-2.44, -1.68)	-3.82* (-5.02, -2.62)	0.91 (0.26, 3.02)
DPP4	-0.11 (-0.34, 0.11)	-2.69* (-3.12, -2.25)	-4.25* (-5.83, -2.67)	0.62 (0.17, 2.24)
Pioglitazone	0.15 (-0.13, 0.43)	-5.43* (-6.07, -4.73)	-4.45* (-7.19, -1.74)	0.41 (0.08, 1.88)
Sulphonylurea	0.21 (-0.11, 0.55)	-2.89 (-3.83, -2.03)*	-5.12 (-10.47, 0.27)	0.18* (0.03, 0.89)
* indicates statistically significant result. Key: Hypo: hypoglycaemia; SBP: systolic blood pressure				

4.22 The company presented results for sensitivity analyses. It stated that there were only small differences between the base case and sensitivity analyses, indicating results were not highly sensitive to these parameters.

4.23 The company and the Assessment Group noted that some patients taking placebo in some of the dapagliflozin trials had a response to treatment with placebo, which is not seen in other dapagliflozin trials, or in trials for other SGLT2 inhibitors. It stated this may be because of the short duration of the trials, and a motivated placebo group receiving diet and exercise interventions for the first time.

4.24 The Assessment Group stated that the key limitation of the network meta-analysis for Astrazeneca was the lack of evidence included about individual treatments. This led the company to consider treatments by treatment class, despite differences between individual treatments within each class, which caused heterogeneity, difficulties in interpreting results, and possible conflict between the direct and indirect evidence.

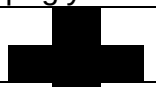
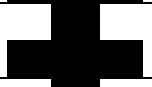
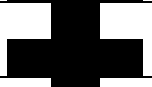
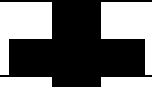
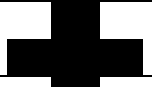
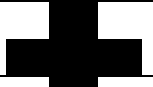
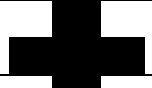
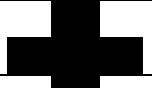
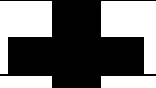
Empagliflozin network meta-analysis

4.25 Boehringer Ingelheim presented outcomes for the following interventions in its network meta-analyses: SGLT2 inhibitors (canagliflozin 100 mg and 300mg, dapagliflozin 5mg and 10mg, and empagliflozin 10mg and 25mg),

SUs (as a class), DPP4s (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin), pioglitazone and repaglinide. The company noted that its economic model only considered sitagliptin 100mg as a proxy for all DPP4 inhibitors, therefore this pre-meeting briefing document only presents results for this DPP4 inhibitor. The company stated that the majority of the analyses were performed using fixed effects models as there were insufficient studies to estimate the between-study variance with precision. The company considered 3 time points in its network meta-analysis: 24 weeks, 52 weeks and greater than 52 weeks (this pre-meeting briefing document presents only the results for 24 and 52 weeks as these are the results used in the economic model). The company also presented results for a meta-regression analysis, where results were adjusted for baseline HbA1c.

4.26 The company presented results for its 24 week network meta-analysis (Table 6). It included 37 studies. For hypoglycaemia and urinary tract infection (UTI) (fixed effects) outcomes, the company found no statistically significant differences for any treatment compared with placebo at any time point, however it noted that studies reported low numbers or zero events, therefore results were unreliable with wide credible intervals.

Table 6 Boehringer Ingelheim 24 week network meta-analysis, treatment compared with placebo

	HbA1c	Weight	Systolic blood press.	Hypoglycaemia	Urinary tract infection
Empagliflozin 10					
Empagliflozin 25					
Canagliflozin 100					
Canagliflozin 300					
Dapagliflozin 10					
Dapagliflozin 5					
Pioglitazone 45					
Sitagliptin 100					
Sulphonylurea					
Outcomes HbA1c, weight and systolic blood pressure are presented as treatment differences. Outcomes hypoglycaemia and UTI are odds ratios					

4.27 The company presented the results of a meta-regression, which adjusted for baseline HbA1c and weight. For the HbA1c outcome, the company stated that this adjustment led to similar conclusions about effectiveness compared with the base case, with the majority of treatments demonstrating statistically significantly greater reductions in HbA1c compared with placebo.

4.28 Results for the 52 week network meta-analysis were as follows:

Table 7 Boehringer Ingelheim 52 week network meta-analysis, treatment compared with placebo

	HbA1c	Weight	Hypo
Empagliflozin 10	[redacted]	[redacted]	[redacted]
Empagliflozin 25	[redacted]	[redacted]	[redacted]
Pioglitazone 45	[redacted]	[redacted]	[redacted]
Repaglinide 1 mg	[redacted]	[redacted]	
Sitagliptin 100	[redacted]	[redacted]	[redacted]
SUs	[redacted]	[redacted]	[redacted]
Outcomes HbA1c and weight are presented as treatment differences. Hypoglycaemia ('hypo') is presented as an odds ratio			

4.29 The company conducted sensitivity analyses to remove the results of 2 trials from the network meta-analysis (Lewin et al. 2015 and the sitagliptin 100 mg treatment arm of Roden et al. 2014). It stated that the removal of these trials had minimal impact on the results of the network meta-analysis.

4.30 The Assessment Group stated that although the company undertook many of the steps needed to conduct an appropriate network meta-analysis, its reporting was not completely transparent. The main issue was a lack of evidence for several comparisons in the network, which prevented many of the random-effects and meta-regression models from converging, limiting the analyses to the less conservative fixed-effects

models. Therefore there was uncertainty about the outcomes of the network meta-analyses and the variance in the treatment effects.

Assessment Group network meta-analysis

4.31 The Assessment Group considered the following interventions in its network meta-analysis: canagliflozin (100mg and 300mg), dapagliflozin (10mg), empagliflozin (10mg and 25mg), SUs (as a class, using gliclazide, indirectly linked to linagliptin and pioglitazone because no placebo-controlled trials were available), DPP4 inhibitors (linagliptin, sitagliptin and vildagliptin) and pioglitazone. The AG found no appropriate trials for repaglinide. It presented both fixed and random effects Bayesian models (choosing the most model based on the deviance information criterion). The AG used trials of 24 to 26 weeks where placebo was the comparator.

4.32 The AG used a Bayesian approach to provide probability distributions for treatment effects, with 95% credible intervals. Results are as follows:

Table 8 Assessment Group network meta-analysis results (Intervention compared with placebo, mean difference with 95% credible interval)

	HbA1c	Weight change	Systolic blood pressure
Canagliflozin 100mg	-0.95 (-1.06 to -0.84)	-2.02 (-2.41 to -1.65)	-4.22 (-6.03 to -2.42)
Canagliflozin 300mg	-1.19 (-1.34 to -1.04)	-2.91 (-3.22 to -2.59)	-1.18 (-3.26 to 0.97)
Dapagliflozin 10mg	-0.59 (-0.70 to -0.48)	-1.58 (-2.01 to -1.14)	-2.72 (-4.69 to -0.69)
Empagliflozin 10mg	-0.76 (-0.87 to -0.65)	-1.74 (-2.15 to -1.33)	-2.61 (-4.86 to -0.29)
Empagliflozin 25mg	-0.88 (-0.99 to -0.77)	-1.89 (-2.29 to -1.49)	-3.38 (-5.63 to -1.08)
Gliclazide	-0.95 (-1.27 to -0.64)	1.97 (0.76 to 3.20)	Not reported
Linagliptin 5mg	-0.61 (-0.71 to -0.51)	0.31 (-0.17 to 0.79)	Not reported
Pioglitazone	-1.13 (-1.49 to -0.78)	3.80 (3.20 to 4.40)	Not reported
Sitagliptin 100mg	-0.76 (-0.87 to -0.65)	0.74 (0.39 to 1.10)	0.78 (-1.41 to 3.10)
Vildagliptin 50mg	-0.72 (-0.98 to -0.46)	1.16 (0.07 to 2.26)	Not reported

4.33 The Assessment Group considered the effectiveness of the SGLT2 inhibitors compared with each other. It noted that both doses of canagliflozin lowered HbA1c slightly more than dapagliflozin and both doses of empagliflozin, in some instances statistically significantly. It stated some of this reduction may be because studies suggest that canagliflozin, unlike other SGLT2 inhibitors, may also have an effect on the SGLT1 receptor (which reduces absorption of glucose in the gut). However, it could not be certain whether this dual mechanism of action was clinically significant.

4.34 The Assessment Group stated that there were several issues to consider when interpreting the results of their network meta-analysis:

- The higher doses of canagliflozin and empagliflozin were more effective than the starting doses. However in the clinical trials, people could start on the larger dose, rather than have to titrate to it if the starting dose was not effective (as required in the marketing authorisations). Therefore it was not clear if the results seen for people starting on larger doses would be seen in clinical practice for the population who titrate to it.
- In the dapagliflozin clinical trials in the network, the patients in the placebo arm had a response. It stated this could be due to better access to lifestyle advice, but this was unlikely.
- Many trials included in the network provided data on only some of the variables which are used in the UKPDS Outcomes model.
- There was a lack of data in the trials to calculate the cholesterol ratio (ratio of total cholesterol to high density lipoprotein, or TC: HDL ratio), and where it was reported, it was often high – these high results were not likely to reflect current clinical practice because of the increased use of statins.
- Some of the trial evidence was the intervention given as combination therapy, for example most available evidence for SUs for HbA1c and weight gain were from studies where it was given in addition to

metformin. This may not be representative of its effectiveness when used as monotherapy.

- Several trials noted issues with the durability of the effect of SUs (that is, the initial response was followed by a relatively rapid deterioration). In one trial the AG noted that 34% of patients receiving SUs needed additional treatment by 5 years compared with 15% of those receiving rosiglitazone.

5 Comments from other consultees

5.1 The patient organisation described the treatment pathway for type 2 diabetes. It noted that in some cases diabetes can be treated with a healthy diet and increased physical activity. Otherwise, tablets or insulin are required.

5.2 The patient organisation described living with the condition. It stated that type 2 diabetes is not easy to live with and has a big impact on the day to day lives of people with the condition, their families and their carers. It heard from patients there were misconceptions about the disease or its management, which affected their ability to self-manage. It further heard from patients that their main concern is the disease developing further, where they would be required to inject insulin, or develop complications. This caused anxiety, which was further increased when people felt their blood glucose levels were not well controlled.

5.3 The patient organisation noted there were a number of complications of diabetes that people lived with, which could affect their ability to self-manage. This included deteriorating eye sight or neuropathy, which could make it difficult for people to take their medication, to manage their blood glucose levels or to stay active.

5.4 The patient organisation stated that the most important treatment outcomes for patients were lowering blood glucose levels with minimum side-effects, and treatment that does not negatively impact on the day-to-day life of the person living with diabetes. It stated that lowering blood

glucose levels and achieving good diabetes control minimises the risk of developing complications, reduces the likelihood that someone will need to inject insulin to manage their disease, and can help to reduce anxiety and depression caused by the stress of managing diabetes.

5.5 The patient group stated that people with diabetes reported the following advantages of dapagliflozin (when used as combination therapy, as currently recommended by NICE): lowered blood glucose levels leading to increased self-confidence in overall diabetes management, tablets are easy to self-administer, and no requirement to take the tablets with food. One person reported that dapagliflozin causes less stomach upset than other medication.

5.6 The patient organisation reported that a patient concern about the treatment was severe thrush. Also some people taking dapagliflozin noted lowered blood glucose levels, whereas others taking it reported no change.

5.7 The patient organisation described groups who may particularly benefit from SGLT2 inhibitors. It noted that the treatment has been shown to have positive effects on weight management, so may be of increased benefit to people with Type 2 diabetes who are overweight.

6 Cost-effectiveness evidence

6.1 The Assessment Group (AG) carried out a systematic review of the literature to identify studies assessing the cost effectiveness of selective sodium glucose-cotransporter 2 (SGLT2) inhibitor monotherapy compared with sulphonylureas (SUs), dipeptidyl peptidase 4 inhibitors (DPP4s), pioglitazone and repaglinide for treating people with type 2 diabetes for whom metformin was not appropriate. No studies were found relevant to all SGLT2 inhibitors, and the Assessment Group and all companies developed new economic models.

6.2 The Assessment Group noted that the UKPDS (UK prospective diabetes survey) had been used for many assumptions in the cost effectiveness analyses. It explained that the UKPDS68 included a number of equations for estimating the progression of HbA1c, systolic blood pressure, cholesterol ratio (ratio of total cholesterol to high density lipoprotein, or TC:HDL) and smoking status over time, and the annual risk of micro and macro vascular events associated with diabetes, for example stoke and blindness. It also predicts the annual risk of death. UKPDS68 was used by Oxford University to derive the OM1 cost effectiveness model. UKPD68 has recently been updated by UKPDS82, providing an alternative set of equations based on longer follow-up data to that used in UKPDS68. The UKPDS also provides costs associated with events, the latest version is UKPDS84. For more information, please see p.119 of Assessment report.

Overview – All models

6.3 In all of the models, patients entered receiving 1 of the scope interventions (see section 3). This intervention determined the initial achievement of outcomes HbA1c, systolic blood pressure, weight change, and TC: HDL. The initial outcomes achieved by modelled patients 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). Throughout the model, patients received a pre-specified treatment sequence dependent on the initial treatment received.

6.4 All models included micro- and macro-vascular health states for morbidities and increased mortality associated with diabetes. Microvascular health states included retinopathy (including macular oedema and blindness), chronic kidney disease (ranging from stage 1 to end stage renal disease), and neuropathy (including peripheral vascular disease and amputation). Macro-vascular health states included ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure. Models also accounted for weight change, hypoglycaemia,

UTIs, genital tract infections, peripheral oedema, and discontinuations. In addition, models included a health state where modelled patients were free from complications. Health states were associated with costs, utility values, and in some cases a possible treatment contraindication or with excess risk of death (for example through stroke or myocardial infarction).

6.5 The following table provides an overview of the key assumptions in the model. The AG stated that the assumptions used in the Janssen model differed noticeably from those of the other 2 submissions. The main difference was the assumption used to model the change in outcomes HbA1c, SBP and TC: HDL over time. Astrazeneca, Boehringer Ingelheim and the AG all used the UK prospective diabetes survey 68 (UKPDS68), whereas Janssen assumed a linear change in these outcomes, and for HbA1c this was treatment specific. For weight outcomes, all models assumed linear evolution. All models submitted were conducted from the perspective of the NHS and Personal Social Services, discounted costs and health effects at 3.5% annually, and had a time horizon of 40 years.

Table 9 Model details

	Janssen	Astrazeneca	BI	AG
Model type	ECHO-T2DM	CARDIFF	UKPDS OM1	UKPDS OM1
Time horizon	40 years			
Cycle length	12 months	6 months	12 months	12 months
Comparators	**1.**Cana 100/300/dose increase **2.** Dapa 10mg **3.** Empa 10/25 **4.** Sita 100 **5.** Pioglitazone **6.** SU	All treatments as a class: **1.** SGLT2 **2.** DPP4s **3.** Pioglitazone **4.** SUs	**1.** Cana 100/300 **2.** Dapa 10 **3.** Empa 10/25 **4.** Sita. 100 **5.** Pioglitazone **6.** SU **7.** Repaglinide.	**1.** Cana 300 **2.** Dapa 10 **3.** Empa 25 **4.** Sita.100 **5.** Pioglitazone **6.** SU **7**. Repaglinide
Main evidence source	•NMA (HbA1c, SBP, weight) •Trial data (Cholesterol, AE, discontinuation)	•NMA (HbA1c, SBP, weight, hypoglycaemia) •Trial data (UTI and GI) •Note: value of 0 assumed for cholesterol	•NMA	•NMA (HbA1c, SBP and weight) •Trial data (AE) •Note: Value of 3.0 assumed for TC:HDL
Initiate next treatment:	When HbA1c>7.5%			
Source of Drift				
HbA1c	Linear	UKPDS68		
SBP	Linear	UKPDS68		
TC:HDL	Linear	UKPDS68		
Weight	Linear			
Complications modelling	Variety	UKPDS82	UKPDS68	UKPDS68
Quality of life main source	CODE-2	UKPDS62	UKPDS68	UKPDS62
Costs main source	UKPDS84	UKPDS65/84	UKPDS84	UKPDS84

AE: adverse events; NMA: network meta-analysis; SBP: systolic blood pressure; sita: sitagliptin; TC:HDL: ratio of total cholesterol to high density lipoprotein; UKPDS: UK prospective diabetes survey; UTI: urinary tract infection; GI: genital infection

6.6 The AG noted there were some differences in patient characteristics between the various models that could have impacted outcomes. Age varied across the models from 55 years (dapagliflozin) to 63 years (empagliflozin). The AG stated this variation could impact on the amount of time patients spend on treatment in each model. The AG also noted there was a large variation in the proportions of current smokers, from 9%

(canagliflozin) to 36.9% (dapagliflozin). Please see table 104 of Assessment Report.

Key clinical effectiveness, quality of life and cost data for all models

6.7 The following presents a summary of the main clinical effectiveness assumptions, and quality of life and cost values for each model. The companies and the AG took most of their clinical effectiveness values from their own network meta-analyses. Some data were also taken from the literature or trial data, and in some instances assumptions were used for missing values. Please see the individual model descriptions for more detail about the assumptions used. The AG noted that the summary of values for utilities and costs may be biased against Janssen, because it does not fully capture all health states in the model.

Table 10 Main model clinical effectiveness assumptions for companies and Assessment Group

	HbA1c				Systolic blood pressure				Weight			
	Janssen	AZ	BI	AG	Janssen	AZ	BI	AG	Janssen	AZ	BI	AG
Cana. 100mg	-0.97	-0.74	[redacted]		-3.71	-5.87	[redacted]		-2.40	-2.81	[redacted]	
Cana. 300mg	-1.2		[redacted]	-1.153	-5.41		[redacted]	-1.338	-3.42		[redacted]	-3.577
Dapa. 10mg	-0.64		[redacted]	-0.704	-3.21		[redacted]	-2.931	-1.61		[redacted]	-2.457
Empa. 10mg	-0.73		[redacted]		-2.6		[redacted]		-1.72		[redacted]	
Empa. 25mg	-0.85		[redacted]	-0.87	-3.4		[redacted]	-3.743	-1.84		[redacted]	-2.471
DPP4s	-0.72	-0.64	[redacted]	-0.723	0.8	-1.53	[redacted]	0.394	+0.82	-0.13	[redacted]	-0.003
Pioglitazone	-0.78	-0.9	[redacted]	-1.2	0.88	-1.31	[redacted]	-1.400*	+2.35	2.61	[redacted]	2.962
Sulfonylurea	-0.59	-0.95	[redacted]	-1.301	0.19	-0.65	[redacted]	-0.600*	+0.62	0.07	[redacted]	1.397
Repaglinide	-1.28		[redacted]	-1.200*	+0.19*		[redacted]	-1.000*	+0.62		[redacted]	+0.100*

Note: In the Boehringer Ingelheim model empagliflozin 25mg has 24 and 52 week data; only 24 week data is presented in this table
*Assumed as no estimate in network meta-analysis
AG: Assessment Group; AZ: Astrazeneca; BI: Boehringer Ingelheim

6.8 The AG, Astrazeneca and Boehringer Ingelheim all based their quality of life values on data from UKPDS, and Janssen used the CODE-2 (Cost of Diabetes in Europe, Type 2) study dataset as its main source of quality of life values. The AG stated that all sources used to derive quality of life values by the companies were appropriate. Key quality of life values are shown in Table 11.

Table 11 Main health state quality of life values for companies and Assessment Group

	Janssen	Astrazeneca	BI	AG
No complications	0.843	0.882	0.72	0.801
MI (year before)	-0.028	-0.055	-0.065	-0.055
MI (prior history)	-0.028	-0.055	-0.008	-0.055
IHD	-0.028	-0.09	-0.028	-0.09
Stroke	-0.115	-0.164	-0.165	-0.164
CHF	-0.028	-0.108	-0.101	-0.108
Amputation	-0.272	-0.280	-0.172	-0.28
Blindness	-0.057	-0.074	-0.033	-0.074
ESRD	-0.175	-0.263		
per BMI > 25	-0.0061			
Severe hypo	-0.047			
Non-severe hypo	-0.0142			
UTI	-0.0043	-0.0028		-0.0073
GTI	-0.0046	-0.0028	n.a.	-0.0096
AG: Assessment Group; BI: Boehringer Ingelheim; CHF: congestive heart failure; ESRD: end stage renal disease; GTI: genital tract infection; hypo: hypoglycaemia; IHD: ischaemic heart disease; MI: myocardial infarction; n.a.: not applicable; UTI: urinary tract infection				

6.9 The following presents the main costs used in the AG and company models.

6.10 Table 12 presents drug costs, and Table 13 presents health state costs. Some of the costs presented represent an average of the actual costs used:

Table 12 Monotherapy direct drug costs for companies and Assessment Group

	Janssen	AZ	BI	AG
Empagliflozin 10 and 25mg	Approx. £477.30			
Dapagliflozin 10mg	Approx. £476.98			
Canagliflozin 100mg	Approx. £476.93			
Canagliflozin 300mg*	£608.63	n.a.	£608.21	£476.93
SU (Gliclazide)	£25.81	£65.70	£68.36	£62.18
Pioglitazone	£20.48	£19.03	£24.25	£20.99
Repaglinide	£71.10	n.a.	£93.40	£71.91
Sitagliptin 100mg	Approx. £433.86			
*300mg now costs the same as the 100mg dose. Key: see Table 11				

Table 13 Main health state costs for companies and Assessment Group

	Janssen	Astrazeneca	BI	AG
No complications	£0	£0	£459	£1,019
Complications 1st year				
Fatal MI	£1,566	£2,605	£1,521	£1,564
Fatal IHD	£3,818	£0	£3,766	£3,873
Fatal stroke	£4,255	£5,188	£3,954	£4,066
Fatal CHF	£3,366	£0	£3,191	n.a.
Non-fatal MI	£6,665	£7,938	£6,379	£7,550
Non-fatal IHD	£10,116	£12,762	£9,767	£10,932
Non-fatal stroke	£7,247	£11,450	£6,805	£8,120
Non-fatal CHF	£3,337	£5,180	£3,191	£4,288
Amputation	£11,810	£13,499	£9,546	£12,592
Blindness	£2,260	£6,502	£1,355	£3,234
ESRD	£26,297	£18,776	£35,715	£36,801
Subsequent years				
MI	£875	£2,177	£1,154	£1,877
IHD	£920	£1,395	£1,215	£1,922
Stroke	£934	£1,378	£1,125	£1,934
CHF	£1,527	£1,656	£1,473	£2,515
Amputation	£2,531	£4,618	£1,792	£3,499
Blindness	£215	£2,307	£453	£1,225
ESRD	£26,152	£18,776	£35,631	£36,801
Adverse events				
Severe hypo	£380	£424	£380	£411
UTI	£82	£46	£36	£73
GTI	£51	£46	n.a.	£51
Key: See Table 11				

6.11 The AG noted that direct drug costs in the models were similar, but that it added additional costs of £72.26 for BNP monitoring (£26.26 for the test itself and £46.00 for a dedicated GP appointment) to the costs of pioglitazone in its model. For health state costs, the AG stated there was variation in the models:

- the first year costs for Janssen were similar to the AG model, but costs for those with a history of event were lower. The AG stated this may be because the costs in the Janssen model did not include outpatient costs.
- the costs used by Astrazeneca were higher than those assumed by the AG, but the AG stated it was not sure why there was a discrepancy.
- Boehringer Ingelheim appeared to only apply the inpatient costs of the UKPDS84, and to have ignored the outpatient costs.

Company economic model (Janssen, canagliflozin)

6.12 Janssen used the ECHO-T2DM model, a stochastic micro-simulation model that creates individual patients and models them over time. It uses Monte Carlo techniques for first order (random) uncertainty, with second order (parameter) uncertainty captured by using many cohorts of patients with unique characteristics for key parameters (such as treatment effects), taken from probability distributions.

6.13 Modelled patients were assigned one of the following treatments (SGLT2 inhibitors were individually modelled, all other treatments were modelled as a class): canagliflozin ([redacted]), dapagliflozin (10mg), empagliflozin (10mg or 25mg), SUs (gliclazide), glitazones (pioglitazone 30mg), and DPP4i (sitagliptin 100mg). The company also included repaglinide in a scenario analysis. For canagliflozin, the company considered how many people progressed to the higher 300mg dose in clinical practice. It stated that there was no data available for this, but that canagliflozin 300mg was not routinely used as monotherapy in clinical practice, and it estimated approximately [redacted]% of patients progress to the

higher dosage. In the base case, at first intensification, an SU was added for treatments other than SUs (sitagliptin added). For all treatments the 2nd and 3rd line intensifications were the same: Neutral Protamine Hagedorn (NPH) insulin, followed by NPH insulin plus insulin aspart. Most patients in the model were also treated with medications for hypertension and dyslipidaemia, because the company stated these are major co-morbidities in type 2 diabetes.

6.14 The company derived treatment effects for HbA1c, systolic blood pressure and weight for the main interventions from their 26 week network meta-analysis (see Table 4 and Table 10), with an assumption that outcomes would be maintained at 52 weeks. Cholesterol levels, adverse events (hypoglycaemia, UTI, GMI and peripheral oedema) and discontinuations were derived from pooled trial data (

6.15 Table 14). For hypoglycaemia, event rates were adjusted using a relative risk multiplier of 1.43 for every 1% increase in HbA1c. Pioglitazone was modelled to include a higher incidence of oedema and congestive heart failure (assuming a hazard ratio of 1.41 compared with other comparators). For cholesterol levels, rates were zero for non-SGLT2 treatments. For all SGLT2 inhibitor treatments, total cholesterol mean change from baseline was 4.512 (other than canagliflozin 300mg [7.544]) LDL mean change from baseline was approximately 1.655 (other than canagliflozin 300mg [6.156]) and HDL levels were approximately 3.477 (other than canagliflozin 300mg [3.236]). Safety and effectiveness rates for insulin were taken from the literature (Rosenstock et al., 2008).

Table 14 Rates of adverse events and first year discontinuation because of adverse events for all treatments

	SGLT2	All other treatments
Female GMI	0.208 (other than cana 300mg, 0.161)	0.065
Male GMI	0.047 (other than cana 300mg, 0.165)	0.015
Upper UTI	0.008 (other than cana 300mg, 0.000)	0.000
Lower UTI	0.107 (other than cana 300mg, 0.109)	0.071
Severe hypo	0.008 (other than cana 300mg, 0.000, and dapa, 0.003)	Range 0.002 (pioglitazone and DPP4) to 0.034 (SU)
Non-severe hypo	0.046 (other than cana 300mg, 0.065, and dapa, 0.057)	Range 0.027 (pioglitazone) to 0.508 (SU)
1st year AE discontinuation	0.025 (other than cana 300mg, 0.02)	0.011
Peripheral oedema		
Year 1	0.119	0.119 (other than pioglitazone, 0.254)
Subsequent	0.058 (other than pioglitazone, 0.085)	
Key: GMI: genital mycotic infection; UTI: urinary tract infection; SU: sulphonylurea		

6.16

6.17 Table 15 shows the rate of drift in the model. Rates were assumed to drift annually upwards at a linear rate. HbA1c drift was derived from the ADOPT trial (which compared rosiglitazone, glibenclamide, and metformin for newly diagnosed type 2 diabetes). SGLT2 inhibitors were assumed to have the same drift as metformin, pioglitazone the same as rosiglitazone, and repaglinide the same as SUs. Drift for systolic blood pressure and lipids were derived from UKPDS, and drift for weight was derived from the NICE technology appraisal for dapagliflozin (TA288). At intensification, if another treatment was added the annual rate of HbA1c drift is assumed to be the average of the HbA1c annual drifts of the two treatments being used as dual therapy.

Table 15 Annual drift assumptions

	Treatment	Annual Drift Value
HbA1c	SGLT2 & DPP-4-i	0.14%
	Pioglitazone	0.07%
	SU, repaglinide	0.24%
	Insulin	0.15%
SBP	All	0.30 mmHg
Lipids	All	0.03 mg/dl
Weight	All	0.1kg/year
eGFR	All	Varies by eGFR category & whether patient micro- or macro-albuminuria
Key. EGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; SU: sulphonylurea Note: weight was converted to BMI for the model		

6.18 The company used data from the CODE2 trial for most health related quality of life values, an observational study of 4000 people with T2DM in Europe (including UK) based on EQ5D and using a UK tariff. The company did not identify any sources to determine disutility rates associated with adverse events, therefore it did a time trade off (TTO) study of participants in the UK determine the quality of life impacts from UTIs and genital tract infections. Please see section 6.8 for utility values.

6.19 The company derived direct drug costs from BNF69. It assumed there were no administration costs for any treatment (because all were self-administered), however additional monitoring was required in the first year for those who self-injected treatments. The company assumed repaglinide, SUs, pioglitazone and insulin regimens required regular self-monitoring of blood glucose, with costs derived from an average in the NICE draft clinical guideline update for diabetes. The costs of blindness, ischaemic heart disease, myocardial infarction, congestive heart failure and stroke were derived from the UKPDS 84. UTIs and GMIs costs were derived using assumptions from the clinical guideline and costs taken from the Hospital and Community Health Services index and the BNF. For hypoglycaemia, only severe hypoglycaemia was assumed to incur a cost, taken from the NICE draft clinical guideline update, which included direct healthcare costs (primary care visits, hospital costs, ambulance services

and treatment costs). Please see section 6.9 to 610 for more detail on costs.

6.20 The company presented incremental cost effectiveness results (ICERs) for all treatments. Canagliflozin was presented as 3 arms: 100mg, 300mg, and 100mg increased to 300mg (hereafter referred to as 'canagliflozin dose increase'). The company presented results with and without pioglitazone, because it stated that the usage of pioglitazone was declining in the UK. Compared with pioglitazone, SUs and DPP4s were dominated, and ICERs for other comparators ranged from approximately £47,500 (canagliflozin 300mg) to £416,000 (dapagliflozin) per QALY gained. Results for all comparators compared with SUs and DPP4s are presented in Table 16. In other pairwise comparisons, canagliflozin 100mg dominated dapagliflozin and empagliflozin (10mg and 25mg), and was cheaper but less effective than both other canagliflozin doses (£12,070 saved per QALY lost compared with canagliflozin dose increase, and £17,845 saved per QALY lost compared with canagliflozin 300mg).

Table 16 Janssen base case incremental cost-effectiveness results (ICER)

	Cost	QALY	vs SU			vs DPP4		
			Δ £	Δ Q	ICER	Δ £	Δ Q	ICER
Pioglitazone	£20,264	9.998						
SU	£23,220	9.949						
DPP4	£23,443	9.981	£223	0.032	£6,969			
Cana. 100	£23,525	10.039	£305	0.09	£3,377	£82	0.058	£1,414
Empa. 25mg	£23,528	10.024	£308	0.075	£4,107	£85	0.043	£1,977
Empa.10mg	£23,580	10.01	£360	0.061	£5,902	£137	0.029	£4,724
Dapa.	£23,594	10.006	£374	0.057	£6,561	£151	0.025	£6,040
Cana. 100/300	£23,669	10.051	£449	0.102	£4,402	£226	0.07	£3,229
Cana. 300	£24,302	10.083	£1,082	0.134	£8,075	£859	0.102	£8,422
Note: Table subject to rounding errors. Key: Δ: change; ICER: incremental cost-effectiveness ratio; Q: quality adjusted life year								

6.21 The company performed deterministic sensitivity analyses, all of which used canagliflozin 100mg as the intervention arm. The company stated that it dominated dapagliflozin and empagliflozin in most analyses and results were relatively stable compared with all comparators.

6.22 The company conducted scenario analyses, on 17 key drivers of cost effectiveness in the economic model (for details of these see page 57 of company submission). Compared with SGLT2 inhibitors, most analyses had no impact on the results. In the scenario including a comparison with repaglinide, canagliflozin had an ICER of £20,982 per QALY gained. The assumption of HbA1c drift had the biggest impact on results. When HbA1c drift equations were taken from UKPDS instead of the linear assumption, the ICERs for canagliflozin 100mg were:

- £71,395 per QALY gained compared with dapagliflozin
- £50,826 per QALY gained compared with empagliflozin 10mg
- £133,274 compared with SUs.

6.23 The company presented probabilistic analyses for canagliflozin 100mg compared with all comparators. The probability of canagliflozin 100mg being cost effective at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained were approximately 70% and 40% respectively. The probabilities for all other treatments were less than 20%.

6.24 The AG reviewed the model submitted by Janssen. It stated it was not clear what happened to patients who discontinued after adverse events. It noted that the main result of interest was that modelling was very sensitive to the annual rate of HbA1c drift that is assumed for canagliflozin (decreasing and increasing the base case 0.14% annual rate of drift by 20%). The AG stated the changes are likely more because of the time spent on therapy and its immediate effects upon treatment cost, weight, adverse events and hypoglycaemia than any changes in the modelled complications of diabetes. Results were as follows for canagliflozin 100mg compared with (results presented as decrease and increase in HbA1c drift for canagliflozin):

- pioglitazone: £45,862 and £211,446 per QALY gained
- SUs: £593 and £8,751 per QALY gained
- DPP4s: canagliflozin dominant and £8,528 per QALY gained

6.25 The AG stated that for the comparison of canagliflozin with dapagliflozin and empagliflozin the main scenario analyses of interest were: using patient characteristics from the database used in the NICE clinical guideline update, using UKPDS68 HbA1c evolution, and using UKPDS68 HbA1c evolution and quality of life (whilst also assuming patients can intensify to NPH insulin but not basal-bolus insulin). These change the ICERs from canagliflozin 100mg dominating to between £5000 to £10,000 per QALY gained.

Company model (AstraZeneca)

6.26 Astrazeneca used the Cardiff diabetes model (a stochastic simulation model) with a Microsoft Excel based front end. The company conducted analyses for all drugs as a class, including the SGLT2 inhibitors. The company stated SGLT2 inhibitors were considered as a class because they have similar safety and effectiveness, and also because there is a limited amount of evidence for the individual treatments as monotherapy. The company stated that its primary analyses were those where SGLT2 inhibitors were compared with DPP4 inhibitors, because these are the treatments that it expected SGLT2 inhibitors to displace in clinical practice. Comparisons of SGLT2 inhibitors compared with SUs and glitazones were also conducted, but the company stated it expected these to be less relevant (because the low price of SUs meant they would likely be used before SGLT2s and DPP4s in clinical practice, and glitazones are used very little in clinical practice). The company did not do comparisons with repaglinide because there was no evidence identified to allow a comparison, however it stated it is not expected to be a key comparator because it is not used often as monotherapy in clinical practice. The company assumed that all treatment arms received the same additional treatments – following the failure of any treatment, all patients first received NPH insulin, followed by intensified (by 50%) insulin. The company stated this was because allowing intensifications to vary for each arm would not allow a fair assessment of the monotherapies and would instead show comparisons of treatment sequences.

Clinical effectiveness estimates were taken from the network meta-analysis for HbA1c, analysis for HbA1c, weight change, systolic blood pressure and hypoglycaemic events (see hypoglycaemic events (see

6.27 Table 5 and Table 10). The company assumed values of 0.00 for change in total cholesterol and HDL-C, because no data were available from the network meta-analysis. The adverse events urinary tract infections and genital infections were taken from pooled clinical trial data. Clinical effectiveness estimates for insulin were drawn from Monami et al (2009) for NPH and from Waugh et al (2010) for intensified NPH. The company used UKPDS for drift assumptions. For weight change, the company assumed all SGLT2 inhibitors were associated with a weight loss that was maintained for 2 years before rebound to starting weight (the company stated this was a conservative assumption as there was evidence it could have a longer effect). For comparators, only DPP4 inhibitors were found to be associated with weight loss, and in the model the company assumed this was maintained for 1 year before rebound. Weight increases were assumed for glitazones and SUs. For all treatments, weight increased by 0.1kg annually. Weight change was associated with an impact on health related quality of life and increase of cardiovascular risk. All-cause mortality events were estimated using gender specific life tables for the UK.

Table 17 Astrazeneca probability of adverse event

Parameter	SGLT2	DPP4	Pioglitazone	Sulphonylurea
Severe hypo event (95% CrI)	0.01 (0.003, 0.036)	0.016 (0.008, 0.031)	0.024 (0.007, 0.076)	0.055 (0.015, 0.176)
UTI	0.092	0.022	0.153	0.000
GI	0.074	0.002	0.000	0.000
Discontinuation	0.034	0.039	0.177	0.061
CrI: credible interval; Hypo: hypoglycaemic event; GI: genital infection; UTI: urinary tract infection				

6.28 The company derived a baseline utility value for a patient without any complications of 0.882, derived from EQ5D data in the Health Survey for England 2003. This result declined over time. The company assumed that the disutility values for patients experiencing more than one complication was additive. See section 6.8 for more quality of life values.

6.29 The company used BNF 69 for direct drug costs, using weighted average costs based on UK market share. The company assumed there were no administration costs for SGLT2s and DPP4 inhibitors because they are administered orally. It also assumed insulin was self-administered. The company stated that patient monitoring including renal monitoring is part of routine clinical practice, therefore an additional cost was not added. However it did add a single incremental cost (one GP visit and a 24 hour urine creatinine clearance test) for the introduction of renal monitoring for any patient who started SGLT2 inhibitor treatment. Costs for end stage renal disease were not available from UKPDS therefore costs for dialysis were taken from a study in the UK setting (Baboolal et al., 2008). See section 6.9 and 6.10 for more costs.

6.30 The company presented their base case results.

Table 18 Astrazeneca pairwise cost effectiveness results for SGLT2 inhibitors compared with comparator

	Inc. cost	Inc. QALY	ICER
Vs DPP4	£106	0.018	£5904
Vs pioglitazone	£1912	0.095	£20,089
Vs SU	£1397	0.027	£52,047

6.31 The company presented results of one way sensitivity analyses, including varying HbA1c and weight change outcomes using 95% credible intervals:

- Compared with DPP4s, the ICER was less than £10,000 per QALY gained in all sensitivity analyses.
- Compared with pioglitazone, the ICER was most sensitive to the disutility associated with body mass index (BMI) increase, which had a range of £14,626 to £32,065 per QALY gained
- Compared with SUs, the company noted that the ICER was sensitive to uncertainty about the relative efficacy of SGLT2 inhibitors and SUs for HbA1c (£42,274 to £165,409 per QALY gained) and weight change (£28,422 to £68,366 per QALY gained); and in utility value for decrease in BMI (£4434 to £62,810 per QALY gained). The company stated

these ICERs reflected the greater relative uncertainty in the network meta-analysis for the comparison of SGLT2 with SUs.

6.32 The company presented a range of scenario analyses for SGLT2 inhibitors compared with comparator, including varying the HbA1c values at baseline and HbA1c thresholds for intensifying treatment, altering the assumptions around maintenance of weight effects and the drug costs that were applied:

- Compared with DPP4s, the ICER was most sensitive to using the lowest priced DPP4 (£22,756 per QALY gained).
- Compared with pioglitazone, assuming weight convergence between SGLT2 inhibitors and DPP4s at the second treatment switch increased the ICER to £38,199 per QALY gained (although the company stated weight convergence was unlikely to occur in reality).
- Compared with SUs, the ICER remained above £40,000 per QALY gained. The company stated that the base case ICER and scenario analyses compared with SUs were likely to be overestimates because of a 'J' effect, where SUs have an initially high clinical effectiveness estimate but which has a faster drift than other treatments.

6.33 The company conducted probabilistic sensitivity analyses. At a maximum acceptable ICER of £20,000 per QALY gained the probability that the SGLT2 inhibitors were cost-effective compared with DPP4s was 66%. Compared with pioglitazone and SUs the probabilities were 51% and 13% respectively.

6.34 The Assessment Group stated it had concerns with the calculation of costs in the company model. It stated that it appeared the UKPDS84 average inpatient costs and outpatient costs for those without any of the modelled complications had not been included within the modelling. It stated that if this was the case, it would be a serious omission, and would bias the analysis in favour of the more effective treatment. It also noted that the company had used the same source for costs of complications of

diabetes (blindness and amputation) (UKPDS84) as the AG, but that the AG had derived lower values, and it could not identify why.

Company model (Boehringer Ingelheim)

6.35 The company presented 2 economic models based on OM1, which uses patient level data from the UKPDS to extrapolate diabetes risk and predict long term costs and outcomes. Both models were similar and included a Microsoft Excel 'front end' where 9211 patients were treated with an anti-diabetes agent for a year. In model A, patients then entered the OM1 model with these treatment effects (for hypoglycaemia, urinary tract infection and weight change), and progression of disease was informed by UKPDS, with no further direct treatment effects, discontinuations, switches or intensifications. In the first year, modelled patients could not die, and costs, quality of life and adverse events not related to treatment were not considered. The company stated this accounted for the short-term nature of treatment effectiveness evidence. In model B, the more complex model, patients could experience treatment discontinuation, switching and intensification. The company stated they ran model B for a year at a time for added granularity of modelling. The company noted limitations of the OM1 model, including the age of the underlying randomised controlled trial, the data being based on a population with newly diagnosed diabetes (an issue if modelling treatment intensification) and a limited set of outcomes modelled for first occurrence.

6.36 In both models, patients could receive one of the following treatments: empagliflozin (10mg and 25mg), canagliflozin (100mg and 300mg), dapagliflozin (5mg and 10mg), DPP4 inhibitors (considered as a class – sitagliptin 100mg only), SUs (the company stated all doses were combined together), pioglitazone (45mg only) and repaglinide (1mg). All patients received SUs (gliclazide) at first intensification, other than the SU arm, which received a DPP4 inhibitor (sitagliptin). At the second intensification, all patients received NPH insulin.

6.37 Treatment effectiveness was mainly taken from the network meta-analyses. The company presented results using 2 different sets of data: 24 weeks (available for all comparators) and 52 weeks (not available for canagliflozin and dapagliflozin, but the company stated the longer period of efficacy data informing the model would allow for more credible results). In common with Astrazeneca, Boehringer Ingelheim noted a 'treatment rebound' effect for SUs (Boehringer Ingelheim also stated a similar effect was also possible for repaglinide), where the treatments are initially effective but have a more rapid drift back towards baseline (section 6.29), and that longer term data would account for this. The company noted that 52 week data were not available for UTIs and systolic blood pressure, therefore 24 week data were used. At intensifications, the company used the 52 week network meta-analysis to derive the value for either SU or DPP4 inhibitor (first intensification) relative to placebo for HbA1c, systolic blood pressure and weight change; or it used values from the literature for NPH insulin (second intensification) relative to placebo for HbA1c (Khunti et al. 2014) and systolic blood pressure (Yale et al. 2013).

6.38 The company used UKPDS for drift assumptions for HbA1c, cholesterol, and systolic blood pressure. For weight change, any weight losses in the first year were assumed to rebound to baseline at the end of the second year. Weight gains were assumed to be maintained indefinitely. A 0.1kg per year annual weight gain was applied. The company assumed pioglitazone and repaglinide had no effect on the rates of systolic blood pressure and UTI.

6.39 The company presented quality of life values. It based most quality of life values at baseline and for the complications of diabetes based on the UKPDS. See section 6.8 for utility data.

6.40 The company presented treatment costs. Prescription costs were based on March 2015 Monthly Index of Medical Specialities (MIMS). The costs of diabetes without complications, and the costs of the complications of diabetes, were taken from UKPDS 84. The company added the cost of

testing strips and lancets to the cost for SU and repaglinide. See section 6.9 and 6.10 for more costs.

6.41 The company presented results for model A and model B, both of which had 2 sets of results, using 24 week data and 52 week data.

6.42 The results for model A are presented in Table 19. In pairwise comparisons for model A using both 24 and 52 week data, ICERs for empagliflozin 10mg compared with pioglitazone, SUs and repaglinide were all less than £10,000 per QALY gained. Empagliflozin 10mg dominated sitagliptin and dapagliflozin; was dominated by empagliflozin 25mg and canagliflozin 100mg; and it was less costly but less effective compared with canagliflozin 300mg.

Table 19 Model A cost effectiveness results (24 and 52 week), empagliflozin 10mg compared with comparator

	Inc. costs	Inc. QALY	ICER
52 week			
Pioglitazone	£304	0.043	£7,015
SU	£299	0.035	Extendedly dominated by pioglitazone & Empa 25
Repaglinide	£274	0.034	Extendedly dominated by pioglitazone & Empa 25
Empagliflozin 25mg	£21	-0.007	Dominates Empa 10
Sitagliptin	-£59	0.029	Dominated by Empa 10
24 week			
Canagliflozin 100mg	£43	-0.015	Dominates Empa 10
Empagliflozin 25mg	£16	-0.007	Dominates Empa 10
Dapagliflozin 10mg	-£1	0.004	Dominated by Empa 10
Dapagliflozin 5mg	-£12	0.005	Dominated by Empa 10
Canagliflozin 300mg	-£21	-0.036	£596 (bottom left quadrant)

6.43 The company did not present one way sensitivity analyses or scenario analyses for model A. In probabilistic sensitivity analyses for model A, when assuming a maximum acceptable ICER of £20,000 per QALY gained at 52 weeks, empagliflozin 25mg had an 87.5% likelihood of being the most cost effective treatment option, and empagliflozin 10mg had an 11.75% chance of being the most cost effective treatment. When assuming a maximum acceptable ICER of £30,000 per QALY gained, the probabilities were 88.5% and 11.5% respectively. For 24 week data, when assuming a maximum ICER of £20,000 per QALY gained, the company noted that empagliflozin is not the most cost effective treatment, but that the differences between treatments were small, therefore it could be misleading to view these results on a cost effectiveness acceptability curve.

6.44 The company presented results for model B relative to the cheapest treatment (compared with pioglitazone in 52 week data, and dapagliflozin in 24 week data) (

6.45 Table 20). In pairwise comparisons using 52 week data, empagliflozin 10mg had ICERs of approximately £30,000, £50,000 and £70,000 per QALY gained compared with SUs, pioglitazone and repaglinide respectively. When using 24 week data, empagliflozin 10mg had ICERs of approximately £9834 and £2500 per QALY gained compared with dapagliflozin and canagliflozin 100mg respectively; was cheaper but less effective than canagliflozin 300mg; and was dominated by empagliflozin 25mg.

Table 20 Model B cost effectiveness results

Treatment	Incremental Costs	Incremental QALYs	ICERs
Model B results – 52 week ICERs (vs pio)			
EMPA 25mg od	2834.03	0.06	46,480
EMPA 10mg od	2836.63	0.06	50,892
PIO 45mg od	Baseline	Baseline	Baseline
REPA 1mg od	634.77	0.03	25,349
SITA 100mg od	2503.70	0.02	163,917
SU	1526.77	0.01	121,660
Model B results – 24 week ICERs (vs dapa 10)			
EMPA 25mg od	45.98	0.02	2172
EMPA 10mg od	67.89	0.01	9834
CANA 300mg od	969.93	0.06	17,363
CANA 100mg od	1.29	0.03	39
DAPA 10mg od	Baseline	Baseline	Baseline
DAPA 5mg od	42.88	0.00	31,836

6.46 The company did not present any sensitivity or scenario analyses for model B.

6.47 The Assessment Group stated that based on a comparison of the written submission with the electronic model B it appeared that the placebo effects had not been included in the model (apart from hypoglycaemia and urinary tract infection rates), which could have underestimated the absolute treatment effects from baseline to 24 or 52 weeks. The AG also stated that it was concerned about why the reported UKPDS costs of Model B were around half of those of Model A, whereas the QALY values of model A and B were more similar. It stated that the reason for the discrepancy was unclear.

Summary of main company cost effectiveness results

6.48 The following table summarises the main cost effectiveness results for SGLT2 inhibitors in all models.

Table 21 Summary of the main company cost effectiveness results

	Incr. Costs (£)	Incr. QALY	ICER (£)
Janssen: Canagliflozin (cana) 100mg dose			
vs. CANA 300mg	-777	-0.044	17,845
vs. CANA 100mg Dose Increase	-144	-0.012	12,070
vs. DAPA 10 mg	-69	0.033	Dominates
vs. EMPA 10 mg	-55	0.029	Dominates
vs. EMPA 25 mg	-3	0.015	Dominates
vs. pioglitazone 30 mg	3,261	0.042	78,518
vs. SU	305	0.09	3377
vs. DPP-4-I	82	0.058	1407
AZ: Dapagliflozin (dapa) ((SGLT2 as a class)			
Vs DPP4	106	0.018	5904
Vs pioglitazone	1912	0.095	20,089
Vs SU	1397	0.027	52,047
BI: Empagliflozin (empa) 10mg (model A not presented)			
*Model B 52 weeks (comparator vs **pioglitazone**)*			
EMPA 25mg	2834	0.061	46,480
EMPA 10mg	2837	0.056	50,892
*Model B 24 weeks (comparator vs **dapagliflozin**)*			
EMPA 25mg	46	0.021	2172
EMPA 10mg	68	0.007	9834
CANA 300mg	970	0.056	17,363
CANA 100mg	1	0.033	39

Independent Assessment Group's economic model

6.49 The Assessment Group, in common with BI, used the OM1 for its submission. Patients started in the model receiving monotherapy (canagliflozin [300mg], dapagliflozin, empagliflozin [25mg] repaglinide, SUs [gliclazide], pioglitazone, DPP4 inhibitors [sitagliptin]). The AG used the larger doses of canagliflozin and empagliflozin rather than the starting doses because it assumed that patients would be at the maximum tolerated dose of each monotherapy drug before moving to dual therapy. The Assessment Group noted that there are a wide range of options for treatment intensification in clinical practice, creating a large number of theoretical pathways, which were beyond the scope of the appraisal to consider. For intensification to dual therapy, it therefore assumed a sulfonylurea was used as the second drug, except after SU monotherapy, when the second drug was pioglitazone. The AG stated that a sulfonylurea was preferred to pioglitazone because there was a worse

safety record for pioglitazone. For intensification to triple therapy, the AG assumed all patients received NPH insulin, as recommended by the NICE draft clinical guideline for diabetes. It stated that some patients will progress to needing short-acting insulin to control blood glucose after meals, therefore it assumed that after patients move to a basal-bolus insulin regimen, the sulfonylurea will be stopped.

6.50 The AG used their network meta-analysis for most clinical effectiveness estimates in the model (see Table 8 and Table 10). For treatment intensifications, the AG assumed that (because of a lack of data), treatments had the same clinical effectiveness regardless of what they were added to.

6.51 The Assessment Group described the utility values used in the model. It derived most values from UKPD62. Treatment discontinuations included a QALY decrement associated with nausea (-0.00462 from Matza et al.). For adverse events urinary and genital tract infections, the AG assumed none progressed to a more serious condition. Please see section 6.8 for main utility values.

6.52 The AG described the costs used in its model. Drug costs were based on the NHS drug tariff or list prices. For the cost of adverse events, the AG noted that their treatment assumptions were broadly similar to Janssen. The AG received clinical confirmation of the validity of the assumptions. Urinary and genital tract infections were costed assuming a GP appointment and medication. Medication for UTIs was assumed to be seven days of trimethropim 200mg twice daily, for male genital tract infections fluconazole 200mg and for female genital tract infections 3 200mg clotrizamole pessaries. For the cost of hypoglycaemic events, the AG followed the current draft NICE clinical guideline. The costs of diabetes and the complications of diabetes were taken from UKPDS84. The AG stated that the costs were for a representative 60 year old male patient with one complication.

6.53 Table 22 below presents lifetime costs and QALYs for the treatments in the model. The AG noted that the SGLT2 inhibitors were of similar cost, but canagliflozin overall costs were cheaper. This was because the greater HbA1c effect of canagliflozin meant that patients intensified to the more expensive subsequent lines of treatment slightly later. The AG noted that because patients remain in initial treatment for the duration of the model, the initial expense of the SGLT2 inhibitors and the DPP4 inhibitor sitagliptin compared with other treatments is maintained over the time horizon of the model. The AG noted that a key difference between the AG modelling and that of the companies was that the AG assumed that patients remained on monotherapy and added treatments to it. Retaining the original monotherapy increased the total costs, and in particular increased the total cost for the SGLT2 inhibitors, and also sitagliptin. Please see section 6.9 and 6.10 for further costs.

6.54 For weight change, the AG assumed an increase in weight of 0.1 kg per year. However the AG stated there was debate about the length of duration of the effects of treatment on weight, as initial weight loss may be transient, and weight gain more permanent. Therefore it modelled 5 different scenarios for BMI, with a decrement of 0.0061 for each point above a BMI of 25kg/2 (as well as a scenario where it was assumed BMI had no impact on quality of life). Scenarios were presented where weight:

- changes maintained with no rebound to natural history (BMI1)
- gains maintained, and weight losses rebound to natural history after one year (BMI2)
- gains maintained, and weight losses rebound to natural history at intensification (BMI3)
- changes rebound to natural history after one year (BMI4)
- changes rebound to natural history at intensification (BMI5)

6.55 QALY gains for SGLT2 inhibitors were lowest when it was assumed BMI had no impact on quality of life, with higher lifetime QALY gains for gliclazide, repaglinide and pioglitazone than SGLT2 inhibitors. However, if

QALY gains for BMI were taken into account, the lifetime QALY gain was highest for SGLT2 inhibitors. These gains were reduced if it was assumed that weight losses rebound after one year, and if it was assumed that weight losses rebound at treatment change.

Table 22 Assessment Group lifetime costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
SU	£27,314	10.39	9.63	9.63	9.63	9.77	9.74
Repaglinide	£27,413	10.39	9.66	9.66	9.66	9.77	9.74
Pioglitazone	£27,543	10.38	9.61	9.61	9.61	9.76	9.73
DPP4	£32,358	10.36	9.66	9.66	9.66	9.74	9.72
Cana. 300	£32,676	10.38	9.78	9.69	9.71	9.77	9.77
Empa. 25	£32,775	10.38	9.75	9.68	9.69	9.77	9.76
Dapa. 10	£32,866	10.37	9.73	9.67	9.68	9.76	9.75

The AG presented their results relative to the next least costly treatment that was not that was not dominated (

6.56 Table 23). The AG stated that the SGLT2 inhibitors and sitagliptin were considerably more expensive than the other comparators, and if there were no direct quality of life effects from weight changes, the SGLT2 inhibitors were estimated to be dominated. When assuming weight changes were maintained with no rebound, canagliflozin had a cost effectiveness estimate of £44,994 per QALY compared with repaglinide, and dominated the other SGLT2 inhibitors. For the other BMI scenarios in comparisons with repaglinide, the cost effectiveness estimates for canagliflozin 300mg were over £100,000 per QALY gained. Compared with pioglitazone, the cost effectiveness estimates for canagliflozin 300mg and empagliflozin 25mg were £30,537 per QALY and £38,889 per QALY gained respectively.

Table 23 Assessment Group cost effectiveness results

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
SU.	..	..	..	..	..	..
Repaglinide	Dom	£3,331	£3,331	£3,331	Dom	£18,507
Pioglitazone	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£44,994	£192k	£119k	Dom	£235k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom: dominated (more costly and less effective than another treatment)						

6.57 The AG presented comparisons of SGLT2 inhibitors with sitagliptin, which removed the cheaper alternatives. ICERs ranged from £2590 per QALY gained (canagliflozin 300mg when assuming weight changes were maintained with no rebound to natural history) to £40,383 per QALY gained (dapagliflozin when assuming there was no effect of BMI on quality of life).

Table 24 Assessment Group cost effectiveness results for SGLT2 inhibitors compared with sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Canagliflozin 300	£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
Empagliflozin 25mg	£18,341	£4,676	£14,716	£10,841	£15,734	£11,300
Dapagliflozin	£40,383	£6,632	£30,710	£19,787	£30,487	£19,679

6.58 The AG presented several scenario analyses, including urinary and genital tract infection rate applied to all cycles and assuming linear evolution of HbA1c. When compared with the cheaper treatments, most scenarios did not have a substantial effect on results. When compared with sitagliptin and assuming weight changes maintained with no rebound to natural history (best-case scenario for SGLT2 inhibitors), ICERs remained under £10,000 per QALY gained. Table 25 presents results for SGLT2 inhibitors compared with sitagliptin when assuming BMI has no effect on utility (worst-case scenario for SGLT2 inhibitors).

Table 25 Assessment Group scenario analyses (assuming BMI has no effect on utility, worst-case scenario for SGLT2 inhibitors) compared with DPP4s

	Cana. 300	Empa. 25	Dapa. 10
At 3rd intensification patients switch to insulin+gliclazide & cease other treatment	£6,567	£5,054	£10,739
Applying UTI & GTI rates to all model cycles	£15,805	£21,167	£52,010
HbA1c 7.5% when starting monotherapy	£24,939	£30,150	£54,863
Adjusting HbA1c for patient baseline HbA1c	£8,314	£16,222	£37,733
Applying UKPDS68 year 2 for HbA1c drift	£10,601	£14,657	£33,394
Intensifying when adding SU having -0.47% HbA1c effect	£11,125	£17,003	£43,173
Applying Janssen linear evolutions of HbA1c	£11,125	£17,003	£43,173
GTI: genital trach infection; UTI: urinary tract infection			

6.59 The AG presented probabilistic ICERs, which were similar to the deterministic ICERs:

- In probabilistic analyses when assuming no utility gain from the impact of BMI:
  - Including all comparators, SGLT2 inhibitors and sitagliptin had a 0% chance of cost effectiveness even at maximum acceptable ICERs of £50,000 per QALY gained.
  - Compared with DPP4s only, the probabilities were canagliflozin 45%, dapagliflozin 4%, empagliflozin 26%, and sitagliptin 26%, when assuming a maximum acceptable ICER of £20,000 per QALY gained.
- In probabilistic analyses assuming weight changes were maintained indefinitely:
  - Including all comparators, the probabilities were canagliflozin 6%, repaglinide 74%, and SU 20%, when assuming a maximum acceptable ICER of £30,000 per QALY gained.
  - Compared with DPP4s only, the probabilities were canagliflozin 93%, dapagliflozin 0%, empagliflozin 6%, and sitagliptin 0%, when assuming maximum acceptable ICERs of £20,000 per QALY gained.

Assessment Group erratum

6.60 Following consultation on the Assessment Report, the AG noted that the baseline assumption for ischaemic heart disease prevalence had been incorrectly set to zero. The AG corrected this, which increased costs, reduced utility values, and generally had minor impacts on cost effectiveness results. It therefore presented a revised base case (setting baseline ischaemic heart disease to 2.7%) and 2 scenario analyses (setting the baseline prevalence of all complications to zero; and setting baseline prevalence of ischaemic heard disease and heart failure to zero). The revised base case is below (showing a slight improvement in the cost-effectiveness of SGLT2 inhibitors), and the AG noted that the scenario analyses had limited impact on results.

Table 26 Assessment Group revised lifetime costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
SU	£27,600	10.376	9.618	9.618	9.618	9.755	9.723
Repaglinide.	£27,704	10.374	9.649	9.649	9.649	9.755	9.73
Pioglitazone	£27,827	10.367	9.596	9.596	9.596	9.746	9.712
Sita. 100	£32,631	10.337	9.641	9.638	9.639	9.723	9.702
Cana. 300	£32,933	10.362	9.763	9.674	9.691	9.753	9.75
Empa. 25	£33,031	10.36	9.73	9.667	9.678	9.749	9.739
Dapa. 10	£33,136	10.35	9.718	9.656	9.665	9.74	9.729

Table 27 Assessment Group revised cost effectiveness results

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
SU	..	..	..	..	..	..
Repaglinide	Dom.	£3,388	£3,388	£3,388	£434k	£16,413
Pioglitazone	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,641	£207k	£124k	Dom.	£259k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom: dominated (more costly and less effective than another treatment)						

Table 28 Assessment Group revised cost effectiveness results for SGLT2 inhibitors compared with sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,034	£2,467	£8,494	£5,820	£9,777	£6,312
Empa. 25	£17,278	£4,471	£13,917	£10,294	£14,864	£10,724
Dapa. 10	£37,871	£6,542	£29,341	£19,172	£29,116	£19,062

7 Equality issues

7.1 No equalities issues have been identified.

8 Innovation

8.1 The company for dapagliflozin stated that most monotherapies for patients for whom metformin is not tolerated or is contraindicated are either associated with weight gain or are weight neutral. It also stated that SUs and repaglinide are associated with increased risks of hypoglycaemia. It therefore stated that SGLT2s inhibitors may represent an innovative approach to monotherapy in these patients because the novel mechanism of action results in weight loss (an important outcome for people with diabetes) and a low risk of hypoglycaemia.

8.2 One patient expert stated it considered the SGLT2 inhibitors to be innovative because it prevents or delays the need to take insulin, it can be taken at any time of day if necessary without the need for food, and because it is easy and not unpleasant to self-administer.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Diabetic foot problems: prevention and management (2015). NICE guideline 19.
- Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (2015). NICE guideline 3.
- Canagliflozin in combination therapy for treating type 2 diabetes (2014). NICE technology appraisal guidance 315
- Dapagliflozin in combination therapy for treating type 2 diabetes (2013). NICE technology appraisal guidance 288
- Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes (partial update of CG66, 2009). NICE clinical guideline 87
- Type 2 diabetes: the management of type 2 diabetes (partially updated by CG87, 2008). NICE clinical guideline 66

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Type 2 diabetes in adults: management of type 2 diabetes in adults. NICE clinical guideline, expected publication December 2015.

NICE pathways

- There is a NICE pathway on diabetes, which is available from http://pathways.nice.org.uk/pathways/diabetes

4th October 2015

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation.

Warwick Evidence

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Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/177/01

Dr McGrane has spoken at educational meetings sponsored by AstraZeneca, Lilly, Sanofi, MSD, Takeda, Novo Nordisk , Janssen, and has served on Advisory Boards for Lilly, Sanofi, Novo Nordisk.

Acknowledgement. We thank Emma Loveman for checking data extractions.

Contributions of authors
Pamela Royle did literature searches, generated the list of references and edited and formatted the final report.
Christine Clar, Rachel Court, Bee Tan and Saran Shantikumar extracted data from the trials in Chapter 2. Christine Clar drafted the clinical effectiveness section. Bee Tan drafted the section on UTIs and GTIs.
Christine Clar and Jill Colquitt extracted data for the network meta-analysis which was carried out by Olakan Uthman.
Andrew Clegg provide a technical critique of the methods of the manufacturers' NMAs
Rhona Johnstone and Ewen Cummins wrote additions to the UKPDS Outcomes model and carried out the economic modeling.
Norman Waugh drafted chapters 1 and 6, wrote various other sections, and edited the final report.
David McGrane, Paul O'Hare and Tim Holt provided clinical advice.

Competing interests:
Dr O'Hare has received lecture fees, advisory board meeting fees, and grants for research from Novo Nordisk and Sanofi. All fees are paid through University of Warwick to fund access to insulin projects in Sub Saharan Africa

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List of Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin-Converting Enzyme Inhibitor
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AG	Assessment Group
AHA	Anti-Hyperglycaemic Agents
ARB	Angiotensin-Receptor Blocker
BDR	Background Diabetic Retinopathy
BMI	Body Mass Index
BNF	British National Formulary
BNP	B-type Natriuretic Peptides
BP	Blood Pressure
CANTATA-M	CANagliflozin Treatment and Trial Analysis - Monotherapy
CDM	CARDIFF Diabetes Model
CEAC	Cost-Effectiveness Acceptability Curve
CG	Clinical Guideline
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CODE-2	Cost of Diabetes in Europe – Type 2
CPRD	Clinical Practice Research Datalink
CrI	Credible Interval
CSII	Continuous Subcutaneous Insulin Infusion
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DIC	Deviation Information Criterion
DKA	Diabetic ketoacidosis
DPP4	Dipeptidyl peptidase-4
DURATION-1	Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly
ECHO-T2DM	Economic and Health Outcomes Model for Type 2 Diabetes Mellitus
EDICT	Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMPA-REG BASAL	Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin
EMPA-REG METSU	Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes

EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EMPA-REG RENAL	Efficacy and Safety of Empagliflozin in Patients With Type 2 Diabetes and Renal Impairment
EQ-5D	European Quality of Life-5 Dimensions
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GDG	Guideline Development Group
GLP-1	Glucagon-like peptide-1
GPRD	General Practice Research Database
GTI	Genital Tract Infection
GUIDE	GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride
HbA1c	Glycated haemoglobin (A1c)
HDL	High-Density Lipoprotein
HFS	Hypoglyceamic Fear Survey
HOPE	Heart Outcomes Prevention Evaluation Study
ICERs	Incremental Cost-Effectiveness Ratio
IHD	Ischaemic Heart Disease
IQR	Interquartile range
ITT	Intention-to-treat
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MDI	Multiple Daily Injections
MO	Macular Oedema
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial Infarction
MR	Modified Release
MS	Manufacturer Submission
NAFLD	Non-alcoholic fatty liver disease
NMA	Network Meta-Analysis
NPH	Neutral Protamine Hagedorn
OLS	Ordinary Least Squares
OM1	UKPDS Outcomes Model v1
PDR	Proliferative diabetic retinopathy
PPARG	Peroxisome proliferator-activated receptor gamma
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral Vascular Disease
QALY	Quality-Adjusted Life Year

QoL	Quality of Life
QWB	Quality of Wellbeing
RCT	Randomised Controlled Trial
RR	Risk Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT1	Sodium-Glucose coTransporter 1
SGLT2	Sodium-glucose co-transporter-2
SIGN	Scottish Intercollegiate Guidelines Network
SLC5A2	Solute Carrier family 5 (sodium/glucose cotransporter), member 2
SMBG	Self monitoring of blood glucose
SmPC	Summary of Product Characteristics
SU	Sulphonylurea or Sulfonylurea
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
THIN	The Health Improvement Network
TTO	Time Trade-Off
TZDs	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary Tract Infection
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WMD	Weighted Mean Difference
YHPHO	York and Humber Public Health Observatory

Summary

The prevalence of type 2 diabetes has been increasing in the UK, and over 3.5 million people in England have the disease. It has at times been described as “mild” diabetes, in contrast to type 1 (insulin-dependent) diabetes, but this term was incorrect since people with type 2 diabetes are also at risk of complications of diabetes, including visual loss, renal failure and neuropathy, and an excess risk of cardiovascular disease, particularly coronary artery disease.

Most people with type 2 diabetes are overweight, so treatment starts with lifestyle advice, aimed at reducing weight and increasing physical activity. Even modest amounts of weight loss can improve control of blood glucose.

If drug treatment is necessary, the drug of first choice is metformin. However some people cannot tolerate metformin. It causes troublesome diarrhoea in 5-10% of people. There is also a contraindication to using metformin in people with renal impairment.

If drug treatment is required to control high blood glucose levels when metformin cannot be used, the other options suggested in the NICE guideline include;

- Sulfonylureas
- Pioglitazone
- The DPP4 inhibitors
- Repaglinide

All of these are oral medications and licensed for use in monotherapy. The sulfonylureas have been used for decades and are available in inexpensive generic forms. Gliclazide costs around £30 a year, or around £60-80 a year for the modified release form. Their safety record is well established. They can cause weight gain and hypoglycaemia.
Pioglitazone is also available in inexpensive generic form, costing around £21 a year. It has rather more adverse effects, including weight gain, oedema, heart failure and fractures. There has been concern over an increased risk of bladder cancer but this is unproven, and recent research is reassuring.

The DPP4 inhibitors, such as sitagliptin, are a more recent group, with no generic forms, and cost around £430 a year. They have been approved by NICE for use in combination therapy. They are very well tolerated, and have the advantage of being weight neutral.

The newest group of drugs to be licensed for monotherapy are the sodium-glucose co-transporter 2 (SGLT2) inhibitors. These inhibit a mechanism in the kidney that conserves glucose by reabsorbing it from the urine. This means that glucose is lost in the urine, which reduces the blood glucose level and also leads to a loss of calories, which leads to weight loss. They also act like a mild diuretic and have a modest blood pressure lowering effect. They cost around £470 a year.

The purpose of this report is to review the clinical effectiveness and cost-effectiveness of three SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin, in monotherapy in people who cannt take metformin. All three drugs have previously been approved by NICE for use in combination treatment, which is therefore not addressed in this report.

Methods

Searches were carried out in Medline and Embase, looking for randomised controlled trials lasting 24 weeks or more. The trials were then critically appraised and summarised. Submissions from the three manufacturers were checked for any additional trials – none were found. For adverse events, a wider range of studies were used, including trials of combinations. A network meta-analysis was carried out involving the three SGLT2 inhibitors and key comparators. Cost-effectiveness modelling was done using the UKPDS Outcome model, version 1, because the Assessment Group was unable to obtain access to version 2 in time.

Results

Seven relevant trials were obtained, three of dapagliflozin and two each for canagliflozin and empagliflozin. All these trials were of good quality. The canagliflozin and dapagliflozin trials compared them with placebo, but the two empagliflozin trials included active comparators, one sitagliptin and one linagliptin. All three drugs were shown to be effective in improving glycaemic control, promoting weight loss and lowering blood pressure. The main outcome was glycaemic control as reflected in reductions in HbA1c, where a reduction of 0.5% or more is regarded as clinically useful.

In the three trials of dapagliflozin 10mg daily, HbA1c was reduced by 0.39%, 0.66% and 0.82% more than on placebo. The trial with the smallest reduction had the lowest baseline HbA1c, of 7.5%. Generally speaking the higher the baseline HbA1c, the greater the reduction seen. On dapagliflozin 10mg daily, patients lost between 1.1kg and 2kg in weight more than in the placebo groups, though it is worth noting that two trials were carried out in China and Japan where starting BMIs were around 26. The placebo groups lost between 0.27 kg and 2.2 kg, and also improved their HbA1cs (by 0.23%, 0.29% and 0.06%), and some of this might have been due to the circumstances of being in a trial, so

the differences due to dapagliflozin might be greater in routine care. Systolic blood pressure fell by 2.7 to 3.1 mmHg.

One canagliflozin trial was carried out in Japan and the other in 17 countries. On canagliflozin 100mg daily, HbA1c was reduced by 0.91% and 1.01% more than on placebo, from baselines of 8.0%. One trial also used a dose of 300mg, which reduced HbA1c by 1.17%. On 100mg daily, weight loss was around 2kg, and systolic blood pressure by 3.7 and 5.2 mm Hg. On 300mg daily, weight loss was 2.9kg. In both the canagliflozin trials, the placebogroup HbA1c rose (by 0.14% and 0.29%).

One empagliflozin trial was carried out in 197 centres in 22 countries, and the other in 124 centres in 9 countries, mainly western countries but including China, India and Japan. Compared to placebo, empagliflozin 10 mg reduced HbA1c by 0.74% and empagliflozin 25 mg by 0.86%. Weight loss was about 2 kg, and SBP was reduced by 2.6 and 3.4 mm Hg.

The only significant adverse effects reported in the trials were increases in urinary and genital tract infections, mainly in women. Both UTIs and GTIs occurred in about 4% to 9% in women.

Long-term cardiovascular outcome studies are being carried out on all three drugs, but the only one to report is the empagliflozin outcomes trial, in September 2015. This recruited 7020 patients in 42 countries, randomised to empagliflozin 10mg and 25mg, and placebo, added to the diabetes medications they were already on. Half were on insulin-containing regimens. They were selected as being at high risk of cardiovascular disease. Other glucose-lowering drugs could be added and this occurred in 31.5% of the placebo group and 19.5% of the empagliflozin groups. The mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group.
All-cause mortality at a median of 3 years was 8.3% in the placebo group and 5.7% in the pooled empagliflozin group.This was mainly due to differences in cardiovascular deaths – 5.9% and 3.7%. The primary outcome was a composite of death from cardiovascular causes, non-fatal MI and non-fatal stroke, and this occurred in 12.1% of the placebo group and 10.5% of the empagliflozin group, giving a hazard ratio of 0.86 (95% CI 0.74-0.99). There were no significant differences in death from MI or in non-fatal MI. The proportions of MIs reported as fatal were surprisingly low at 4.0% and 4.4% for placebo and empagliflozin respectively. The difference in cardiovascular mortality was mainly due to sudden death (1.6% and 1.1%), heart failure (0.8% and 0.2%) and an ill-defined category of “other cardiovascular deaths” (2.4% and 1.6%). Subgroup analyses showed that the primary outcome only reached statistical significance in Asians. The Kaplan-Meier curves for deaths separate after a few months. They show a curious acceleration in the placebo group after 42 months.

Over the years, UTIs were no more frequent in the empagliflozin group than the placebo one, but GTIs were about three times as frequent. However in some trials the untreated controls might also have had an increased risk of UTIs due to poor control and hence glycosuria.

Network meta-analysis

We included the three SGLT2 inhibitors, pioglitazone, gliclazide, sitagliptin, vildagliptin and linagliptin in an NMA using placebo as a common comparator as far as possible. Compared to placebo, reductions in HbA1c were;

Canagliflozin 300mg	1.19%
Canagliflozin 100mg	0.95%
Empagliflozin 25mg	0.88%
Empagliflozin 10mg	0.76%
Dapagliflozin 10mg	0.59%

A caveat is necessary regarding the effects of the larger doses of canagliflozin and empagliflozin, which is that according to the licences, the larger doses should only be used in people who have tolerated the starting doses but have had an insufficient response. Those who do not respond well to the starting dose might not achieve the same effects as did people in the trials randomised to the larger disease from the start.

Only one dose of dapagliflozin is used, despite larger effects being reported with larger doses such as 20mg daily. In considering the smaller effect size with dapagliflozin 10mg, the improvements in the placebo groups in the dapagliflozin trials should be noted.

The reductions in HbA1c with pioglitazone and gliclazide were 1.13% and 0.95%.

A caveat is required regarding effect sizes in NMAs. Many trials recruit patients with quite high HbA1c levels, and the reductions seen in HbA1c may be much larger than would be seen in patients managed according to NICE guidelines with frequent monitoring and prompt intensification once their HbA1c exceeded 7.5%.

Cost effectiveness

Janssen, Astrazeneca and Boehringer Ingelheim each submitted cost effectiveness modelling exercises. Boehringer Ingelheim submitted four modelling exercises. The following summary concentrates upon the Boehringer Ingelheim lifetime modelling, the model B, which compared empagliflozin with pioglitazone, repaglinide, gliclazide and sitagliptin. The other three Boehringer Ingelheim models are summarised in the main body of the AG report.

All the company submissions apply the old £608 annual cost for canagliflozin 300mg, rather than the price reduction in August 2015 to the same £477 annual price for canagliflozin 100mg. As a

consequence, the summary of cost effectiveness results of the companies concentrates upon the canagliflozin 100mg results.

Janssen stands out for having used the ECHO-T2DM model. Astrazeneca, Boehringer Ingelheim and the AG used models based upon either the UKPDS68 or upon a combination of the UKPDS68 and the UKPDS82.

The Janssen model assumed that after an initial treatment effect HbA1c would increase at a constant rate. This rate was treatment specific. As a consequence, the annual rate of increase in HbA1c associated with a treatment could be as important as the initial treatment effect upon HbA1c.

Due in part to the assumed slow annual increase in HbA1c with pioglitazone, Janssen estimated that it has the lowest total lifetime costs of £20,264 and yields an average 9.998 QALYs. Gliclazide was estimated to be somewhat more expensive than pioglitazone with total costs of £20,956 and to yield 9.949 QALYs so is dominated by pioglitazone. Sitagliptin was also more expensive with a total cost of £23,442 and to yield a total of 9.981 per QALY so was dominated by pioglitazone, though has a cost effectiveness estimate compared to gliclazide of £6,969 per QALY.

Janssen estimated that canagliflozin 100mg has total costs of £23,525 and yields 10.039 QALYs which implies a cost effectiveness estimate of £79,537 per QALY compared to pioglitazone. The cost effectiveness estimate compared to gliclazide was £3,377 per QALY, this being largely due to the higher costs in the gliclazide arm (using the modified release form) compared to pioglitazone. Canagliflozin 100mg was estimated to dominate empagliflozin 10mg, empagliflozin 25mg and dapagliflozin 10mg.

The Janssen cost effectiveness estimates for the flozins compared to sitagliptin were £1,414 per QALY for canagliflozin 100mg, £1,977 per QALY for empagliflozin 25mg, £4,724 per QALY for empagliflozin 10mg and £6,040 per QALY for sitagliptin.

If the annual rate of increase in HbA1c was equalised between the treatments and repaglinide was included as a comparator it appears that this worsened the cost effectiveness estimate for canagliflozin compared to repaglinide to £189k per QALY. The cost effectiveness estimates for canagliflozin 100mg compared to gliclazide and sitagliptin worsened to £21,580 per QALY and £21,470 per QALY respectively. Applying the UKPDS68 evolution of HbA1c across all treatments resulted in broad clinical equivalence between canagliflozin 100mg and gliclazide, but the costs of canagliflozin 100mg are £744 greater.

The Astrazeneca submission used the CARDIFF diabetes model (CDM) which has been revised to use the equations of UKPDS68 to evolve the risk factors and the equations of UKPDS82 to calculate the probabilities of events and death. The UKPDS82 is a partial update of the UKPDS68.

Astrazeneca pooled the flozins into a class effect. Given this pioglitazone was estimated to be the least costly with total costs of £26,067 and to yield 13.111 QALYs. The sulfonylureas were estimated to have a total cost of £26,582 so £515 higher than pioglitazone, and to yield 13.179 QALYs so have a cost effectiveness estimate of £7,574 per QALY compared to pioglitazone. The gliptins were estimated to have a total cost of £27,873 and to yield 13.188 QALYs or only 0.009 QALYs more than the sulfonylureas, hence have a cost effectiveness compared to the sulfonylureas of £143k per QALY. The flozins were only £106 more expensive than the glitpins and yielded an additional 0.018 QALYs so had a cost effectiveness compared to the gliptins of £5,904 per QALY. But the flozins cost effectiveness compared to the sulfonylureas was poor at £52,047 per QALY.

Astrazeneca sensitivity analyses showed results were sensitive to the HbA1c intensification threshold and to the assumptions around the evolution of weight.

The Boehringer Ingelheim submission built a visual basic front and back end to the UKPDS OM1 model. The OM1 model uses the UKPDS68 equations for the evolution of the risk factors and the calculation of the probability of events.

Boehringer Ingelheim estimates that pioglitazone is the least expensive treatment with a total cost of [redacted] and yields [redacted] QALYs. Only repaglinide is close to being cost effective compared to pioglitazone, yielding an additional 0.025 QALYs at an additional cost of £635 hence a cost effectiveness estimate of £25,349 per QALY. Boehringer include costs ([redacted]) of self-monitoring of blood glucose for both repaglinide and pioglitazone whereas it would be unnecessary with pioglitazone. Empagliflozin 25mg and empagliflozin 10mg are estimated to be £2,834 and £2,834 more expensive than pioglitazone to yield an additional 0.061 and 0.056 QALYs, so have cost effectiveness estimates of £46,480 per QALY and £50,892 per QALY compared to pioglitazone. The cost effectiveness estimates for empagliflozin 25mg and 10mg compared to sitagliptin were somewhat better. The net costs are estimated to be [redacted] and [redacted] with additional patient gains of [redacted] and [redacted], resulting in cost effectiveness estimates of around £7,333 per QALY and £8,325 per QALY respectively.

The intention specified within the protocol was for the AG to use the UKPDS OM2. In common with the updated CDM, the OM2 uses the equations of UKPDS68 to evolve the risk factors and the equations of UKPDS82 to calculate the probabilities of events and death. But the OM2 was not made

available to the AG. As a consequence and as also specified in the protocol, the AG fell back upon writing a visual basic front and back end to the UKPDS OM1 model.

The AG modelling suggests that gliclazide is the least expensive with total costs of £27,314. Repaglinide and pioglitazone have similar total costs of £27,413 and £27,543 respectively. The increased costs for pioglitazone are due in part to the AG including a £72 allowance for annual BNP monitoring. Costs increase quite markedly with sitagliptin at a total cost of £32,358, and increase further with the flozins being clustered between £32,676 and £32,866. Sitagliptin is estimated to be £5,045 more expensive than gliclazide, and the flozins between £5,362 and £5,553 more expensive than gliclazide.

If there are no direct quality of life impacts from weight changes gliclazide is estimated to yield 10.392 QALYs. This is the highest total QALYs for this BMI scenario and as a consequence gliclazide dominates all the other treatments.

Including direct quality of life impacts from weight changes and assuming that the weight changes associated with the monotherapies persist indefinitely results in repaglinide now being superior to gliclazide by 0.030 QALYs and so having a cost effectiveness estimate of £3,331 per QALY. Repaglinide formally dominates pioglitazone and sitagliptin, but canagliflozin yields an additional 0.177 QALYs at an additional cost of £5,262 so has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. If weight losses associated with treatment tend to rebound at either one year or at treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £192k per QALY and £119k per QALY respectively.

Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin. With no direct quality of life effects from weight changes it is estimated to be marginally more effective by 0.002 QALYs than empagliflozin and more effective by 0.013 QALYs than dapagliflozin. Including the effects of weight upon quality of life increases these net gains to 0.034 QALYs and 0.046 QALYs if weight changes persist indefinitely. If they rebound after one year these gains fall to 0.007 QALYs and 0.019 QALYs, while if they rebound at treatment change they fall to 0.014 QALYs and 0.026 QALYs.
These very small differences in QALY gains lead to ICERs that can vary widely.

Both canagliflozin and empagliflozin have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY even if there are no quality of life impacts from weight changes. Including these effects improves their cost effectiveness estimates compared to sitagliptin.

Dapagliflozin fares slightly worse compared to sitagliptin. It costs an additional £508 but only yields an additional 0.013 QALYs if there are no direct quality of life impacts from weight changes, so has a cost effectiveness estimate of £40,383 per QALY compared to sitagliptin. This improves to £6,632 per QALY if weight changes have a quality of life impact and are assumed to persist indefinitely. If they only persist for one year the cost effectiveness estimate worsens to a little over £30,000 per QALY, but if they persist until treatment change the cost effectiveness estimate worsens but only to a little under £20,000 per QALY.

The base case applied the baseline HbA1c values for those starting a monotherapy of the NICE CG which had a mean of 8.4% (s.d. 1.8%). This differs from some of the companies' modelling, which assumed a common baseline HbA1c of 7.5%. As would be expected this both improved patient outcomes and lowered total costs. It did not alter the patterns of dominance, and while the cost effectiveness estimates for the flozins compared to repaglinide worsened the effect was not major.

Of more interest was that the cost effectiveness estimates of the flozins compared to sitagliptin worsened. With no direct quality of life impacts from weight these worsened to £24,939 per QALY for canagliflozin, £30,150 per QALY for empagliflozin and £54,863 per QALY for dapagliflozin. With the monotherapy BMI effects persisting for the patient lifetime these cost effectiveness estimates improve to £3,717 per QALY, £6,042 per QALY and £7,442 per QALY respectively. Weight loss rebound after one year reduces the improvements to £14,961 per QALY, £21,643 per QALY and £38,256 per QALY, while weight loss rebound at treatment change reduces the improvements to £8,237 per QALY, £13,310 per QALY, and £19,902 per QALY respectively.

Making the HbA1c treatment effect a function of patients' baseline HbA1c had little practical impact upon the cost effectiveness estimates for the flozins compared to gliclazide, repaglinide and pioglitazone. But it improved the cost effectiveness estimates for canagliflozin compared to sitagliptin by around one third. The impact for empagliflozin is less, and there was little impact for dapagliflozin. This is as would be expected given the greater HbA1c effect for canagliflozin compared to sitagliptin, the slightly greater effect for empagliflozin and broad equivalence between dapagliflozin and sitagliptin.

Janssen applied linear evolutions of HbA1c with the annual rate of change being treatment specific, and slower on pioglitazone. Applying the same annual rates of change within the AG modelling reduced total costs and increased total QALYs quite considerably. It also caused pioglitazone to be estimated as the cheapest treatment, with it dominating gliclazide. Pioglitazone also dominated repaglinide if there were no direct quality of life impacts from weight changes. Including these with

no rebound for weight gains caused the cost effectiveness of repaglinide compared to pioglitazone to improve to £15,633 per QALY. The pattern of dominance was not otherwise altered.

The linear HbA1c evolutions still saw the flozins dominated unless there were direct quality of life impacts from weight changes. Given these, the cost effectiveness estimates for canagliflozin compared to repaglinide were surprisingly similar to those of the base case, though the higher cost effectiveness estimates varied more due to the divisions by small net QALY gains.

Assuming that adding gliclazide at the 1st intensification causes only a -0.47% reduction in HbA1c (based on starting it at HbA1c of just over 7.5%) compared to the -1.01% reduction of the base case has little to no impact for gliclazide and repaglinide as patients will not use this intensification. But it increases costs and reduces QALYs in the other arms, so worsening the cost effectiveness estimates for the flozins. The cost effectiveness estimates for the flozins compared to sitagliptin are not particularly affected, though those for dapagliflozin do worsen slightly.

Assuming that the UTI and GTI rates apply throughout the modelling rather than just for the first cycle has little practical impact upon results.

Overall, the flozins are not cost-effective compared to gliclazide and pioglitazone, but can compete with sitagliptin.
The average costs per QALY will apply to the "average patient" and there will be instances where patients may be more susceptible to adverse effects. For example, the risks of fracture with pioglitazone will be greater in women with reduced bone density.

Research needs.
The main research need is for long-term data on cardiovascular outcomes for canagliflozin and dapagliflozin. Large studies are underway.

Conclusions
Dapagliflozin, canagliflozin and empagliflozin are effective in reducing hyperlycaemia and improving glycaemic control, with added benefits of some reductions in blood pressure and weight. The only common adverse effects are increases in urinary and genital tract infections, but in a small proportion of users. Only empagliflozin has long-term cardiovascular outcomes reported yet, showing a reduction in mortality. In monotherapy, the three drugs do not appear cost-effective compared to gliclazide or pioglitazone, but may be competitive against sitagliptin.

Plain English Summary

In type 2 diabetes, it is important to try to get blood glucose levels back down to as near normal as possible to reduce the risk of long-term complications such as damage to eyesight and kidneys, and heart disease. The SGLT2 inhibitors are the newest type of oral drugs. They work by increasing the amount of glucose in the urine, which leads to calorie loss, leading to some weight loss. However they are much more expensive than older drugs such as gliclazide and pioglitazone.

The NHS has to decide whether a new treatment is good value. There is only one NHS budget and this needs to be spent so as to get the most benefit for patients as a whole. If a new treatment is adopted this means that savings must be made elsewhere and other treatments reduced or stopped. A new treatment may result in patient gains. If these patient gains are more than those that are lost when the other treatments are reduced, patients as a whole gain and the treatment is good value. But if the gains from the new treatment are less than those that are lost when the other treatments are reduced ot stopped, patients as a whole lose out and the treatment is bad value.

Diabetes increases the likelihood of patients experiencing a range of complications, ranging from heart disease to sight loss due to diabetic retinopathy. Treatments for type 2 diabetes help patients control their condition. If a patient has good control over their diabetes they are less likely to experience these complications. Avoiding these complications not only benefits the patient, but also means that the NHS does not have to treat these complications which frees up resources for other patients. These elements are taken into account when deciding whether a treatment is good value.

An additional element that has to be considered is that treatments for diabetes may increase or decrease a patient's weight by as much as a few kilograms. One of the main uncertainties is how large any patient benefits are from the direct impact weight changes have upon their day to day living. This is dependent upon how much a few kilograms gained or lost affects a patient's day to day living, the weight gains and losses associated with the various treatments for diabetes and how long these weight changes last for.

If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin over the more traditional treatments of pioglitazone, repaglinide and gliclazide. The traditional treatments may even provide more patient benefits. The flozins and sitagliptin cost around £400 more each year than the traditional treatments. As a consequence, the flozins represent very poor value for patients as a whole.

If a patient's day to day living is affected by whether a few kilograms are gained or lost this tends to increase the patient gains from the flozins. But compared to the traditional treatments these patient gains are typically still not large enough to justify the higher cost of the flozins and sitagliptin. The flozins still represent poor value for patients as a whole.

But if patients who would receive flozins would otherwise be treated with sitagliptin the additional cost of the flozins is only around £40 more each year. This means that fewer treatments elsewhere need to scaled back or discontinued to fund the adoption of the flozins, and that the flozins are good value for patients as a whole. The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins. But if a patient's day to day living is affected by whether a few kilograms are gained or lost and the treatments' effects upon weight changes last a reasonably long time dapagliflozin also represents good value for patients as a whole.

Chapter 1. Background

The York and Humber Public Health Observatory (YHPHO) estimate that in 2015, around 3.5 million people in England have type 2 diabetes, with a prevalence of about 8%.[1] The prevalence has been increasing, partly due to demographic change, partly due to better detection, but mainly due to increased prevalence of overweight and obesity. Diabetes is costly to the National Health Service (NHS), with a recent study estimating that 10% of all NHS expenditure is on diabetes.[2]

The report, Prescribing for Diabetes, from the Health and Social Care Information Centre estimated that in 2013/14, 9.5% of prescribing costs were for diabetes, including drugs and blood glucose testing strips.[3]

There are two characteristics of type 2 diabetes: insulin resistance and a loss of insulin-producing capacity in the pancreas. Insulin resistance is the initial state, which the pancreas initially copes with by increased production of insulin from its beta cells. Over time, pancreatic insulin production falls. It is generally accepted that by the time T2DM is diagnosed, the pancreas has lost half its insulin-producing capacity.

Type 2 diabetes is regarded as a progressive disease. The UKPDS trial showed a deterioration in HbA1c of about 0.2% a year.[4] The UKPDS 49 paper reported that by 3 years, only 50% could maintain HbA1c under 7% on monotherapy and that this proportion fell to 25% after 9 years.[5]

However some people with early T2DM who manage to lose weight and increase physical activity, may then have enough beta cell capacity to remain well-controlled on diet alone or on diet plus monotherapy. They are probably a small minority, though a study in Trent region in 2003 found that 31% of people with type 2 diabetes were being managed on diet alone with over 80% achieving HbA1c of 7.5% or under.[6] Most patients do not lose sufficient weight and so their diabetes is expected to progress over time. They will require additional drug therapies, with about a third progressing to requiring insulin injections to try to control blood glucose levels. Progression may be slow. In a population-based study in Denmark, 79% of people with type 2 diabetes who started metformin, were still on metformin monotherapy 3 years later.[7]

Clinical Guideline 87

The NICE clinical guideline CG 87[8] was issued in May 2009, and is currently being updated. The recommendations in CG 87 included;

- Start drug treatment with metformin in patients who are overweight or obese, and whose control is inadequate with lifestyle measures (diet and physical activity) alone
- In patients who are not overweight, either metformin or a sulfonylurea should be considered
- When glycaemic control becomes unsatisfactory on metformin, start dual therapy by adding a sulfonylurea
- Consider using a DPP4 inhibitor (sitagliptin or vildagliptin then) instead of a sulfonylurea in dual therapy where hypoglycaemia would be a particular hazard
- Consider using pioglitazone instead of a sulfonylurea when hypoglycaemia would be a particular hazard
- Consider a DDP4 inhibitor or pioglitazone in triple therapy with metformin and a sulfonylurea when dual therapy was insufficient to achieve adequate control
- Pioglitazone might be preferred to a DPP4 inhibitor if there was marked insulin resistance
- If either a DPP4 inhibitor or pioglitazone would be suitable, consider patient preference.
- Addition of another drug, referred to as intensification of treatment, was when HbA1c was 7.5% or over (though with a recommendation that targets be adjusted for individual circumstances)
- The target for control was set at HbA1c 6.5%

We prefer to use the terms "dual therapy" and "triple therapy" to "second-line" and "third-line" because the latter terms could cover substitution as well as addition.

At the time when CG87 was produced, pioglitazone was still covered by patent. The patent has since expired and the price has dropped dramatically since generic forms entered the market. The DPP4 inhibitors were new, and the SGLT2 inhibitors had not been introduced. The only glucagon-like peptide agonist was twice daily exenatide.

Drugs for type 2 diabetes

We now have nine classes of glucose-lowering drugs for T2DM, though some contain only a single drug. Those which are used in monotherapy are;

- Metformin
- Sulfonylurea (SUs): usually 2nd or 3rd generation drugs - gliclazide, glimepiride and glipizide
- Pioglitazone
- Acarbose
- Meglitinides: nateglinide and repaglinide, though only the latter is licensed for monotherapy. These drugs act in the same way as the SUs, promoting release of insulin.

- The dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as the 'gliptins', not currently recommended by NICE for monotherapy (because of cost). There are now five available: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin
- The sodium glucose co-transporter 2 (SGLT2) receptor inhibitors. In the UK dapagliflozin, empagliflozin and canagliflozin have been approved by NICE in combination therapy

There are two classes which are injectable treatments. Neither is commonly used in monotherapy. Because of both cost and because they need to be injected, they appear later in the treatment pathway;

- The glucagon like peptide-1 (GLP-1) analogues: exenatide, albiglutide and dulaglutide given once weekly, and liraglutide and lixisenatide given once daily. There is also a form of exenatide given twice daily. Exenatide, liraglutide and lixisenatide are being covered in the update of the NICE guideline on type 2 diabetes, but dulaglutide and albiglutide are not. Both dulaglutide and albiglutide are licensed in Europe for use in monotherapy, when metformin cannot be used, as well as for combination therapy.[9, 10]
- Insulins. In T2DM, insulin treatment starts with once daily basal insulin (NICE recommends NPH insulin as first choice) but if intensification is needed, short-acting insulins may be added at mealtimes, or twice daily biphasic insulin may be used.

There are now combinations of GLP-1 analogues with basal insulins such as insulin degludec combined with liraglutide (Xultophy, Nov Nordisk, Denmark) and insulin glargine and lixisenatide (Lixilan, Sanofi).

There are quite marked differences in costs of GLP-1 analogues, ranging from daily lixisenatide at around £690 to weekly dulaglutide at almost £1200. Patients may prefer to inject once a week. There may be differences in adverse effects. Longer-acting drugs increase heart rate more than shorter-acting ones though the importance of this is as yet uncertain.[11]

Despite the number of classes, there is still a need for drugs that that will lower glucose without causing hypoglycaemia or weight gain, and that can improve cardiovascular outcomes. The SUs, repaglinide and insulin cause varying degrees of weight gain, which may worsen insulin resistance. They can cause hypoglycaemia. The gliptins do not cause weight gain or hypoglycaemia, but have not been shown to improve cardiovascular outcomes..

The NICE guideline (CG87) on the management of T2DM is currently being revised. The first draft recommended that patients who cannot take or tolerate metformin should take repaglinide, a

meglitinide analogue. The meglitinide analogues are insulin secretagogues, shorter acting than the SUs.[12] They have not been widely used in the UK.
Pioglitazone is recognised as causing weight gain but does not cause hypoglycaemia. Metformin does not cause either weight gain or hypoglycaemia.

The diagram below (Figure 1) shows the flowchart proposed in the draft NICE guideline.

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

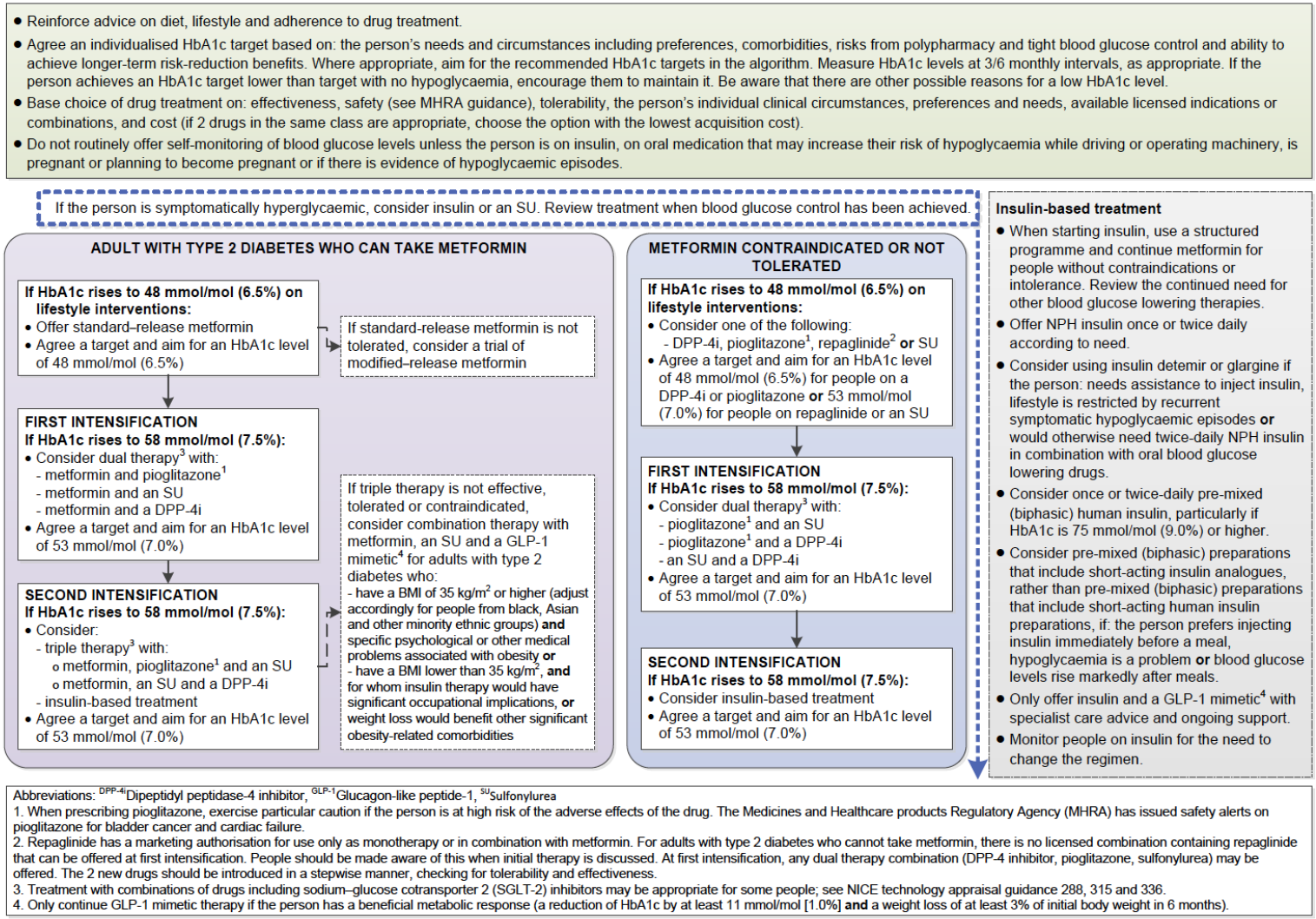

Figure 1 Flowchart proposed in the draft NICE guideline

The rational for choosing repaglinide was two-fold;

- a network meta-analysis showed repaglinide reduced HbA1c more than sulfonylureas, by 0.19%, and was non-significantly safer than SUs in terms of hypos. However, the draft NICE mentions a mixture of sulfonylureas, including tolbutamide, glibenclamide, glipizide, glimepiride and gliclazide. The largest number of trials comparing repaglinide with SUs featured glibenclamide. Gliclazide has been reported to cause fewer hypos than other SUs so a direct comparison of repaglinide with gliclazide might not have given the same results. Gliclazide is the SU preferred by clinicians in the UK.
- costing that assumed SMBG was required because of risk of hypoglycaemia on SUs and pioglitazone, but not for repaglinide, which is odd given that repaglinide causes hypos and pioglitazone does not. If this assumption is reversed, pioglitazone becomes the choice if metformin cannot be taken, though only just.

One drawback to using repaglinide in monotherapy in people who cannot take metformin, is that it is only licensed in dual therapy with metformin. So if repaglinide monotherapy was insufficient, dual therapy would mean starting two new drugs.

For the second round of consultation the position was changed as follows;
(a) metformin extended-release is recommended as an option for metformin-intolerant people;
(b) the other options for people who cannot take metformin were put on an equal footing with DPP4 inhibitors, pioglitazone, repaglinide and SUs all recommended as options.

Sulfonylureas

The sulfonylureas are insulin-secretagogues, which means that they work largely by stimulating insulin release by the beta cells in the pancreas. There is also some data to suggest that they have a peripheral action on muscle sensitivity to insulin, and this lies behind the practice, begun in the UKPDS trial, of continuing SU treatment even when therapy is escalated to insulin as a result of beta-cell failure. However, once the beta cell capacity falls, the SUs become less effective. There is some evidence that the duration of effectiveness is longer with gliclazide than glibenclamide.[13]

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The main adverse effects of the sulfonylureas are weight gain and hypoglycaemia. A population-based study from Tayside found an incidence of severe hypoglycaemia amongst people on sulphonylureas of 0.9 per 100 patient years.[14] This rate is similar to the 0.8% seen in the meta-analysis by Schopman and colleagues[15] Monami and colleagues in a good quality meta-analysis of 69 trials involving sulfonylureas, reported a cumulative incidence of at least one episode of severe hypoglycaemia of 1.2%, but this was based on 24 trials because the others did not have severe hypoglycaemia. There was some evidence that hypoglycaemia was less common with gliclazide than

with other SUs.[16] Schopman and colleagues reported that 0.1% of patients on gliclazide had severe hypoglycaemia and that 1.4% had PG under 3.1 mmol/l at some point in trials that ranged in duration from 24 to 104 weeks.[15] . Schernthaner and colleagues from the 27-week GUIDE trial, using modified release gliclazide, reported that 3.7% of patients had at least one PG < 3mmol/l, but that none need assistance. Compared to the glimepiride arm, there were about 50% fewer hypoglycaemic episodes, despite a reduction in HbA1c of 1.2% on gliclazide and 1.0% on glimepiride.[17]

The Schopman meta-analysis reported that overall, 0.8% of patients on sulfonylureas had a severe hypoglycaemic episode, but the proportions ranged from 0.1% for gliclazide to 2.1% for glipizide. In the ORIGIN trial, 75% of patients on standard treatment (25% of whom were on sulfonylureas) never had any hypoglycaemia.[18]

In the very large (11,140 patients) ADVANCE trial, gliclazide MR was used in two arms, intensive and standard. In the intensive arm, the aim was to achieve HbA1c of 6.5% or less.[19] This was achieved in 65% in the intensive arm and 29% in the standard arm. Severe hypoglycaemia event rates were 0.07 per 1000 patient years in the intensive arm and 0.04 per 1000 patient years in the standard arm. Minor hypoglycaemic events occurred at rates of 12 and 9 per 1000 patient years in intensive and standard arms respectively.

These rates of hypoglycaemia on sulfonylureas are much lower than the 7% reported for severe hypos by the UK Hypoglycaemia Study Group[20], but the patients in that study were recruited only from secondary care clinics.

In the Netherlands, the guideline for the management of type 2 diabetes advises that gliclazide is the sulfonylurea of choice, partly because of its safety in renal failure.[21, 22] A meta-analysis of sulfonylurea trials concluded that severe hypoglycaemia was rare with gliclazide, especially if the dose does not exceed 240mg daily. Non-severe hypoglycaemia was seen mainly in those on 320mg daily.[21]

Simpson and colleagues argued that since different sulfonylureas had different tissue selectivity and risk of hypoglycaemia, the cardiovascular risk might also vary.[23]They carried out a systematic review and network meta-analysis, and used glibenclamide as the reference risk. Compared to people taking glibenclamide, those on gliclazide had a relative risk for total mortality of 0.65 (95% Cr I 0.53-0.79). For cardiovascular mortality, the RR for gliclazide was 0.60 (95% Cr I 0.45-0.84), whereas other sulfonylureas showed no significant difference from glibenclamide.

Schramm and colleagues [24]used Danish record linkage data to compare the mortality and cardiovascular risks amongst patients on monotherapy with sulfonylureas and repaglinide, with those on metformin. The risks were higher on most sulfonylureas but not for gliclazide or repaglinide.

The risk of severe hypoglycaemia with sulfonylureas may have been over-estimated, but it remains a problem which can lead to hospital admission as well causing anxiety and interrupting usual activities.

SIGN recommends that sulfonylureas should be considered as first line in patients who cannot take metformin.[25] The 2015 ADA position statement expresses no preference amongst sulfonylureas, pioglitazone, flozins, and gliptins, in people who cannot take metformin.[26]

If sulfonylureas were the same price as the newer drugs such as the gliptins or the flozins, they would probably be superseded. But they are very cheap, and have been used for so long that all their adverse effects are known.
In this report, based on the evidence reported above, we use gliclazide as the sulfonylurea of choice. There are two forms of gliclazide, standard and modified release. The Diamicron Study Group reported these to be clinically equivalent in a 10 month study in 800 patients.[27] The MR form was given once a day and 3-120mg was equivalent to 80-320mg of the standard form taken twice daily. No severe hypoglycaemia occurred. Mild or moderate hypoglycaemia was seen in 5% of those on the MR form. Once daily administration may help adherence, but the MR form costs more - £62 a year at 60mg a day, £89 at 90mg. The standard form costs about £28 a year.

Pioglitazone

Pioglitazone, the only glitazone used in the UK, can cause oedema, which can precipitate congestive heart failure, and fractures. Congestive heart failure is a common cause of admission to hospital, and the second commonest first presentation of cardiovascular disease (after peripheral arterial disease).[28] A five-fold risk of macular oedema has also been reported.[29]
There is an increased risk of fractures amongst people taking pioglitazone. The fractures were originally reported as being atypical fractures of long bones [30] but Scottish data also show an increase in hip fractures.[31]

More recently there has been concern over bladder cancer. Pioglitazone use has now been discontinued in France.

However the evidence is inconsistent. A Canadian study using UK data [32] reported an increased risk of 1.83 (95% CI 1.10- 3.05). A French study reported a doubling of a very small risk of bladder

cancer.[33] The large Kaiser Permanente study from the USA reported an increase in risk with pioglitazone with RR of 1.18 but this was not statistically significant.[34] 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.[35] 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.[36]

A 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.[37]

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.[38] Amongst those with duration over 5 years, RR was 1.08.
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.[39] The MHRA concurred.[40]

Patients should be screened for haematuria before starting pioglitazone and then at least annually afterwards.

There are some cardiovascular benefits from pioglitazone (the reverse of what was seen with rosiglitazone) with a reported reduced risk of myocardial infarction, but there is clearly an increased risk of heart failure[30, 35], and regular monitoring with BNP seems advisable for the safest use of this drug.[41] 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.

Despite its side effects, including progressive weight gain by as much as 5 kg, pioglitazone can be a valuable diabetes therapy, as it is an insulin sensitizer and allows reduction in insulin resistance, still known to be a major factor in the pathogenesis of type 2 diabetes and glucose intolerance. Early studies using genetic profiling showed that the Pro12Ala of the PPARG gene showed a population attributable risk of approximately 50% and taken together with clinical risk factors might define those most at risk of renal sodium retention and oedema. Unfortunately probably because of the fact that the PPAR gamma agonists also show greater metabolic efficacy in those with the Pro12Ala variant

this approach has not been developed in clinical practice, as those who would benefit most would have to be excluded.[42]

Many people with type 2 diabetes are considerably overweight and may develop non-alcoholic fatty liver disease (NAFLD). Pioglitazone has been reported to improve NAFLD[43] so if attempts at weight loss are unsuccessful and the NAFLD is progressing, pioglitazone may need to be considered for this group of patients. 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. NAFLD is strongly associated with insulin resistance.

Despite its adverse effects, pioglitazone is still widely used, though its use may be declining, with new initiations falling in recent years. The Health and Social Care Information Centre Report gives figures for items prescribed in 2013/14[3] (see Table 1)

Table 1 Prescriptions 2013/14

Metformin	18,100,000
Sulfonylureas	8,400,000
Sitagliptin	2,020,100
Pioglitazone	1,408,600
Linagliptin	329,400
Vildagliptin	173,200
Repaglinide	83,800

The strongest argument for using pioglitazone is the very low cost, but the costs of adverse effects need to be considered.

The DPP4 inhibitors

The first two of these to reach the market, sitagliptin and vildagliptin, were appraised for CG87, and recommended for use in combination therapy.[8] There are now five DPP4 inhibitors with slightly different licensed indications. Others are coming including two that are taken only once a week, trelagliptin and omarigliptin, both now licensed in Japan.

The CG87 guidance is reproduced in Box 1

1.6.1 DPP-4 inhibitors (sitagliptin, vildagliptin)

1.6.1.1 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

1.6.1.2 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- the person does not tolerate metformin, or metformin is contraindicated.

1.6.1.3 Consider adding sitagliptin[5] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[6].

1.6.1.4 Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).

A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to pioglitazone if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or
- pioglitazone is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione.

The current draft of the updated guideline has at present omitted the stopping rule in 1.6.1.4.

Repaglinide

Repaglinide acts on the same receptor in the pancreas as the sulfonylureas (and another receptor) but is shorter-acting and was therefore thought to be particularly useful in controlling hyperglycaemia after meals. Like the SUs, its adverse effects include significant weight gain and hypoglycaemia.

The relevant recommendation in CG87[8], was "to consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle". This presumably related to unpredictability of mealtimes, when there would be a case for using a shorter-acting meglitinide analogue instead of a sulfonylurea.

The cost of repaglinide treatment will depend on dosages used. It was designed to be taken to reduce post-prandial hyperglycaemia, which means it should be taken at meal-times. The NICE guideline costing assumes a total daily dose of 4mg. If that was comprised of 2 x 2mg tablets twice a day, the annual cost would be about £48. However that assumes that people take it at only two meals. If a third 2mg dose was added, the annual cost would be £72. But if the third dose was only 1mg (say to cover a small breakfast or lunch), the annual cost would be £92, because the 1mg tablets are almost double the price of the 2 mg ones. The variability in doses used in the repaglinide studies makes comparison with the sulphonylureas difficult.

The SGLT2 inhibitors

The Sodium Glucose Transporter 2 inhibitors (SGLT2 inhibitors), hereafter referred to as the flozins, have a unique mechanism of action. In the non-diabetic state glucose is allowed through the filter in the renal glomeruli but is fully reabsorbed in the renal tubules through sodium/glucose cotransporter mechanisms. Glycosuria (glucose in the urine) occurs when the renal threshold for glucose (blood glucose of approximately10 mmol/l) is exceeded. The main transport mechanism responsible for glucose reabsorption, SGLT2, is found in the proximal kidney tubule. This is encoded by the gene for the solute carrier family 5 sodium/glucose cotransporter (SLC5A2). Some people have a mutation in the SLC5A2 gene that causes a defective SGLT2 protein, resulting in glycosuria. Individuals who have this mutation do not have significant problems related to the glycosuria, such as urinary tract infections (UTIs), and they have a normal life expectancy with no increase in cardiovascular mortality or urogenital cancers. [44]This implies that blocking the transport mechanism should not cause problems.

The flozins block the SGLT2 system and so mimic the effect of the SLC5A2 mutation and reduce the reabsorption of renal filtered glucose back into the bloodstream, thereby lowering blood glucose levels. Due to their insulin-independent mode of action, they do this without weight gain or hypoglycaemia.[45]

For uncertain reasons, the SGLT2 inhibitors do not block all glucose reabsorption. Around 160-180mg of glucose is filtered into the urine each day, and the SGLT2 system reabsorbs 80-90% of that. The amount blocked appears to vary amongst the different drugs, with dapagliflozin 10mg blocking only about a third of reabsorption.[46, 47] Even very large doses of dapagliflozin (such as 100mg) do not block all glucose reabsorption in people with type 2 diabetes .[48]

There is also a SGLT1 transport mechanism, which is present both in the kidney and the gut. In the kidney, it is much less important than SGLT2. Inhibition of gut SGLT1 reduces absorption of glucose there, and it has been suggested that canagliflozin may have a dual action. This was reported first in healthy volunteers[49] but has since been reported in a study of people with type 2 diabetes.[50]

Because these drugs act through an insulin independent mechanism, they can be effective when other drugs that depend entirely (sulfonylureas and meglitinides) or in part (gliptins and GLP-1 analogues) on stimulating insulin release have lost effectiveness. In type 2 diabetes, the capacity of the pancreatic beta cells to produce insulin often falls over time.

In addition to improving glycaemic control, the SGLT2 inhibitors also reduce blood pressure. In a meta-analysis of 27 RCTs with 12,960 patients, Baker and colleagues reported a mean reduction in SBP of 4mm Hg.[51]

Marketing authorisations

The marketing authorisations for the three flozins licensed for use in monotherapy are similar;
"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".

NICE recommendations differ slightly for the three flozins as shown in Box 2

Box 2: NICE recommendations for SGLT2 inhibitors

Dapagliflozin has been approved by NICE as follows[52];

- in a dual therapy regimen in combination with metformin, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).
- Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial. This was because at the time of the dapagliflozin appraisal, there was insufficient evidence on its use in triple therapy.

Canagliflozin has been approved by NICE, as follows[53];

- in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if a sulfonylurea 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 metformin and either a sulfonylurea or pioglitazone
- Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

Empagliflozin has been approved by NICE as follows[54];

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

- A sulphonylurea is contraindicated or not tolerated
- The person is at significant risk of hypoglycaemia or its consequences

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

- Metformin and a sulphonylurea
- Metformin and pioglitazone

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

Renal impairment

The dapagliflozin, canagliflozin and empagliflozin guidances differ also in use in moderate renal impairment. The guidance on dapagliflozin says that it should not be used in patients with GFRs below 60 ml/min, whereas the guidances on canagliflozin and empagliflozin say that if started before renal function declined to a eGFR of 60 ml/min, it may be continued till eGFR falls below 45 ml/min.

Age

Dapagliflozin is not recommended in people over 75 but there is no such restriction for canagliflozin or empagliflozin.

Pioglitazone

Dapagliflozin is not licensed for use in combination with pioglitazone. Both canagliflozin and empagliflozin are.

Dosages

There are two doses of canagliflozin and empagliflozin. Canagliflozin comes as 100mg and 300mg. The licence states that the 300mg dose may be used in those who tolerate the 100mg dose – so ruling out canagliflozin 300mg as a starting dose. Similarly, with empagliflozin, the 25mg dose is licenced for those who can tolerate the 10mg starting dose.

Newer SGLT2 inhibitors include luseogliflozin (Taisho and Novartis), ipragliflozin (Astella Pharma), tofogliflozin (Sanofi and Takeda) and remogliflozin (BHV Pharma) but these are not included in the NICE scope. Some are still in pre-licensing trials.

The therapeutic pathway

Where should SGLT2 inhibitors fit into the therapeutic pathway? Factors to be considered include:

- Effect on glycaemic control as reflected in HbA1c reductions
- Effect on weight, compared to other drugs, some of which cause marked weight gain
- Effect on cardiovascular risk, including on blood pressure and lipid levels, and ideally as reflected in longer-term cardiovascular outcomes.
- Adverse effects, particularly increased genital and urinary infections
- Duration of diabetes. In long-standing T2DM, the efficacy of the flozins will not be affected by a fall in endogenous insulin production
- Interactions with other drugs, especially in patients on treatment for co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

Figure 2 shows the annual costs of the drugs for T2DM (drug costs only)

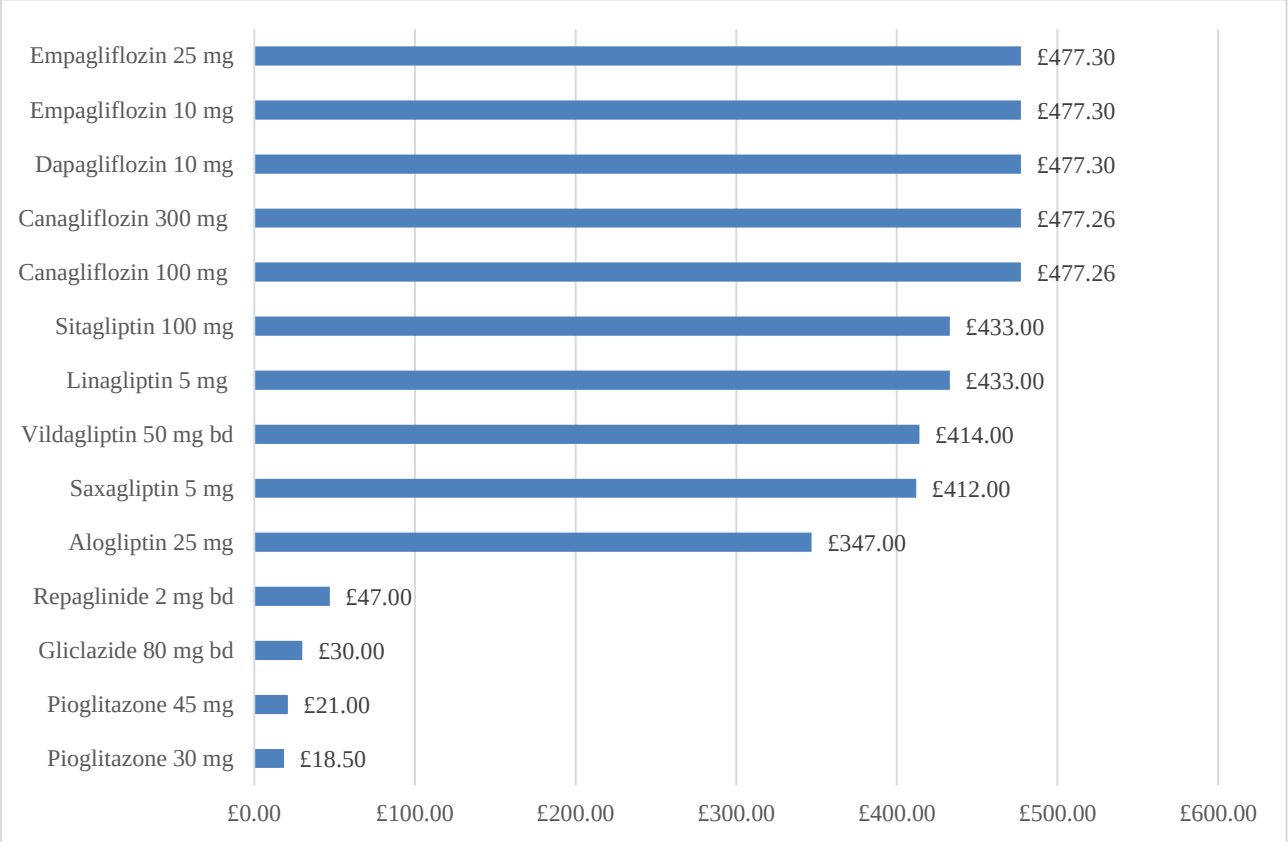

Figure 2 Costs of different pharmacological interventions for diabetes
Source: Drug Tariff[55]; Manufacturer submission/ERG report of Canagliflozin

Decision Problem

The objective of the appraisal as stated by NICE is;

"To appraise the clinical and cost effectiveness of canagliflozin, dapagliflozin and empagliflozin monotherapy within their licensed indications for treating type 2 diabetes."

In PICO (Population, Intervention, Comparator, Outcomes) terms;

- The population is people with type 2 diabetes, not currently on glucose-lowering drugs, but requiring a glucose-lowering agent, but who cannot take metformin
- The interventions are the SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin
- The comparators listed in the NICE scope are repaglinide, sulfonylureas, pioglitazone and the DPP-4 inhibitors, hereafter referred to as the gliptins

- The outcomes would ideally be the rates of complications of diabetes, but most trials of new diabetes drugs are short term, and rely on modelling changes in HbA1c, blood pressure, weight and lipids to predict longer term outcomes.

As noted above, both the NICE guideline CG87 and the current draft update recommend starting with diet and lifestyle, adding metformin if lifestyle change is insufficient. However 5-15% of people with type 2 diabetes cannot take metformin, either because they cannot tolerate it, or because of contraindications to use. The intolerance is usually because of gastrointestinal side-effects such as diarrhoea, especially with higher doses. Faecal incontinence can occur. Bailey and Turner[56] reported that 5% of people could not tolerate any dose of metformin, and Garber[57] also reported that 5% had to stop. Of those who could take it, over half could manage the maximum dose (2250mg/day). De Fronzo[58] reported that with gradual dose escalation, 85% could take 2250mg per day. The adverse effects are reduced by using slow-release metformin: diarrhoea from 18% to 8%; any GI adverse effects from 26% to 12 %.[59] So the slow-release form should be tried before abandoning metformin. Scarpello et al reported that use of bile acid sequestrants could improve tolerance to metformin but many patients find these drugs impalatable.[60, 61]

The main contraindication to metformin use is chronic renal impairment, and NICE recommends that metformin should not be used once eGFR falls below 30ml/minute, and used with caution if eGFR is in the range <45ml/min to >30ml/minute.

The guidance on contra-indications may be over-cautious, and are largely with lactic acidosis in mind. Emslie-Smith and colleagues[62] using population-based data in Tayside found 621 episodes of contra-indications, but in only10% of patients was metformin stopped. Overall, 25% of people on metformin had contra-indications but adverse effects were rare. The fear of lactic acidosis with metformin use may be a carry-over from problems with phenformin, the other biguanide, which increases lactate levels – metformin does not. Phenformin was withdrawn from use in the UK many years ago because of the lactic acidosis risk. The Cochrane review of metformin and lactic acidosis concluded that there was no increase in lactic acidosis with metformin.[63]

For who cannot tolerate metformin or in whom it is contra-indicated, the usual next drug has been a sulphonylurea such as gliclazide. CG87 recommended that a sulfonylurea may be considered as first line monotherapy if the person is not overweight; or if

- metformin is not tolerated or is contraindicated, or
- a rapid therapeutic response is required because of hyperglycaemic symptoms

CG87 mentioned the meglitinide analogues only briefly;

- a rapid acting insulin secretagogue may be considered for a person with an erratic lifestyle

It also listed acarbose as being considered if a person is unable to use other oral glucose lowering agents.

Issues

The patients involved will be those who cannot take metformin. One issue is that trials of flozins and other drugs as monotherapy have not been restricted to patients that have not been able to tolerate metformin. A literature search found few studies comparing people who got diarrhoea on metformin with those who did not. A study from Japan[64] identified several factors that increased the incidence of diarrhoea (often transient, in first few days): female gender, initial dose of 750mg, age under 65, and BMI over 25.

Given the lack of data, it is necessary to assume that the effectiveness of other drugs, and the effect on long-term complications, is no different in those who get gastro-intestinal adverse effects with metformin, than from those who can tolerate it. However some renal function restrictions also apply to other drugs such as the flozins.

Some previous appraisals of diabetes drugs have often found very little differences in lifetime QALY gains and sometime in lifetime costs. For example, Table 38 of the ERG report on empagliflozin in combination therapy noted a difference in lifetime cost of £40 and in QALYs of 0.030 – which means 11 days. Another QALY difference noted was 0.003 – 1.1 days. There are two problems with such differences. Firstly, they result in very unstable ICERs. Secondly and more importantly, such differences are effectively meaningless over a lifetime. It would be useful if NICE could decide what the smallest meaningful difference in QALYs is. 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 should be expressed as a proportion of expected life expectancy.

Similarly small cost differences should be discarded, especially as many costs will change over the modelling timescale, including drug prices. Current methods assume that drug prices remain constant for the duration.

Targets

We note that the consultation draft for the NICE Type 2 diabetes guideline update suggests that an HbA1c of 7.5% should be the switching point for intensification (as in CG 87) aiming at a target of 7.0% (Section 1.3.4). In section 1.5, Recommendation 38, the target of 6.5% is suggested for most adults managed on the combination of diet and a single drug not associated with hypoglycaemia. However the draft notes the need for individualised setting of targets.
These individual targets may take the following factors into account.[65]

- the duration of diabetes. Patients who have not developed complications such as retinopathy after 20 years duration are unlikely to do so, and have less to gain from tight control
- age and life expectancy, and hence time to develop complications. Intensification may be unnecessary and possibly harmful in people over 75 years of age with no symptoms of diabetes
- the risk of severe hypoglycaemia
- co-morbidities
- patient preferences

Glycaemic targets are based mainly on reducing the risk of microvascular disease. With a greater number of younger people being diagnosed with type 2 diabetes, glycaemic control becomes increasingly important to reduce the potential microvascular disease burden. There is less evidence that tight control using existing treatments reduces macrovascular disease or overall mortality[66] though this may be because trials are not long enough. In the UKPDS, there was no difference in macrovascular outcomes at study end[67] but with the longer term follow-up, a significant difference emerged[68] despite a considerable narrowing of the difference in glycaemic control. However neither the ACCORD trial[69] nor the ADVANCE trial[70] showed that intensive control (HbA1c 6.4% and 6.3% respectively) reduced cardiovascular outcomes compared to standard therapy (HbA1cs 7.5% and 7.0%). A meta-analysis by Boussageon and colleagues (BMJ 2011/343/d4169. Effect of intensive glucose lowering) showed no reduction in all-cause mortality or cardiovascular death in trials of intensive versus standard regimens.

Targets also need to take account of potential benefits and harms. Vijan and colleagues[71] used data from the UKPDS to model likely benefits of improving glycaemin control at different ages and by different means (metformin, insulin), taking into account the burden of treatment. For older people the benefits of intensifying treatmen could be outweighed by even minor adverse effects and other inconvenience. A reduction of 1% in HbA1c in a 45-year old might gain 0.8 QALYs (10 months) but the same reduction in someone aged 75 might gain 0.06 QALYs (22 days). If that was achieved using insulin, the adverse effects on quality of life from insulin treatment could mean that the net effect was a QALY loss.

Chapter 2 Clinical effectiveness.

Methods

Inclusion criteria

Types of studies

We included randomised controlled trials (RCTs) with a minimum duration of 24 weeks. Observational studies were included to assess safety data.

Types of participants

We included trials in people with Type 2 diabetes on diet and exercise therapy only or in people on monotherapy with a glucose-lowering agent after a washout period. The target group was patients with type 2 diabetes unable to take metformin, but this distinction was not made in the trials.

A search was carried out for studies comparing people who can and cannot tolerate metformin, looking for any differences in factors that might affect the modelling, such as weight, blood pressure, cholesterol. Nothing significant was found.

Types of interventions

Only trials of monotherapy were included.

To be included, trials had to investigate canagliflozin (100 mg or 300 mg), dapagliflozin (10 mg) or empagliflozin (10 mg or 25 mg). Eligible comparators were repaglinide, gliclazide as representative of the sulfonylureas, pioglitazone, DPP-4 inhibitors (the gliptins), or placebo.

The three flozins were also compared with each other. As there were no head to head trials of the flozins, data from a network meta-analysis was required.

Types of outcomes

Studies were eligible if they investigated at least one of the following outcomes:

- 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

Search strategy

Searches were run in Ovid Medline, Embase and Web of Science from the inception of the databases until February 2015. Thereafter weekly auto-alerts were run in PubMed in process and Embase until September 2015 to check for newly emerging studies. The searches were not restricted by language or publication type. The full search strategy is shown in Appendix 1.

Selection of studies

Two reviewers independently checked titles and abstracts of the search results against the inclusion criteria. Studies were retrieved in full if they appeared to fulfil the inclusion criteria or when eligibility could not be determined from the search results alone.

Assessment of study quality

The quality of the RCTs was assessed using the Cochrane risk of bias tool, which included the following items (rated as adequate, unclear, not reported, or inadequate):

- Method of randomisation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data (>20% drop-out regarded as inadequate)
- Intention-to-treat analysis
- Selective reporting
- Similarity at baseline
- Other (e.g. power analysis)

Overall quality was expressed in terms of proportion of items rated as ‘adequate’.

Quality was assessed by one reviewer and checked by a second reviewer.

Data extraction

Data were extracted using a pre-designed data extraction table, with one reviewer extracting and another reviewer checking the data.

Results were expressed as means and standard deviations. Standard errors and confidence intervals were converted to standard deviations using the equations provided in the Cochrane handbook. Results for lipids were expressed as mmol/L. Cholesterol values expressed in mg/dL were converted to mmol/L by dividing by 38.67 and lipid values expressed in mg/dL were converted to mmol/L by dividing by 88.57.

Data summary

Data were summarised using text and tables.

The following subgroup analyses were considered:

- BMI <25, 25-29, 30 and over
- baseline HbA1c

Results

Search results

Seven studies were included in the final analysis. We will usually refer to them by first author and year. They were;

Canagliflozin

- CANTATA-M 2013[72]
- Inagaki 2014[73]

Dapagliflozin

- Ferrannini 2010 (with Bailey and colleagues 2014)[74, 75]
- Ji 2014[76]
- Kaku 2014[77]

Empagliflozin

- Lewin 2015[78]
- Roden 2013/4[79, 80]

A list of excluded studies, and reasons for exclusion, is in Appendix 2

Characteristics of included studies

A summary of study characteristics is shown in Table 2.

Table 2 Summary study characteristics

Study	Intervention	n	Age (years)	Diabetes duration (years)	HbA1c (%)	BMI (kg/m^2)
CANAGLIFLOZIN						
CANTATA-M (Stenlöf 2013)[72]	canagliflozin 100 mg/day	195	55.1 SD10.8	4.5 SD4.4	8.1 SD1.0	31.3 SD6.6
Quality 5/9 criteria adequate	canagliflozin 300 mg/day	197	55.3 SD10.2	4.3 SD4.7	8.0 SD1.0	31.7 SD6.0
	Placebo	192	55.7 SD10.9	4.2 SD4.1	8.0 SD1.0	31.8 SD6.2
	100 mg/day HbA1c >10%	47	49.7 SD11.1	4.6 SD4.6	10.6 SD0.9	30.4 SD7.1
	300 mg/day HbA1c >10%	44	48.8 SD10.8	5.2 SD4.8	10.6 SD0.6	30.5 SD5.5
Inagaki 2014[73]	canagliflozin 100 mg/day	90	58.4 SD10.4	4.7 SD4.6	8.0 SD0.7	25.6 SD4.2
Quality 8/9 criteria adequate	placebo	93	58.2 SD11.0	5.6 SD5.8	8.0 SD0.7	25.9 SD4.4
DAPAGLIFLOZIN						
Ferrannini 2010 / Bailey 2014[74, 75]	dapagliflozin 10 mg/day am	70	50.6 SD10.0	0.45 (0.1, 3.4) (median, IQR)	8.0 SD0.9	33.6 SD5.4
Quality 8/9 adequate	dapagliflozin 10 mg/day pm	76	50.7 SD9.7	0.40 (0.1, 2.45)	8.0 SD1.1	33.3 SD5.6
	placebo	75	52.7 SD10.3	0.5 (0.1, 3.4)	7.8 SD0.9	32.3 SD5.5
	dapagliflozin 10 mg/day HbA1c >10%	39	47.9 SD12.1	1.4 (0.2, 3.5)	10.7 SD0.9	31.1 SD5.9
Ji 2014[76]	dapagliflozin 10 mg/day	133	51.2 SD9.9	1.7 SD2.8	8.3 SD1.0	25.8 SD3.4
Quality 9/9 adequate	placebo	132	49.9 SD10.9	1.3 SD2.0	8.4 SD1.0	25.9 SD3.6
Kaku 2014[77]	dapagliflozin 10 mg/day	88	57.5 SD9.3	4.9 SD4.5	7.5 SD0.6	26.1 SD4.5
Quality 6/9 adequate	placebo	87	60.4 SD9.7	5.3 SD6.2	7.5 SD0.6	25.2 SD4.4

Study	Intervention	n	Age (years)	Diabetes duration (years)	HbA1c (%)	BMI (kg/m^2)
EMPAGLIFLOZIN						
Lewin 2015[78]	empagliflozin 10 mg/day	132	53.9 SD10.5	32.6% ≤1 yr, 45.5% >1 to 5 yrs, 11.4% >5 to 10 yrs, 10.6% >10 yrs	8.1 SD1.0	31.5 SD5.7
Quality 6/9 adequate	empagliflozin 25 mg/day	133	56.0 SD9.3	36.1% ≤1 yr, 36.1% >1 to 5 yrs, 18.8% >5 to 10 yrs, 9.0% >10 yrs	8.0 SD1.0	31.2 SD5.7
	linagliptin 5 mg/day	133	53.8 SD11.5	37.6% ≤1 yr, 42.9% >1 to 5 yrs, 16.5% >5 to 10 yrs, 3.0% >10 yrs	8.1 SD0.9	31.9 SD5.9
Roden 2013/4[79, 80]	empagliflozin 10 mg/day	224	56.2 SD11.6	39% ≤1 year, 41% 1 to 5 yrs, 13% 5 to 10 yrs, 7% >10 yrs	7.9 SD0.9	28.3 SD5.5
Quality 9/9 adequate	empagliflozin 25 mg/day	224	53.8 SD11.6	41% ≤1 yr, 37% 1 to 5 yrs, 17% 5 to 10 yrs, 6% >10 years	7.9 SD0.9	28.2 SD5.5
	sitagliptin 100 mg/day	223	55.1 SD9.9	42% ≤1 yr, 39% 1 to 5 yrs, 14% 5 to 10 yrs, 5% >10 yrs	7.9 SD0.8	28.2 SD5.2
	placebo	228	54.9 SD10.9	32% ≤1 yr, 46% 1 to 5 yrs, 15% 5 to 10 yrs, 8% >10 yrs	7.9 SD0.8	28.7 SD6.2
	empagliflozin 25 mg/day HbA1c >10%	87	50.2 SD11.3	52% ≤1 yr, 25% 1 to 5 yrs, 14% 5 to 10 yrs, 8% >10 yrs	11.5 SD1.4	28.2 SD5.5

Details can be found in Appendix 3.

Study design. The studies were all double blind multicentre trials and only the two empagliflozin trials had active comparators (Roden 2013/4 and Lewin 2015). Four studies were carried out in centres around the world (CANTATA-M 2013, Ferrannini 2010, Lewin 2015, Roden 2013/4), while three (Inagaki 2014, Ji 2014, Kaku 2014) were in Asian populations. Primary endpoints were generally reported at 24 or 26 weeks, but four trials had extensions, following participants up to 52 weeks (CANTATA-M 2013, Lewin 2015) or 76 to 78 weeks (Ferrannini 2010, Roden 2013/4). However the CANTATA-M study (2013) did not report results for the placebo group for the extension period, so results were not considered here. All studies were sponsored by industry.

Participants. The studies included between 183 and 986 participants, with 70 to 228 participants in the main comparison groups. Three studies included small exploratory groups of patients (n=39 to 87) with HbA1c >10% - however, these were not randomised groups (it being unethical not to treat such high levels) and no relevant comparison group existed. Between 34.1 and 58.7% of participants in the main comparison groups were women and mean age was between 50 and 60 years. In most studies, the entry HbA1c of patients was restricted to between 7% and 10 or 10.5%. Most participants had duration of diabetes of less than five years. Mean baseline HbA1c was between 7.5 and 8.4% in the main comparison groups and between 10.6 and 11.5% in the high HbA1c groups. BMI was between 25 and 34 kg/m^2. Four studies had ethnically mixed populations (CANTATA-M 2013, Ferrannini 2010, Lewin 2015, Rodens 2013/4), while three studies included only Asian participants (Japanese in the Inagaki and Kaku studies, mainly Chinese in Ji 2014).

Interventions. Two studies examined canagliflozin. The CANTATA-M (2013) study compared 100 or 300 mg/day with placebo. After the main intervention period of 26 weeks, placebo was replaced with 100 mg/day of sitagliptin (double blind) for another 26 weeks. Inagaki 2014 compared 100 mg/day of canagliflozin with placebo. They also included a 200 mg/day group, but this is not considered here because it is not a marketed dose.

Three studies examined dapagliflozin. Ferrannini 2010 compared 10 mg/day of dapagliflozin given in the morning with the same amount given in the evening and with placebo. The trial also included groups receiving 2.5 or 5 mg/day of dapagliflozin, but these were not included in the current analysis as they are not recommended doses. After the main intervention period of 24 weeks, participants in the placebo group were switched to low dose metformin (500 mg / day, double blind). Both Ji 2014 and Kaku compared 10 mg/day of dapagliflozin given in the morning with placebo. Both also included a 5 mg/day group which is not considered here.

Two trials studied empagliflozin. Lewin 2015 compared 10 or 25 mg/day of empagliflozin with 5 mg/day of linagliptin. The trial also included groups receiving a fixed combination of empagliflozin and linagliptin (10 or 25 mg/day of empagliflozin and 5 mg/day of linagliptin), but these were not considered here. Roden 2013/4 compared 10 or 25 mg/day of empagliflozin with 100 mg/day of sitagliptin and with placebo.

Some studies included run-in periods for wash-out of previous medication (if required) and to establish a diet / exercise regime.

Rescue therapy was provided as outlined in the detailed data tables (Appendix 3).

Outcomes. The primary outcome in all trials was change in HbA1c from baseline to the end of the main intervention period. Most studies also reported on body weight, blood lipids and blood pressure, as well as on safety parameters including hypoglycaemia. Outcomes with respect to complications of diabetes were not reported, and neither was health-related quality of life.

Three trials defined hypoglycaemia as plasma glucose levels of ≤3.9 mmol/L with or without symptoms (CANTATA-M 2013, Lewin 2015, Roden 2013/4). Inagaki 2014 distinguished between symptomatic (typical hypoglycaemic symptoms irrespective of blood glucose levels) and asymptomatic (blood glucose ≤3.9 mmol/L without symptoms) hypoglycaemia. In Ji 2014 and Ferrannini 2010, hypoglycaemia was defined as plasma glucose levels of ≤3.5 mmol/L. Only three trials defined major hypoglycaemia (CANTATA-M 2013, Ferrannini 2014, Ji 2014). All three trials defined major hypoglycaemia as requiring external assistance and two specified associated blood glucose levels of <3.0 mmol/L (Ferrannini 2014, Ji 2014). Kaku and colleagues 2014 did not define hypoglycaemia.

Note that the 3.9 mmol/l cut-off is above the lower end of the normal range for plasma glucose (3.5mmol/l). It is the threshold for action to avoid hypoglycaemia in people on drugs that may cause it.

Quality of included studies

Details of study quality can be found in Appendix 4.

Two studies fulfilled all the quality criteria (Ji 2014 and Roden 2013/4), two fulfilled eight of the nine quality criteria (Inagaki 2014 and Ferrannini 2010), one only fulfilled six of nine criteria (Kaku 2014) and two only fulfilled five (CANTATA-M 2013, Lewin 2015).

Two studies did not report on the method of randomisation and three did not report on allocation concealment. All studies were double blind, but in two studies it was not clearly reported whether outcome assessors were also blinded to study treatment. Rates of discontinuation were reported by all studies and were between 7 and 20%. In most studies, rates of discontinuation were lower than 20% and balanced between groups. In Inagaki 2014, only 7% discontinued in the canagliflozin group, while 20% discontinued in the placebo group. Only one study did not clearly carry out an intention-to-treat analysis and studies gave no evidence of selective reporting, except that in two studies some results were only shown in graphs and numeric values were not provided. Baseline characteristics were similar for the main comparison groups in all studies and all studies reported on a power analysis.

Outcomes

A summary of results is shown in Table 3

Table 3 Summary of results of trials

	Time	ΔHbA1c (%)	Δ weight (kg)	ΔSBP (mmHg)	ΔTC (mmol/L)	ΔLDL (mmol/L)	ΔHDL (mmol/L)
CANAGLIFLOZIN							
CANTATA-M (Stenlöf 2013)							
canagliflozin 100 mg/day	26 weeks	-0.77 SD0.7	-2.5 SD2.4	-3.3 SD11.1	NR	0 SD0.67	+0.11 SD0.27
canagliflozin 300 mg/day	26 weeks	-1.03 SD0.7	-3.4 SD2.4	-5.0 SD11.2	NR	+0.12 SD0.67	+0.11 SD0.27
placebo	26 weeks	+0.14 SD0.7	-0.5 SD2.4	+0.4 SD11.0	NR	-0.07 SD0.65	+0.04 SD0.26
Inagaki 2014							
canagliflozin 100 mg/day	24 weeks	-0.74 SD0.66	-2.6 SD2.3	-7.9 SD10.3	NR	+0.15 SD0.51	+0.07 SD0.18
placebo	24 weeks	+0.29 SD0.68	-0.5 SD2.3	-2.7 SD10.1	NR	-0.01 SD0.50	-0.03 SD0.18
DAPAGLIFLOZIN							
Ferrannini 2010 / Bailey 2014							
dapagliflozin 10 mg/day am	24 weeks	-0.89 SD0.92	-3.20 SD4.18	-3.6 SD15.9	NR	NR	NR
dapagliflozin 10 mg/day pm	24 weeks	-0.79 SD0.87	-3.10 SD3.49	-2.3 SD12.2	NR	NR	NR
placebo	24 weeks	-0.23 SD0.87	-2.20 SD3.46	-0.9 SD15.6	NR	NR	NR
dapagliflozin 10 mg/day am	102 weeks	-0.61 SD0.70	-3.94 SD3.52	+3.9 SD14.7	NR	NR	NR
placebo / metformin	102 weeks	-0.17 SD0.67	-1.34 SD3.34	+2.1 SD18.6	NR	NR	NR
Ji 2014							
dapagliflozin 10 mg/day	24 weeks	-1.11 SD0.76	-2.25 SD2.60	-2.3 SD11.7	+0.06 SD0.41	+0.19 SD0.72	+0.30 SD0.44
placebo	24 weeks	-0.29 SD0.79	-0.27 SD2.64	+0.8 SD12.8	-0.04 SD0.40	-0.03 SD0.67	+0.11 SD0.41
Kaku 2014							
dapagliflozin 10 mg/day	24 weeks	-0.45 SD0.57	-2.22 SD2.44	-3.2 SD11.2	+0.01 SD0.34	-0.03 SD0.57	+0.16 SD0.38
placebo	24 weeks	-0.06 SD0.57	-0.84 SD2.47	-0.5 SD11.4	+0.02 SD0.33	+0.12 SD0.59	+0.07 SD0.40
EMPAGLIFLOZIN							
Lewin 2015							
empagliflozin 10 mg/day	24 weeks	-0.83 SD0.56	-2.3 SD4.0	NR	+0.2 SD1.2	+0.1 SD1.2	+0.1 SE0.0
empagliflozin 25 mg/day	24 weeks	-0.95 SD0.57	-2.2 SD4.0	NR	+0.2 SD1.2	0 SD1.2	+0.1 SE0.0
linagliptin 5 mg/day	24 weeks	-0.67 SD0.57	-0.8 SD4.0	NR	-0.1 SD1.2	-0.1 SD1.2	0 SE0.0
empagliflozin 10 mg/day	52 weeks	-0.85 SD0.65	-2.3 SD4.3	-2.2 SD10.5	NR	NR	NR
empagliflozin 25 mg/day	52 weeks	-1.01 SD0.66	-2.4 SD4.3	-2.1 SD10.5	NR	NR	NR

	Time	ΔHbA1c (%)	Δ weight (kg)	ΔSBP (mmHg)	ΔTC (mmol/L)	ΔLDL (mmol/L)	ΔHDL (mmol/L)
linagliptin 5 mg/day	52 weeks	-0.51 SD0.66	-0.3 SD4.3	-0.4 SD10.5	NR	NR	NR
Roden 2013/4							
empagliflozin 10 mg/day	24 weeks	-0.66 SD0.76	-2.3 SD2.6	-2.9 SD12.2	+0.07 SD0.75	+0.06 SD0.6	+0.11 SD0.15
empagliflozin 25 mg/day	24 weeks	-0.78 SD0.80	-2.5 SD2.6	-3.7 SD12.2	+0.15 SD0.75	+0.11 SD0.6	+0.13 SD0.15
sitagliptin 100 mg/day	24 weeks	-0.66 SD0.76	+0.18 SD2.6	+0.5 SD12.2	+0.08 SD0.75	+0.03 SD0.6	+0.02 SD0.15
placebo	24 weeks	+0.08 SD0.81	-0.33 SD2.58	-0.3 SD12.3	+0.05 SD0.75	+0.04 SD0.6	+0.04 SD0.15

HbA1c

Canagliflozin.

Canagliflozin at 100 mg/day reduced HbA1c by between 0.74% (Inagaki) and 0.77% (CANTATA-M) from baseline, which amounted to between 0.91 and 1.03% more than with placebo (P< 0.001 for both). Between 31.5% and 44.6% reached HbA1c <7%. With 300 mg/day, HbA1c was reduced by 1.03%, which was 1.17% more than with placebo (p<0.001). In this group, 62.4% reached HbA1c <7%. In both studies, reductions in HbA1c were significantly greater in participants with higher HbA1c values.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced HbA1c by between 0.45% (Kaku) and 1.11% (Ji: p<0.0001) from baseline, which amounted to between 0.39 and 0.82% more than with placebo. Between 48.8 and 51.4% of participants reached HbA1c <7% compared to between 20.5 and 32.0% in the placebo group. There was no significant difference in HbA1c results depending on whether dapagliflozin was given in the morning or in the evening (Ferrannini 2010). Reductions in HbA1c were greater in the exploratory group with HbA1c >10% (Ferrannini 2010) as well as in higher HbA1c subgroups of the main study cohorts (Ferrannini 2010, Ji 2014, Kaku 2014). In Ji 2014, results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, HbA1c reductions were still significantly greater with 10 mg/day dapagliflozin than with low dose metformin (-0.61% compared to baseline and -0.44% compared to placebo).

Empagliflozin.

Empagliflozin at 10 mg/day reduced HbA1c by between 0.66 (Roden) and 0.83% (Lewin) from baseline, which amounted to 0.16% more than with linagliptin, no difference to sitagliptin, and 0.58% more than with placebo. Empagliflozin at 25 mg/day reduced HbA1c by between 0.78 (Roden) and 0.95% (Lewin) from baseline, which amounted to between 0.28% more than with linagliptin, 0.12% more than with sitagliptin, and 0.86% more than with placebo (<0/0001 for comparisons with placebo). Between 35.3 and 38.8% of participants reached HbA1c <7% with 10 mg/day of empagliflozin, 41.5 to 43.6% with 25 mg/day of empagliflozin, 37.5% with sitaglipitin, 32.3% with linagliptin, and 12.0% with placebo. Reductions in HbA1c were greater in the exploratory group with HbA1c >10% (Roden 2013/4) as well as in higher HbA1c subgroups of the main study cohorts (Roden 2013/4, Lewin 2015). In Lewin 2015, at 52 weeks, HbA1c was reduced by 1.01% from baseline, which amounted to 0.5% more than with placebo.

Weight

Canagliflozin.

Canagliflozin at 100 mg/day reduced weight by between 2.5 and 2.6 kg from baseline, which amounted to between 3.0 and 3.1 kg more than with placebo ($p < 0.001$ for both). With 300 mg/day, weight was reduced by 3.4 kg which was 3.9 kg more than with placebo.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced weight by between 2.2 and 3.2 kg from baseline, which amounted to between 0.9 and 2.0 kg more than with placebo. In the study by Ji and colleagues (2014), results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, weight reductions were still significantly greater with 10 mg/day dapagliflozin than with low dose metformin (-3.9 kg compared to baseline and -2.6 kg compared to placebo).

Empagliflozin.

Empagliflozin at 10 or 25 mg/day reduced weight by between 2.2 and 2.5 kg from baseline, which amounted to 1.4 to 1.5 kg more than with linagliptin, 2.5. to 2.7 kg more than with sitagliptin, and 2.0 and 2.2 kg more than with placebo. In Lewin 2015, weight was reduced by 2.3 and 2.4 kg with 10 and 25 mg/day of empagliflozin after 52 weeks, which was 2.0 and 2.1 kg more than with linagliptin.

The weight loss on the SGLT2 inhibitors is less than might be expected from the glucose loss in the urine. Rajeev and colleagues[81] have reviewed possible explanations, such as a compensatory increase in food intake, but the mechanism is uncertain. Ferrannini and colleagues[82] reported that patients in an empagliflozin trial lost only 38% of the weight loss predicted from the calories lost via glycosuria, and suggested that this was due to an increase in food intake.

Lipids

Canagliflozin.

Canagliflozin at 100 mg/day increased LDL-cholesterol levels by between 0 and 0.15 mmol/L from baseline, which amounted to between 0.07 and 0.16 mmol/L more than with placebo. The corresponding HDL-cholesterol levels were increases of between 0.07 and 0.11 mmol/L from baseline and 0.07 to 0.1 mmol/L difference from placebo ($p<0.01$). With 300 mg/day, LDL-cholesterol was increased by 0.12 mmol/L which was 0.19 mmol/L more than with placebo, and HDL-cholesterol was

increased by 0.11 mmol/L which was 0.07 mmol/L different from placebo. The two studies did not report total cholesterol levels.

Dapagliflozin.

Ferrannini 2010 did not report on lipid levels. In the other studies, total cholesterol changed by +0.01 to +0.06 mmol/L from baseline in the 10 mg/day dapagliflozin groups, the difference from placebo was between -0.01 and +0.1 mmol/L. LDL-cholesterol changed by between +0.19 and -0.03 mmol/L from baseline (difference to placebo between +2.2 and -0.15 mmol/L). HDL-cholesterol changed by between +0.16 and +0.3 mmol/L from baseline (difference to placebo between +0.19 and +0.09 mmol/L).

Empagliflozin.

Total cholesterol changed by +0.07 to +0.2 mmol/L from baseline in the 10 or 25 mg/day empagliflozin groups, the difference from control was between +0.02 and +0.3 mmol/L. LDL-cholesterol changed by between +0.06 and +0.11 mmol/L from baseline (difference to control +0.02 mmol/L). HDL-cholesterol changed by between +0.10 and +0.13 mmol/L from baseline (difference to control between +0.07 and 0.1 mmol/L).

Systolic blood pressure

Canagliflozin.

Canagliflozin at 100 mg/day reduced systolic blood pressure by between 3.3 and 7.9 mmHg from baseline, which amounted to between 3.7 and 5.2 mmHg more than with placebo ($p<0.001$). With 300 mg/day, systolic blood pressure was reduced by 0.5 mmHg which was 0.9 mmHg more than with placebo. None of these differences were significant.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced systolic blood pressure by between 2.3 and 3.6 mmHg from baseline, which amounted to between 1.4 and 3.1 mmHg more than with placebo. In Ji 2014, results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, systolic blood pressure was increased by 3.9 mmHg from baseline, which was 1.8 mmHg more than with placebo. None of these values were significant.

Empagliflozin.

Empagliflozin at 10 or 25 mg/day reduced systolic blood pressure by between 2.1 and 3.7 mmHg from baseline, which amounted to between 1.7 and 3.4 mmHg more than in the control group. None of these differences were significant.

Hypoglycaemia

The definition of hypoglycaemia varied amongst trials with most using 4.0 mmol/l as the threshold, which seems a little high, when the lower limit of normal is 3.5 mmol/l (Amiel S. Diabetic Hypoglycemia 2013/5/issue 3). The threshold of 4.0 mmol/l is used as an indicator of the need for corrective action, and is also relevant for driving.

Canagliflozin.

Rates of hypoglycaemia were not substantially different between canagliflozin and placebo groups. The CANTATA-M study (2013) defined hypoglycaemia as PG of under 4.0mmol/l. They reported rates of hypoglycaemia of 3.6% in the 100 mg/day canagliflozin group, 3.0% in the 300 mg/day group and 2.6% in the placebo group. There were no cases of major hypoglycaemia.
In Inagaki 2014, there were two cases of symptomatic (2.2%) and four cases of asymptomatic (4.4%) hypoglycaemia (PG under 4.0mmol/l) in the 100 mg/day canagliflozin group and one case of asymptomatic (1.1%) and two cases of symptomatic (2.2%) hypoglycaemia in the placebo group.

Dapagliflozin.

Rates of hypoglycaemia were not substantially different between dapagliflozin and placebo groups. Over 24 weeks, not more than two cases of hypoglycaemia occurred in any of the comparison groups. There were no cases of major hypoglycaemia.

Empagliflozin.

In Roden 2013/4, there was one case of hypoglycaemia (defined as below 4.0 mmol/l or requiring assistance) in each of the comparison groups over 24 weeks (none of them was symptomatic), and two cases in each group at 76 weeks or more (only one of these in 10 mg/day empagliflozin group was symptomatic). In Lewin 2015, there was one case of hypoglycaemia (also defined as under 4.0 mmol/l) in the linagliptin group and the 25 mg/day empagliflozin group and four cases in the 10 mg/day empagliflozin group. None of these required assistance.

Given the infrequency of reported hypoglycaemia, the similarities of the frequencies of hypoglycaemia in active and placebo arms, and the cut-off level used, the AG considers that it would be reasonable to assume that the flozins do not cause hypoglycaemia.

Table 4 and Table 5 summarise the occurrence of UTIs and GTIs, respectively, in the studies considered for this review.

Table 4 Summary of Urinary Tract Infections

Inagaki 2014		**Canagliflozin 100mg**	**Canagliflozin 200mg**	**Placebo**		
	24 weeks	2/90 (2.2%)	1/89 (1.1%)	1/93 (1.1%)		
	24 weeks (Men)	0/59 (0.0%)	0/73 (0.0%)	1/60 (1.7%)		
	24 weeks (Women)	2/31 (6.5%)	1/16 (6.3%)	0/33 (0.0%)		
Stenlöf 2013		**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Placebo**	**Canagliflozin 100mg (high HbA1c)**	**Canagliflozin 300mg (high HbA1c)**
	26 weeks	12/195 (6.2%)	13/197 (6.6%)	4/192 (2.1%)	6/47 (12.8%)	2/44 (4.5%)
2014	26 weeks (Men)	2/195 (2.5%)	5/197 (5.6%)	0/192 (0.0%)		
	26 weeks (Women)	10/195 (8.8%)	8/197 (7.4%)	4/192 (3.8%)		
	52 weeks	18/195 (9.2%)	18/197 (9.1%)	5/192 (2.6%)		
	52 weeks (Men)	5/195 (6.2%)	8/197 (9.0%)	0/192 (0.0%)		
	52 weeks	13/195 (11.4%)	10/197 (9.3%)	5/192		

	(Women)			(4.8%)		
Kaku 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	2/88 (2.3%)		1/87 (1.1%)		
Ji 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	6/133 (4.5%)		1/132 (0.8%)		
	24 weeks (Chinese)	4/110 (3.6%)		0/110 (0.0%)		
Ferrannini 2010/Bailey 2015		**Dapagliflozin 10mg (AM)**		**Placebo**	**Dapagliflozin 10mg (PM)**	**Dapagliflozin 10mg (high HbA1c)**
	24 weeks	9/70 (12.9%)		1/75 (1.3%)	2/76 (2.6%)	7/39 (17.9%)
	102 weeks	11/70 (15.7%)		1/75 (1.3%)		
	102 weeks (men)	2/34 (5.9%)		0/31 (0.0%)		
	102 weeks (women)	9/36 (25.0%)		1/44 (2.3%)		
Roden 2013/4		**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Placebo**	**Sitagliptin 100mg**	**Empagliflozin 25mg (open-label)**

	24 weeks	7/224 (3.1%)	9/223 (4.0%)	0/229 (0.0%)	2/223 (0.9%)	1/87 (1.1%)
	24 weeks (Men)	4/142 (2.8%)	2/144 (1.4%)	0/124 (0.0%)	1/141 (0.7%)	1/64 (1.6%)
	24 weeks (Women)	3/82 (3.7%)	7/79 (8.9%)	0/105 (0.0%)	1/82 (1.2%)	0/23 (0.0%)
	≥ 76 weeks	13/224 (5.8%)	14/24 (6.3%)	4/228 (1.8%)	2/223 (0.9%)	

Table 5 Summary of Genital Tract Infections

Inagaki 2014		**Canagliflozin 100mg**	**Canagliflozin 200mg**	**Placebo**		
	24 weeks	2/90 (2.2%)	1/89 (1.1%)	1/93 (1.1%)		
	24 weeks (Men)	0/59 (0.0%)	0/73 (0.0%)	1/60 (1.7%)		
	24 weeks (Women)	2/31 (6.5%)	1/16 (6.3%)	0/33 (0.0%)		
Stenlöf 2013		**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Placebo**	**Canagliflozin 100mg (high HbA1c)**	**Canagliflozin 300mg (high HbA1c)**
2014	26 weeks	12/195 (6.2%)	13/197 (6.6%)	4/192 (2.1%)	6/47 (12.8%)	2/44 (4.5%)
	26 weeks (Men)	2/195 (2.5%)	5/197 (5.6%)	0/192 (0.0%)		
	26 weeks (Women)	10/195 (8.8%)	8/197 (7.4%)	4/192 (3.8%)		
	52 weeks	18/195 (9.2%)	18/197 (9.1%)	5/192 (2.6%)		
	52 weeks (Men)	5/195 (6.2%)	8/197 (9.0%)	0/192 (0.0%)		
	52 weeks (Women)	13/195 (11.4%)	10/197 (9.3%)	5/192 (4.8%)		
Kaku 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	2/88 (2.3%)		1/87 (1.1%)		
Ji 2014		**Dapagliflozin 10mg**		**Placebo**		

	24 weeks	6/133 (4.5%)		1/132 (0.8%)		
	24 weeks (Chinese)	4/110 (3.6%)		0/110 (0.0%)		
Ferrannini 2010/Bailey 2015		**Dapagliflozin 10mg (AM)**		**Placebo**	**Dapagliflozin 10mg (PM)**	**Dapagliflozin 10mg (high HbA1c)**
	24 weeks	9/70 (12.9%)		1/75 (1.3%)	2/76 (2.6%)	7/39 (17.9%)
	102 weeks	11/70 (15.7%)		1/75 (1.3%)		
	102 weeks (men)	2/34 (5.9%)		0/31 (0.0%)		
	102 weeks (women)	9/36 (25.0%)		1/44 (2.3%)		
Roden 2013/4		**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Placebo**	**Sitagliptin 100mg**	**Empagliflozin 25mg (open-label)**
	24 weeks	7/224 (3.1%)	9/223 (4.0%)	0/229 (0.0%)	2/223 (0.9%)	1/87 (1.1%)
	24 weeks (Men)	4/142 (2.8%)	2/144 (1.4%)	0/124 (0.0%)	1/141 (0.7%)	1/64 (1.6%)
	24 weeks (Women)	3/82 (3.7%)	7/79 (8.9%)	0/105 (0.0%)	1/82 (1.2%)	0/23 (0.0%)
	≥ 76 weeks	13/224 (5.8%)	14/24 (6.3%)	4/228 (1.8%)	2/223 (0.9%)	
Lewin 2015		**Empagliflozin 10mg**	**Empagliflozin 25mg**		**Linagliptin 5mg**	
	52 weeks	7/135 (5.2%)	6/135 (4.4%)		4/135 (3.0%)	
	52weeks (men)	2/77 (3.1%)	1/64 (1.3%)		1/75 (1.3%)	
	52weeks	5/58 (7.1%)	5/71 (8.8%)		3/60 (5.0%)	

	(women)					

Adverse events

In this section, we include data from trials and other studies in combination therapy as well as monotherapy.

Urogenital Tract Infections

Although most urinary tract infections (UTIs) are mild and easily resolved with appropriate antibiotic treatment, more severe infections can be devastating, resulting in bacteraemia, sepsis and death. Because of the frequency with which they occur, UTIs also impose a substantial economic burden on healthcare systems.[83]

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. Glycosuria also promotes increased adherence of bacteria to uroepithelial cells, in particular *E. coli*.[84] By blocking renal glucose reabsorption, SGLT2 inhibitors cause glycosuria, and increase the risk of UTI in patients.[84] (2).

Glycosuria in patients with T2DM predisposes these patients 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.[85]

Symptoms of genital candidiasis can include itching; burning; genital discharge; pain during sexual intercourse; soreness; redness in the genital area; rash.

Both UTIs and GTIs are more common in females.[86]

Canagliflozin

In the Inagaki study of Japanese patients with T2DM[73], urogenital tract infections were infrequent, mild, managed with standard treatments and did not recur in any of the patients. The low incidence

may be at least partly because patients with a history of such infections were excluded from the trial. The incidence of UTIs was similar across all groups.[73] GTIs were more frequent in the canagliflozin groups compared to placebo, and mostly occurred in women.

In the Stenlöf study (CANTATA-M study) of predominantly white people[72, 87] there were small increases in UTIs with canagliflozin 100mg (7.2% at 24 weeks, 8.2% at 52 weeks) and 300mg (5.1% and 7.1%) compared with placebo (4.2% and 6.3%), All UTIs were mild to moderate in severity and no patients discontinued treatment due to a UTI.

Lavalle-González et al examined the efficacy and safety of canagliflozin 100mg and canagliflozin 300mg versus placebo and sitagliptin, for 26 weeks, in patients with T2DM who were being treated with background metformin; interestingly, the incidence of UTIs was only higher in the canagliflozin 100mg group.[88] The incidence of genital mycotic infections was higher in females and males with canagliflozin compared with placebo, but all were mild to moderate in severity, and responded to standard antifungal treatment. Once again, the incidence was higher in females compared to males as expected[88]; furthermore, the incidence of genital mycotic infections was higher in patients with high HbA1c.[88] No patients discontinued treatment due to a GTI.

In a separate 52-week open-label study by Inagaki of canagliflozin alone or as add-on to other oral antihyperglycaemic drugs in Japanese patients with diabetes, UTI was present in 2/127 (1.6%) with canagliflozin 100mg and 5/253 (2.0%) with canagliflozin 200mg, and none were severe (9). GTIs mostly occurred in females; most of the events were mild in severity and the patients recovered after antifungal therapy.[89]

Leiter et al. also compared canagliflozin 100mg and canagliflozin 300mg with glimepiride over 104 weeks in patients with T2DM inadequately controlled with metformin, and found the incidence of UTIs to be higher in the canagliflozin groups.[90]

Interestingly, Neal et al. looked at canagliflozin 100mg and canagliflozin 300mg when used together with insulin treatment over a 52 week time period and found no increase in the incidence of UTIs.[91]

Further, in a double-blind, Phase 3 clinical study, patients aged > 55 years to < 80 years inadequately controlled with their current treatment regimen (n = 714) were randomized to receive either canagliflozin 100mg or canagliflozin 300mg or placebo. Over 2 years, the incidence of GTIs was higher with canagliflozin 100mg (23.9%) or canagliflozin 300mg (18.7%) 300mg compared with placebo (4.3%) in women and men (5.6 % and 10.9 % versus 1.4 %, respectively). The largest number

of events occurred within 6 months of treatment initiation and declined with time. Most GTIs were mild to moderate in intensity and responded to standard treatment.[92]

In a pooled analysis by Nicolle et al.[93] the association between UTIs and canagliflozin treatment based on data from patients with T2DM enrolled in Phase 3 clinical studies, and on data from individual Phase 3 clinical studies in special patient populations, showed that the incidence of UTIs tended to be higher with canagliflozin 100mg and canagliflozin 300mg compared with placebo, but with no dose-dependence.

Finally, a recent report based on pooled data from patients with T2DM enrolled in Phase 3 clinical studies supports the notion of higher incidences of genital mycotic infections with canagliflozin compared to control patients with T2DM; GTIs being generally mild to moderate in intensity and responding to standard treatments.[94]

In summary, canagliflozin treatment (≥ 24 weeks) is associated with a higher incidence of urogenital tract infections, but there is no evidence of a dose-dependent response. UTIs were mild to moderate in severity and were amenable to standard treatment with no recurrence. This was also true in patients on pre-existing diabetic medication i.e. metformin. GTIs were also higher in females, and in older patients (> 55 years but < 80 years) – the risk of GTIs with canagliflozin use is increased mostly early after treatment initiation i.e. within first 6 months. GTIs were also mild to moderate in severity and were amenable to standard treatment.

Dapagliflozin

Dapagliflozin has been shown to have a dose-dependent effect on glycosuria in patients with T2DM[46], and treatment with dapagliflozin 10 mg as add-on to metformin showed that increased glycosuria with dapagliflozin was maintained for up to 102 weeks.[95] However, there is no demonstrable dose relationship between glycosuria and UTIs.[96]

In the Kaku monotherapy study in Japanese patients[77], after 24 weeks, 2 patients each in the dapagliflozin 10mg and placebo groups experienced at least one event suggestive of UTIs, but they were mild to moderate in severity.[77] Two patients in the dapagliflozin 10mg group and one patient in the placebo group experienced one or more GTI events, and GTIs were mild to moderate in severity.[77]

In a separate 52-week open-label Phase 3 study by Kaku consisting of a single treatment arm with no comparator, dapagliflozin (initiated at 5mg/day and titrated to 10mg/day as required) was administered as monotherapy (n = 249) or combination therapy (n = 479) with other

antihyperglycaemic agents (sulfonylurea, glinides, metformin, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or glucagon-like peptide-1 receptor agonists) in Japanese patients with T2DM with inadequate glycaemic control.[97] (19). Urogenital infections were rare, mild to moderate in intensity, and rates were similar in the monotherapy and combination therapy groups.[97]

In the study by Ji et al in predominantly Chinese patients, urogenital tract infections were few, with higher incidence in the dapagliflozin group (5.3%) compared with placebo (3.0%). All reported events were predominantly of mild or moderate intensity.[76] One patient had urethritis of moderate intensity, which resolved with antibiotic treatment; the patient continued with the study.

In the 24-week study by Ferrannini et al, there was an increased incidence of urogenital tract infections with dapagliflozin treatment compared with placebo.[74] The incidence of urogenital tract infections in the exploratory evening dose cohort was similar to the morning dose cohort. Urogenital tract infections resolved with standard treatment, and rarely led to discontinuation.[74]

In the 102-week Bailey study[95], which is essentially a continuance of the 24-week Ferrannini study[74], low-dose metformin 500mg/day was added to the placebo group.[95] Once again, the incidence of urogenital tract infections with dapagliflozin treatment was higher compared with the placebo + low-dose metformin group.[95] Urogenital tract infections occurred during the first 6 months of dapagliflozin therapy, were more common in women, and most were single episodes of mild or moderate severity (16). All urogenital tract infections responded to standard management.[98] One patient on dapagliflozin discontinued the study because of UTI.

In triple therapy, dapagliflozin as add-on to metformin plus sulfonylurea, in a 24-week, trial was associated with a higher incidence of urogenital tract infections than in the placebo group.[99]

Rosenstock et al in a 24-week trial against saxagliptin reported that urogenital infections were more frequent in the dapagliflozin/metformin arm than either saxagliptin/metformin or saxagliptin/dapagliflozin/metformin groups.[100]

In a recent report by Ptaszynska et al.[101], the association between urogenital tract infections and dapagliflozin treatment based on pooled analyses from 12 placebo-controlled studies of Phase 2b or Phase 3 clinical studies in T2DM patients receiving comparator or dapagliflozin as monotherapy, add-on to antidiabetic therapy, or as initial combination with metformin showed that urogenital tract infections occurred more often with dapagliflozin treatment compared with placebo, but were mild or moderate in severity. Pyelonephritis was rare and balanced among treatments.

In summary, dapagliflozin monotherapies and combination therapies (≥ 24 weeks) are associated with a higher incidence of urogenital tract infections, but there is no evidence of a dose-dependent response. Urogenital infections were generally mild to moderate in severity, tended to occur during the first 6 months of dapagliflozin therapy, were more common in women, and were amenable to standard treatment. Urogenital infection rates were similar between monotherapy and combination therapy groups in all studies with the exception of combination therapies involving saxagliptin.[100]

Empagliflozin

Roden et al.[80, 102] found that after 24 weeks, UTIs were mild to moderate in intensity (only 1 patient in the empagliflozin 25mg group discontinued the study), and more common in women but similar in all arms. After 76 weeks, the frequency of UTIs was again similar in all groups. However, the frequency of GTIs was higher in the empagliflozin groups (3.1% and 4.0%) than the placebo (0%) and sitagliptin (0.9%) groups. GTIs were once again more common in women. GTI events were of moderate intensity in 3 patients in the empagliflozin 25mg group (1 patient discontinued the study); all other events were mild.

Barnett et al in the EMPA-REG RENAL study of empagliflozin versus placebo in patients with renal impairment found that both UTIs and GTIs were more frequent in T2DM patients with Stage 3 CKD and Stage 4 CKD, but not Stage 2 CKD.[103]

In the Lewin trial[78], after 52 weeks, urogenital infections were more common in women, and empagliflozin treatment was almost always associated with a higher incidence of urogenital infections compared with the placebo group. The exceptions were empagliflozin 25mg versus placebo for UTI and empagliflozin 10mg/linagliptin 5mg versus placebo for GTI. One patient (receiving empagliflozin 25mg) had a UTI of severe intensity, but did not lead to discontinuation of the study drug, and 1 patient (receiving empagliflozin 10mg) had chronic pyelonephritis that was mild in intensity and was not considered to be related to the study drug.[78] There were no severe GTI events, but two patients (1 on empagliflozin 25mg/linagliptin 5mg and one on empagliflozin 10mg) discontinued the study because of GTIs.

DeFronzo et al evaluated combinations of empagliflozin/linagliptin (empagliflozin 10mg/linagliptin 5mg and empagliflozin 25mg/linagliptin 5mg) as second-line therapy in subjects with T2DM inadequately controlled on metformin.[104] They found that after 52 weeks, the incidence of UTIs was similar across the empagliflozin 25mg, empagliflozin 10mg and linagliptin 5mg groups. In contrast to UTIs, the frequency of GTIs was higher in the empagliflozin 25mg and empagliflozin 10mg

compared with the linagliptin 5mg group; interestingly, the 2 combinations of empagliflozin/linagliptin therapies had a lower frequency of urogenital infections compared to these 3 groups.

Similar findings were reported from the Rosenstock placebo-controlled trial in obese (BMI ≥ 30kg/m^2 and ≤ 45kg/m^2) inadequately controlled (HbA1c ≥ 7.5 to ≤ 10%) T2DM patients where empagliflozin was added on to multiple daily injections of insulin for 52 weeks i.e. similar rates of UTIs and higher rates of GTIs in the empagliflozin groups compare with the placebo group.[105] However, in the EMPA-REG BASAL study, which enrolled T2DM patients with BMI ≤ 45 kg/m^2, inadequately controlled (HbA1c > 7% to ≤ 10%), despite treatment with basal glargine or detemir insulin (≥ 20IU/day) or NPH insulin (≥ 14IU/day), with or without metformin and/or sulfonylurea use, Rosenstock et al observed that both UTIs as well as GTIs were more frequent in the empagliflozin groups compare with the placebo group.[106]

Häring et al. studied the effect of adding either empagliflozin 10 mg or empagliflozin 25mg or placebo for 24 weeks in T2DM patients inadequately controlled (HbA1c ≥ 7% to ≤ 10%) on metformin and sulfonylurea [EMPA-REG METSU][107]or on metformin alone [EMPA-REG MET].[108] In both studies, the incidence of UTIs was slightly higher and the incidence of GTIs higher in the empagliflozin groups compared with the placebo groups, respectively. 71.2% of patients of the EMPA-REG METSU continued in a double-blind extension for ≥ 52 weeks, named the EMPA-REG EXTEND METSU study[109], and 72.7% of patients of the EMPA-REG MET study continued in a double-blind extension study for ≥ 52 weeks, named the EMPA-REG EXTEND MET study.[110] Both these studies demonstrated that UTIs were not more frequent in the empagliflozin groups compared with the placebo, but GTIs were reported in more patients on empagliflozin therapies than placebo[109, 110] Similar findings were found in the 104-week randomised, active-controlled, double-blind, parallel-group, Phase 3 trial, comparing empagliflozin and glimepiride as add-on therapy to metformin treatment in patients with T2DM, the EMPA-REG H2H-SU study.[111]

The EMPA-REG PIOGLITAZONE compared empagliflozin as add-on therapy to pioglitazone (≥ 30mg/day) with or without metformin (≥ 1500mg/day), at unchanged doses for ≥ 12 weeks, in patients with T2DM.[112] Afterwards, 61.2% of patients who completed 24 weeks of treatment continued in a double-blind extension trial for ≥ 52 weeks (total duration ≥ 76 weeks), the EMPA-REG EXTEND™ PIO study.[113] Both these studies found that UTIs were not more frequent in the empagliflozin groups compared with the placebo arms. However, GTIs were reported in more patients on empagliflozin therapies than placebo.[112, 113]

In summary, empagliflozin monotherapies and combination therapies (≥ 24 weeks) are associated with a higher incidence of GTIs but not UTIs, as almost all studies reported similar rates of UTI across all treatment and placebo groups. Urogenital infections were more common in women, generally mild to moderate in severity and amenable to standard treatment.

Some trials show little difference in UTI results between the SGTL2 inhibitor and placebo arms. A possible explanation is that the placebo group had glycosuria, due to poor diabetes control, leading to an increased risk of UTI. We note that in a trial of dapagliflozin against an active comparator, glipizide, the difference in UTI rates was greater than in most of the trials against placebo.[114]

Frequencies of UTIs.
The trials of different drugs reported different rates of UTIs, but a recent meta-analysis of 19 trials found no significant differences in risk amongst the three drugs. [115]

When do UTIs occur?
Several trials report cumulative incidence of UTIs. Kaku reports 2.3% at 24 weeks and 3.6% by 52 weeks. So 1.3% of UTIs occur in months 7 to 12. Ferrannini reports 5.7% at 24 weeks and 8.6% at 102 weeks. So 2.9% occur from week 24 to week 102. Roden reports 6.7% at week 24 and 9.4% by week 76. So 2.7% occurred from week 24 to week 76.
Patients on SGLT2 inhibitors who have more than one UTI will be switched to another drug. For modelling purposes, we will assume that;

- 60% of flozin-induced UTIs will occur in the first 6 months
- All flozin-induced UTIs will occur in the first two years
- Two UTIs will trigger a change of therapy.

Diabetic ketoacidosis (DKA)

DKA is a serious complication of diabetes, seen predominantly but not exclusively in type 1 diabetes. It is life-threatening. It requires admission to hospital for intensive treatment with intravenous infusion and insulin. It is therefore costly to health care.

In recent months, cases of DKA have been reported associated with treatment with SGLT2 inhibitors. The European Medicines Agency (EMA) has announced a review of the risk of DKA amongst people treated with these drugs.[116] It notes that 101 cases of DKA had been reported worldwide in patients treated with SGLT2 inhibitors, which based on an estimated 500,000 patients-years of use, would be a risk of one in 5000 patient years. The EMA also notes that in some cases the level of blood glucose

was much lower than is usually seen in DKA ("euglycaemic DKA"), and expressed concern that this might lead to delays in diagnosis.

In the USA, the Food and Drug Administration has also announced a review and has issued a safety announcement.[117] The FDA had received notifications of DKA in patients treated with SGLT2 inhibitors.

The manufacturers of canagliflozin, Janssen, have reported that in their series of trials, the incidence of DKA was very low – 0.5 per 1,000 patients years on canagliflozin 100mg daily, 0.8 on canagliflozin 300mg daily, and 0.2 per 1,000 years on placebo.[118] The other manufacturers have yet to publish data, but enquiries by Rosenstock and Ferrannini for a commentary in Diabetes Care elicited rates from the manufacturer for dapagliflozin and empagliflozin of under 0.1%, though no details are given of time period.[119] Rosenstock and Ferrannini suggest that some of the cases reported in the USA may have been in patients with type 1 diabetes.

With greater use of the SGLT2 inhibitors, rare adverse events can be expected. Acute pancreatitis has been reported shortly after canagliflozin was started[120] but cause and effect is not proven. A case of severe hypercalcaemia has been reported[121] possibly linked to the osmotic diuresis and ingestion of calcium-containing indigestion tablets.

Late reporting of adverse events is not unusual. The FDA have also recently issued a safety alert on the gliptins, the DPP4 inhibitors, after reports of severe joint pain.[122]

What is becoming clearer as evidence accumulates, is that the SGLT2 inhibitors have actions beyond the kidney, for example on the pancreas, with an increase in plasma glucagon levels, and effects on blood lipids.[123]

Cardiovascular safety

All three of the SGLT2 inhibitors reviewed in this report are in large, long-term cardiovascular studies, mandated by the FDA to satisfy the post-marketing requirements in the USA. The results of these (CANVAS[124] for canagliflozin and DECLARE[125] for dapagliflozin are awaited but there have been early reports of reductions in cardiovascular events.[126]

Bone health

The FDA has issued a warning on decreases in bone density and an increased risk of fractures in people taking canagliflozin, possibly through effects on phosphate metabolism involving parathyroid

hormone, fibroblast growth factor 23 and vitamin D.[127] Fractures have also been reported amongst people taking dapagliflozin. Kohan and colleagues[128] randomised 252 people with moderate renal impairment (94% in the range 30 to 59 ml/min) to placebo or dapagliflozin. HbA1c fell by 0.44% on dapagliflozin 10mg daily and by 0.32% on placebo, but there was good weight loss on dapagliflozin (reduction by 1.89 kg) and a useful reduction in SBP (6.8 mmHg). However 8 of 85 (9.4%) people on dapagliflozin 10mg suffered fractures, compared to none on placebo.

Kwon[129] reviewed bone safety and canagliflozin for the FDA, using data from the canagliflozin phase 3 programme, for 6177 patients on the drug and 3262 on other treatments. The proportions suffering fractures were 2.1% and 1.6% for canagliflozin and others respectively, with most of the difference being in low trauma fractures (1.6% and 1.2%), with the main difference being in the upper limb (0.7% versus 0.3%). The incidence per 1000 patient years was 18.1 for canagliflozin regimens and 14.2 for other regimens. So the risk of fracture is small but increased by around 30% in people taking canagliflozin.

The mechanism by which canagliflozin increases fracture risk is uncertain.[130] An important issue is that the fracture rate is not increased in the first year of treatment, but appears later. So any increase in fracture risk may not be detected in short trials (Taylor 2015). (The FDA warning however states that fractures can occur as early as 12 weeks after starting canagliflozin.)

The EMPA-REG outcome study

The results of this trial were published on 17th September 2015.[131] The trial recruited 7020 patients at high risk of cardiovascular disease. High risk included having a history of myocardial infarction (MI) or stroke, coronary artery stenosis of 50% or more, previous coronary revascularisation, and peripheral vascular disease. The trial scores quite well with the Cochrane risk of bias score (Appendix 5) with the deficiencies probably due to failure to provide details rather than design or execution flaws.

Patients were randomised to placebo, and empagliflozin 10mg or 25mg. Patients were recruited from 590 sites in 42 countries, an average of 12 per site. 72% were white, 21% Asian and 5% Black including African-Americans. The Asians were from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea. There were no centres in China except Hong Kong, but there were centres in Taiwan and Singapore. Numbers are not given by country. There were 12 UK centres, and 41% of all recruits were from Europe, including Russia. The mean HbA1c at baseline was just under 8.1%. In 57% of patients, duration of diabetes was over 10 years. At baseline 74% were on metformin, 48% on insulin, 43% of sulfonylureas and 11% on DPP-4 inhibitors. About 30% were on monotherapy and 48% on dual therapy, implying that 26% were on more complex regiments

with three drugs or more. Discontinuation from trial medication occurred in 29% of the placebo group and 23% of the empagliflozin group, with 13% and 11.5% being due to adverse events (which did not include need for rescue therapy).

After 12 weeks, other glucose-lowering drugs could be adjusted or added. Targets were not specified centrally but left to local guidelines. Changes were made in 31.5% of the placebo group and 19.5% of the empagliflozin group. The changes in the empagliflozin group included the introduction of insulin (5.8%), a DPP4 inhibitor (5.6%), a sulfonylurea (3.8%), metformin (3.7%), a TZD (1.2%) or a GLP-1 analogue (1.4%). This means that we cannot use the drift upwards of HbA1c of 0.1% per year in the empagliflozin group as a guide to progression of diabetes. Despite the addition of other glucose-lowering drugs, the mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group, a difference of 0.35%.

Being a high risk group, at baseline 95% were on anti-hypertensive medications (81% on angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs); 65% on beta-blockers; 33% on calcium channel blockers). 77% were on statins, 9% on fibrates and 4% on ezetimibe. 43% were on diuretics, unspecified, but loop diuretics are not recommended for use with canagliflozin and dapagliflozin.

According to the supplementary information (Table S12), cardiovascular medications introduced after baseline included, in the empagliflozin arms, ACEIs or ARBs in 23.6%, which does not seem compatible with the 81% on these drugs at baseline. Perhaps there were changes of drug or dosages. Similarly Table S12 reports statins being introduced in 22% of the empagliflozin group, which implies that at study end, 99% were on statins, with 14% also on fibrates.

A range of subgroups was specified in the protocol.[132] The results were analysed by staff from Boehringer Ingelheim who co-funded it with Eli Lilly. The two empagliflozin groups were pooled for the analysis, because event rates were almost identical (CVD deaths 3.8% with 10mg and 3.5% with 25mg). When the main outcomes were assessed for the 10mg and 25mg empagliflozin groups separately, the differences were not significantly different from the placebo group.

The primary outcome was a composite of death from a cardiovascular cause, non-fatal MI and non-fatal stroke. The primary outcome occurred in 10.5% of people on empagliflozin and in 12.1% of those on placebo, giving hazard ratio 0.86 (95% CI 0.74-0.99). Table **6** shows some of the outcomes.

Table 6 Results of EMPA-REG-OUTCOMES trial

	Placebo	Empagliflozin
Number of patients	2333	4687
All-cause mortality	8.3%	5.7%
Cardiovascular mortality	5.9%	3.7%
Non-cardiovascular mortality	2.4%	2.0%
Primary composite outcome	12.1%	10.5%
MI		
non-fatal	5.2%	4.5%
fatal	0.2%	0.3%
silent	1.2%	1.6%
Stroke	3.0%	3.5%
fatal	0.4%	0.3%
non-fatal	2.6%	3.2%
Hospital admission – heart failure	4.1%	2.7%
Hospital admission - unstable angina	2.8%	2.8%
UTIs	18.1%	18.0%
GTIs	1.8%	6.4%
DKA	1 event	4 events

The DKA rate in the empagliflozin was double that in the placebo group but the excess risk was only about 1 in 1500 per year, and numbers were very small.

The proportion of fatal to non-fatal MIs looks odd – 5 deaths out of 126 MIs. Similarly of 69 strokes, only 9 were fatal. This raises the question of where the 137 cardiovascular deaths come from.

Supplementary table S5 reports 11 deaths from acute MI in the placebo group and 15 in the pooled empagliflozin group, but these figures do not match those in table 1 in the main paper. The figures for fatal stroke also differ between main text and supplement 11 versus 9 for placebo, 16 versus 14 for empagliflozin.

Supplementary table S5 gives cardiovascular deaths reproduced in Table **7**.

Table 7 Cardiovascular deaths in the EMPA-REG Outcome trial.

Cause	placebo	Empagliflozin	Difference in %
Sudden death	1.6%	1.1%	0.5%
Heart failure	0.8%	0.2%	0.6%
Acute MI	0.5%	0.3%	0.2%
stroke	0.5%	0.3%	0.2%
Cardiogenic shock	0.1%	0.1%	0
Other cardiovascular deaths	2.4%	1.6%	0.8%

Total mortality was 8.3% in the placebo group and 5.7% in the pooled empagliflozin, a difference of 2.6%.

The ill-defined "other cardiovascular deaths" comprise 41% and 44% of all cardiovascular deaths for placebo and empagliflozin respectively, and they account for 29% and 28% of all deaths respectively. Three causes account for 83% of the observed difference in mortality: sudden death, heart failure and "other cardiovascular deaths".

The totals of proportions having the individual events in the composite primary outcomes exceeds the primary outcome proportion, presumably because some patients had more than one event.
The Kaplan-Meier curves diverge after about 2 months, with curious accelerations in the placebo group curves after 42 months.

How were these cardiovascular benefits achieved?
HbA1c was 0.57% lower in the empagliflozin group than the placebo arm at week 12 but steadily narrowed thereafter to 0.35% at week 206. Given the weak relationship between glycaemic control and cardiovascular disease[66] this difference seems unlikely to have caused the difference.

SBP fell by about 5.5mmH in the empagliflozin group and by about 2 mmHg in the placebo group by week 16 but the difference between the empagliflozin and placebo groups narrowed thereafter to about 2mmHg. There was no difference in BP lowering between doses. Diastolic BP fell by about 2.5 mmHg in all three arms. By 206 weeks, there was no difference between diastolic BP between empagliflozin and placebo groups.

For some complications of diabetes, blood pressure control is as important as glycaemic control, as was shown by the UKPDS study, where "tight" blood pressure control (with a mean BP of 144/82, it was not really tight) reduced overall mortality by 32% (RR 0.68; 95% CI 0.49-0.94).[133]

Weight was reduced by 2kg in the empagliflozin group and by 1.2kg in the placebo group.
Changes in lipids were small. On empagliflozin 25 mg, LDL-c rose (placebo-adjusted) from baseline 2.2 mmol/L to about 2.3 by 12 months, stayed there till about 136 weeks then fell to about 2.21 mmol/l, just below the placebo level. On empagliflozin 25mg, HDL-C rose by about 0.05 mmol/L then fell slightly. The placebo level rose by about 0.01mmol/L. (Figures derived from graph – data not provided in text.) The baseline TC:HDL ratio was 3.5, perhaps because so many were on statins and other lipid-lowering drugs. These lipid changes seem insufficient to explain the mortality results.

However the combination of factors may have more effect than the individual ones, and the reduction in blood pressure, though small, is similar to that seen in the Heart Outcomes Prevention Evaluation (HOPE) trial[134] where a reduction of 2-4mmHg in blood pressure from ramipril (an ACEI) was thought by the HOPE authors to be sufficient to explain about a quarter of the observed 25% reduction in cardiovascular events, in another high risk group with vascular disease and/or diabetes.

Discontinuation rates from study drugs due to adverse events are reported as 19.4% for placebo and 17.3% for empagliflozin in the paper but as 13.0% and 11.5% in appendix H.
Subgroup analysis for the primary composite outcome shows;

- Statistically significant benefit in Asians (a mixed group, with about 44% from north-east Asia) but not in whites, though death from cardiovascular causes is significantly reduced in whites. This implies that whites gained less for non-fatal MI and stroke. The Asian group is rather heterogenous and no details are given of risks in East Asians versus South Asians. There are differences in the balance of insulin deficiency and insulin resistance.
- Statistically significant benefit in those with baseline HbA1c under 8.5% but not in those above that
- Statistically significant benefit in those with BMI < 30 but not in those above that level
- Statistically significant benefit in those on insulin but not in those on non-insulin regimens. 51% in both groups were on insulin.
- Greater benefit in those aged over 65

In a number of subgroups, reductions in cardiovascular death were statistically significant when reductions in the primary outcome were not. To recall, the primary outcome was cardiovascular death, non-fatal MI and non-fatal stroke. Of 282 primary outcome events in the placebo group, 49% were

cardiovascular deaths. Of 490 primary outcome events in the empagliflozin groups, 35% were cardiovascular deaths. So a greater proportion of events in the empagliflozin group was of non-fatal events. The fact that in some subgroups, cardiovascular death rates are significantly different when the composite primary outcome is not, is explained by a lack of any statistically significant differences in non-fatal MI and non-fatal stroke.
Non-fatal MI was diagnosed on the basis of symptoms plus one or more of;

- Troponin or creatine kinase-MB
- ECG changes
- Imaging of new non-viable or non-motile myocardium

This study has attracted world-wide interest. It contrasts with the equivalent studies with the DPP4 inhibitors, which did not show any reduction in cardiovascular outcomes. They were;

- SAVOR for saxagliptin (The Saxagliptin assessment Of Vascular Outcomes Recorded in patients with diabetes mellitus).[135]
- EXAMINE for alogliptin (Examination of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome.[136]
- TECOS for sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin.[137]

There was no difference in cardiovascular outcomes in SAVOR except that more patients on saxagliptin than on placebo (3.5% versus 2.8%: HR 1.27 95% CI 1.07-1.51) were admitted to hospital with heart failure.

The findings in EXAMINE were similar – no difference in endpoints – except an increase in heart failure in a subgroup analysis of patients with no heart failure at baseline (2.2% on alogliptin, 1.3% on placebo; HR 1.76 95% CI 1.07-2.90).

TECOS results were again similar – no differences in a composite primary endpoint of CV death, non-fatal MI and non-fatal stroke, nor in other endpoints including hospital admission for heart failure, and death from any cause.

These results were seen as providing reassurance, in the wake of the rosiglitazone story with an increase in cardiovascular events.[138] They could also be seen as disappointing in that they did not reduce the most important complication of diabetes, the excess of cardiovascular disease. However as has been pointed out by Hirshberg and Katz.[139], these trials ran for only a few years and showed only small changes in HbA1c (reductions of 0.27 to 0.36% compared to placebo) so reducing the chance of showing reductions in cardiovascular events.

The subgroup analyses in EMPA-REG Outcome are interesting. Younger, lighter, better controlled patients did better, as did the Asian group. There could be overlapping features here in that the East Asians tend to be lighter. There was no evidence of overall mortality reduction in white people but some reduction in CVD mortality, which suggests that there were more non-cardiovascular deaths in white people on empagliflozin. Further details will no doubt be released but with such a very large study, further analysis is bound to take time.

The differences observed do not seem sufficient to justify the very optimistic media coverage, such as reports that "Lilly's Jardiance diabetes pill could be a $6 billion-a-year blockbuster".[140]

It is worth noting that the Empa Outcome trial involved patients at high cardiovascular risk who had had diabetes for many years and who were on complex regimens for their diabetes. The results are not applicable to people starting monotherapy with empagliflozin.

Chapter 3. Network meta-analysis of SGLT2 inhibitors and comparators in monotherapy

One question is whether all the three flozins in this appraisal should be regarded as equally potent. In addition to the SGLT2 transport system in the kidney, there is also a related transport system in the gut, SGLT1. Most SGLT2 inhibitors appear to be highly-selective, with no significant effect on SGLT1, but one of the class, canagliflozin, does affect SGLT1, and it has been suggested by Polidori and colleagues[49] that canagliflozin may reduce blood glucose by a dual action in both gut and kidney. However that suggestion followed a very short-term study of canagliflozin in healthy individuals, and the gut effect was seen only with higher doses such as 300mg, and not with the 100mg dose.

A study by Stein and colleagues from Janssen Research and Development[50] looked at the SGLT1 effect in people with type 2 diabetes and found that canagliflozin 300 mg, but not 150 mg, reduced post-prandial plasma glucose, by about 0.5 mmol/l (from graph) for about two hours after administration, since it depends on an intestinal drug action not a systemic one. Hence this reduction would only occur after the single daily dose.

If the SGLT1 effect is clinically significant in people with type 2 diabetes, then one might expect canagliflozin 300 mg to be more potent in reducing HbA1c levels than SGLT2 inhibitors without the SGTL1 effect.

The CANTATA-M study 2013[72] did not report weight SDs for the two doses of canagliflozin so this study could not be included in weight comparison. The weight data for canagliflozin 100 mg comes from Inagaki 2014[73] where the 100 mg and 200 mg doses of canagliflozin were used. We excluded the 200 mg dose since this is not a standard dose.

For assessing the relative merits of the SGLT2 inhibitors in monotherapy, the first comparison is amongst the usual starting doses: canagliflozin 100mg, dapagliflozin 10mg and empagliflozin 10mg. By including empagliflozin 25mg and canagliflozin 300mg, we can assess the effect of increasing the doses. However a caveat is necessary. The empagliflozin 25mg and canagliflozin 300mg are used in people who can tolerate the starting dose, but have an insufficient HbA1c response. Such patients may not respond as well to SGLT2 inhibition as the average patient, and the effect of increasing the doses may be less than seen in the trials.

The aim of our NMA was not only to compare canagliflozin, empagliflozin and dapagliflozin, but also to assess their effects relative to active comparators.

Methods

Selection of trials

We applied the following selection criteria;

- Trials of 24 -26 weeks, starting with placebo as the common comparator
- Trials only of selected drugs. For example, we did not include all sulfonylureas but focused on gliclazide which should be the sulfonylurea for comparison in trials of newer agents.[22] We did not include all DPP4 inhibitors, originally intending to focus on sitagliptin.
- Baseline HbA1c of 7.5% or more, based on the NICE guideline for treatment intensification. There are some RCTs in patients with lower baseline HbA1cs, but they have less scope for lowering HbA1c
- Drop-out rates of no more than 20%

However, the first of these criteria had to be relaxed in order to include gliclazide since we found no trials of gliclazide against placebo. We had to indirectly link gliclazide with placebo via linagliptin and pioglitazone. All the other drugs included had trials against placebo. Unfortunately, we found no satisfactory trials of repaglinide for inclusion.

We searched the lists of trials used for the NICE guideline group on type 2 diabetes, but carried out additional searches specifically for gliclazide trials, since the guideline group pooled trials of sulfonylureas.

The evidence on repaglinide

The annex to the NICE guideline CG87 lists 7 studies on repaglinide but only three gave 24 week data.

Abbatecola et al report a randomised trial comparing repaglinide and glibenclamide.[141] The main outcome measure was cognitive function, with the hypothesis being the tighter control of post-prandial plasma glucose would reduce cognitive decline, in patients aged 60-78, mean age 74. (Note that according to the BNF, repaglinide is "not recommended" in people over 75.)
The baseline HbA1c in patients in this trial was quite low – 7.25%. So it is an exclusion for our purposes. The final HbA1c is not given in the text, but from the graph is about 6.6% with no difference between the drugs.

In the Jovanovic 2000 trial, patients were randomised to placebo, and repaglinide 1mg or 4mg daily. Under 30% of patients were drug naïve, and 10% had been on two glucose lowering drugs.[142]
Baseline HbA1c was 8.6% in the placebo group and rose to 10% at 24 weeks. In those who had been

on previous combination treatment, HbA1c rose by 1.8% on placebo, and fell by inconsequential 0.07% and 0.05% on repaglinide 1mg and 4mg. Drop-out rates were very high – 60% in the placebo group of which half had to start rescue treatment, and 23% and 31% in the repaglinide groups. Given that 70% had been on prior drug therapy, the high proportion in the placebo group requiring rescue treatment is not surprising, but it devalues any conclusions drawn from this study.

The third 24 week study used by NICE was by Saleem et al from Lahore.[143] This compared the effects on HbA1c of repaglinide and glibenclamide. It says that 50 patients were "randomly selected" for each group but gives no details of how this was done, or on allocation concealment. Blinding was not feasible because of different dosing frequencies – one or twice daily for glibenclamide, pre-prandially up to three times a day for repaglinide. No patients are reported to have dropped out. The recruitment period in this study (March 2006 to March 2007) overlaps with that for another paper by the same group (Shah et al 2011)[144] which reports only plasma glucose, in 200 patients. The changes in FPG and 2-hour PG are almost identical in the two studies. The Shah paper has no HbA1c data. Saleem et al 2011 report a reduction by 24 weeks in HbA1c of 0.6% on repaglinide and 0.4% on glibenclamide. The final repaglinide dose was 4.27mg daily, and the final glibenclamide dose was 8.8mg (identical to the Shah et al article). The Shah article states that dosages were reported as being adjusted based on glucose levels, so it is not clear why the final glucose levels are so different, with a reduction in FPG in the repaglinide group which is almost double that in the glibenclamide group. No details of source of funding are given. We think that the patients in the Saleem study may be a subset of those in the Shah study.

We also note the trial by Jibran and colleagues.[145] This paper is very similar to the Saleem et al 2011[143] paper, but has no authors in common. The numbers of patients are the same, and values for baseline age, weight and BMI have identical means and SDs. The result tables are identical in means and SDs. Much of the text is the same. The patients are said to have been recruited in different time periods.

Glibenclamide is a first generation sulphonylurea and was not included in our NMA, so the Saleem/Jibran and Abbatecola trials are not included.

The NICE guideline group also considered evidence on repaglinide at 12 months, from four trials. These included the Abbatecola and Saleem trials mentiond above, and two better quality ones by Derosa et al[146] and Marbury et al.[147]The Derosa trial compared repaglinide with glimepiride, in patients with mean HbA1c of 8.0%, and showed a reduction of 1.2% at 12 months. We use the effect sizes from this study in our modelling, for changes in HbA1c, SBP and weight. However we prefer gliclazide to glimepiride, so the Derosa trial is not included in our NMA. The Marbury trial recruited

both patients who had never had any glucose lowering drugs (13%) and those who had previously been treated with sulfonylureas and other drugs (87%). The reduction in HbA1c was much greater in the pharmacotherapy-naive group – 1.3% at 12 months, similar to the Derosa results. In previously treated patients, the HbA1c actually rose by 0.3%. Mean baseline HbA1c was quite high at 8.7% so the results may be less applicable to patients treated according to the NICE guidelines with close monitoring and prompt intensification when HbA1c exceeded 7.5%. The sulfonylurea comparator was glibenclamide, so the trial is not used in our NMA.

The network diagram is shown in Figure 3. The included trials are listed in Table **8**.

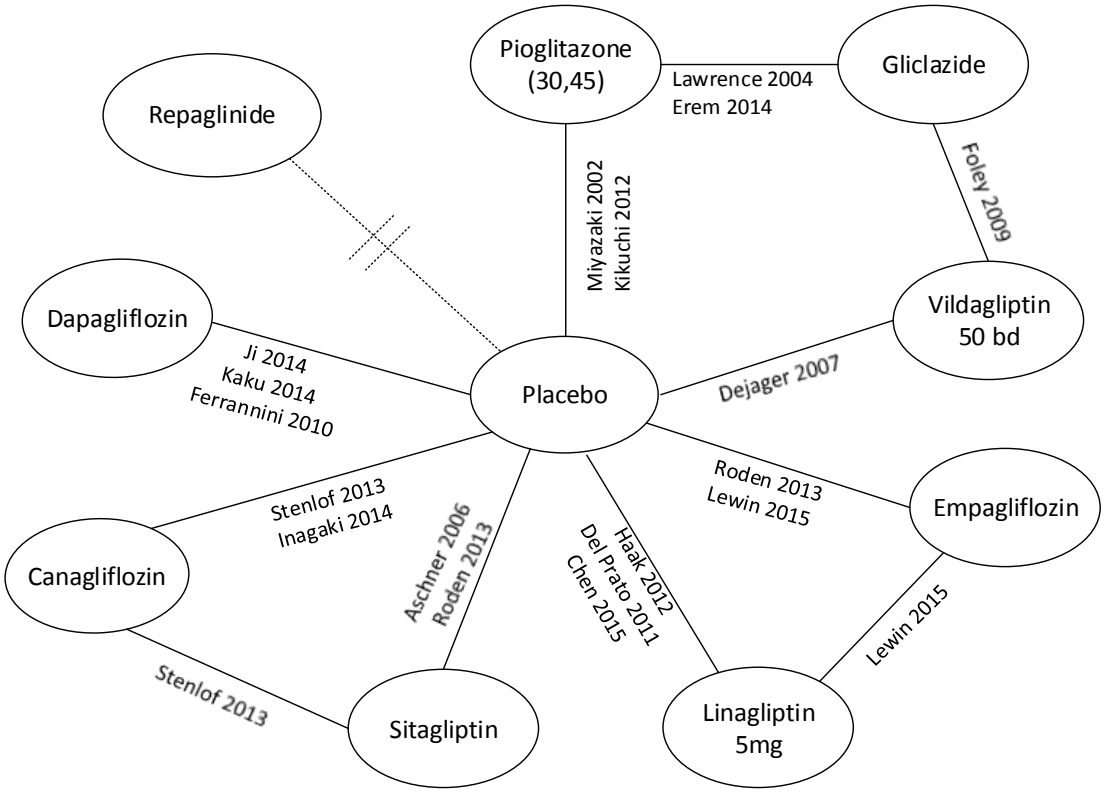

Figure 3 Network meta-analysis diagram

Table 8 Trials included in the NMA

Trial	Drug	Comparator	Notes
Inclusions			
Aschner 2006[148]	Sitagliptin 100mg	Placebo	
Chen 2015[149]	Linagliptin	Placebo	
Dejager 2007[150]	Vildagliptin	Placebo	
Del Prato 2011[151]	Linagliptin	Placebo	
Erem 2014[152]	Pioglitazone	Gliclazide	
Ferranini 2010[74]	Dapagliflozin	Placebo	
Foley 2009[153]	Gliclazide	Vildagliptin	
Haak 2012[154]	Linagliptin	Placebo	
Inagaki 2014[73]	Canagliflozin 100	Placebo	
Ji 2014[76]	Dapagliflozin	Placebo	
Kaku 2014[77]	Dapagliflozin	Placebo	
Kikuchi 2012[155]	Pioglitazone	Placebo	
Lawrence 2004[156]	Pioglitazone	gliclazide	
Lewin 2015[78]	Empagliflozin	Placebo	Linagliptin
Miyazaki 2002[157]	Pioglitazone	Placebo	
Roden 2013[80]	Empagliflozin	Placebo	Sitagliptin
Stenlof 2013[72]	Canagliflozin 100 and 300mg	Placebo	Sitagliptin in extension

Summary measures

The primary measures of treatment effect were the mean differences (MD) in change from baseline for glycated haemoglobin, weight gain, and systolic blood pressure. A negative value indicates improvement in the outcome. In the case of missing values for standard deviation of change from baseline values, the standard deviation was imputed as described in detail in the Cochrane Handbook.[158] In brief, we assumed a correlation of r=0.5 between baseline and follow-up to estimate standard deviation for change from baseline

Data synthesis and model implementation

We used a Bayesian network meta-analysis (NMA) method to analyse all the data, preserving randomized treatment effects within trials and accounting for correlation between comparisons with three-arms or four-arms using the freely available software, WinBUGS 1.4.3. The statistical heterogeneity in treatment effect estimates was estimated using between study variance (i.e. square root of the standard deviation of underlying effects across trials) with 95% CrI.[159] To estimate inconsistency in the networks of evidence, we calculated the difference between indirect and direct estimates whenever indirect estimates could be constructed with a single common comparator.[159] Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CrI

excluding 0 for MD.[160] The model convergence was assessed using trace plots and the Brooks-Gelman-Rubin statistic.[161] The analysis was undertaken using two Markov chains, which was ran simultaneously. The model was found to be converging adequately after 20,000 samples for both chains. We ran the model further using 70,000 samples and the results presented in the paper are based on these samples as we discarded the first 20,000 samples.

We used both the fixed and random effect models. The Bayesian Deviation Information Criterion (DIC) was used to compare the two models to see which was appropriate to compare treatment effects. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The model with the lowest DIC value was considered as the most appropriate NMA model. Based on DIC values obtained from the two models and also because of small number of studies available for the NMA, a fixed effect model was chosen. Due to small number of studies, it would have been difficult to estimate between studies variance if a random effect model was implemented.

All results are reported as posterior medians of mean differences with corresponding 95% credible intervals (CrIs). Credible intervals are the Bayesian equivalent of classic confidence intervals. A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range. Drugs were not ranked, but were considered in terms of effect sizes and uncertainties.

Results

Glycated haemoglobin (haemoglobin A1c)

Networks of eligible comparisons for the glycated haemoglobin (HbA1c) are shown in Figure 4 showing predominantly pairwise comparisons of drugs with placebo. There were eleven comparisons (ten drugs plus placebo).

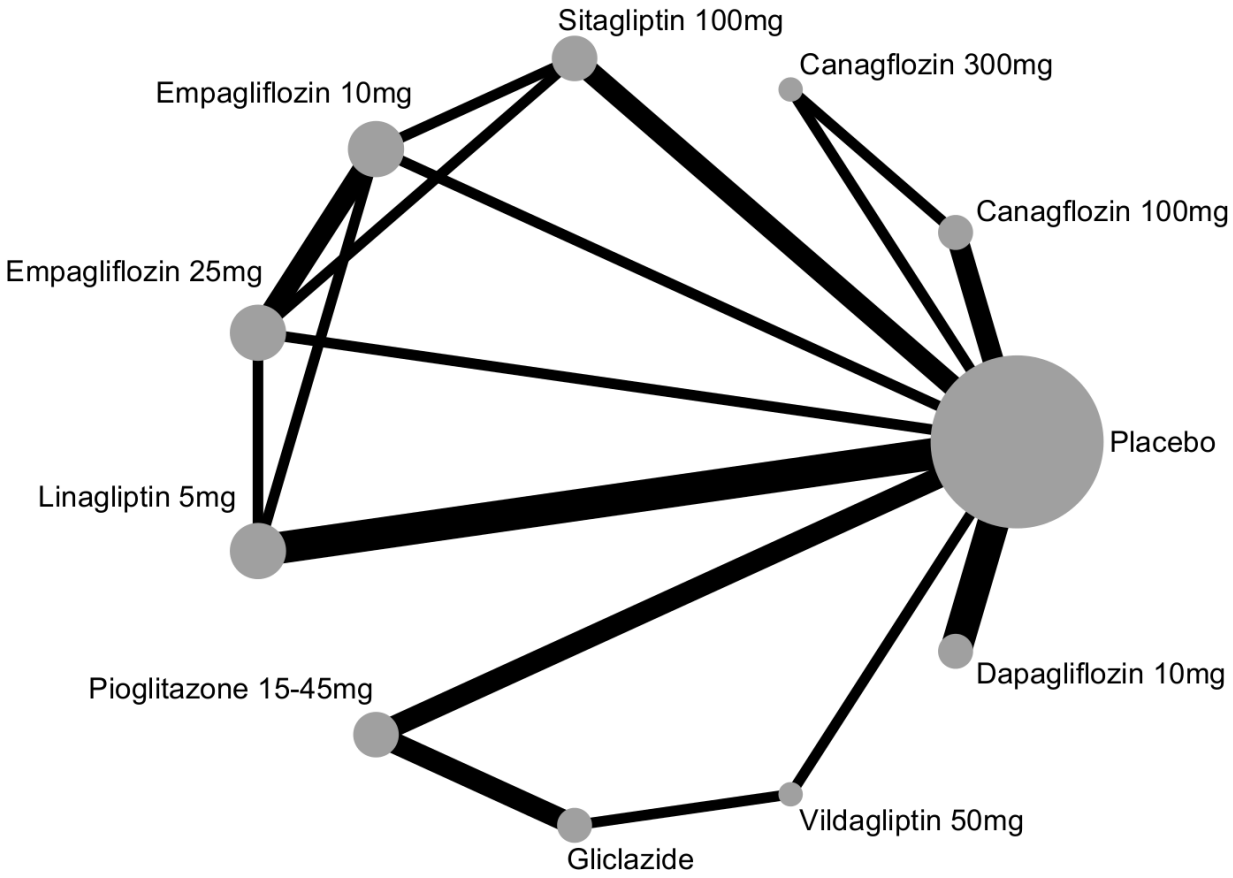

Figure 4 Network plot – glycated haemoglobin (HbA1c)

Figure 5 and Table 9 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in HbA1c (at 24 weeks) from baseline. All SGLT-2 inhibitors were all significantly more effective than placebo in reducing mean change in HbA1c from baseline, with the reduction ranging from -1.19% to -0.59%. Canagliflozin 300mg, pioglitazone and canagliflozin 100mg were significantly more effective in reducing mean change in HbA1c from baseline than linagliptin 5mg, dapagliflozin 10mg and vildagliptin 50mg. The reductions in HbA1c from baseline were similar for linagliptin 5mg and dapagliflozin 10mg. The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for HbA1c.

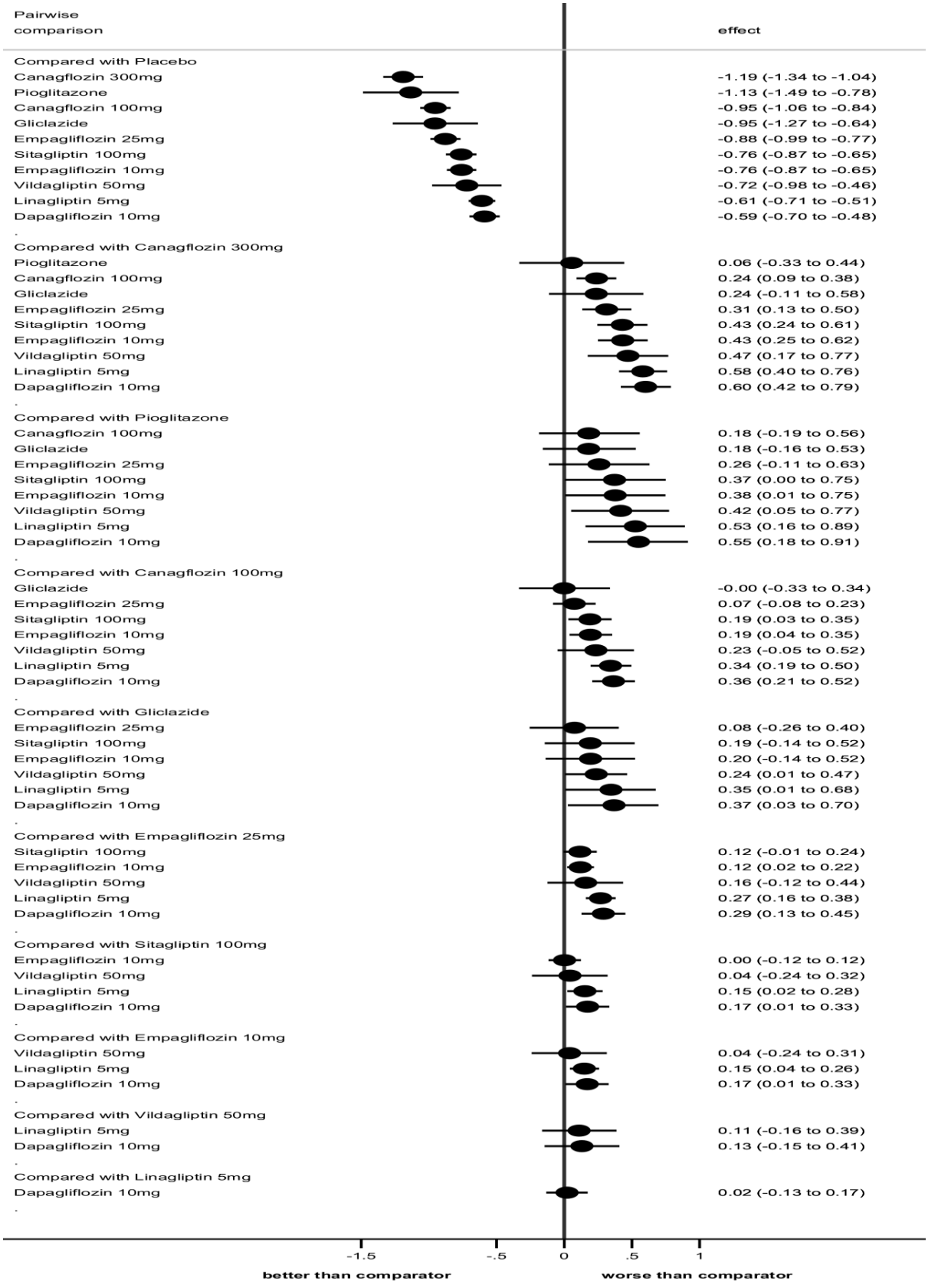

Figure 5 Pairwise comparisons of all drugs for glycated haemoglobin (HbA1c)

Table 9 Pairwise comparisons of all drugs for glycated haemoglobin (HbA1c)

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagliflozin 300mg	-1.19 (-1.34 to -1.04)
Pioglitazone	-1.13 (-1.49 to -0.78)
Canagliflozin 100mg	-0.95 (-1.06 to -0.84)
Gliclazide	-0.95 (-1.27 to -0.64)
Empagliflozin 25mg	-0.88 (-0.99 to -0.77)
Sitagliptin 100mg	-0.76 (-0.87 to -0.65)
Empagliflozin 10mg	-0.76 (-0.87 to -0.65)
Vildagliptin 50mg	-0.72 (-0.98 to -0.46)
Linagliptin 5mg	-0.61 (-0.71 to -0.51)
Dapagliflozin 10mg	-0.59 (-0.70 to -0.48)
Compared with Canagliflozin 300mg	
Pioglitazone	0.06 (-0.33 to 0.44)
Canagliflozin 100mg	0.24 (0.09 to 0.38)
Gliclazide	0.24 (-0.11 to 0.58)
Empagliflozin 25mg	0.31 (0.13 to 0.50)
Sitagliptin 100mg	0.43 (0.24 to 0.61)
Empagliflozin 10mg	0.43 (0.25 to 0.62)
Vildagliptin 50mg	0.47 (0.17 to 0.77)
Linagliptin 5mg	0.58 (0.40 to 0.76)
Dapagliflozin 10mg	0.60 (0.42 to 0.79)
Compared with Pioglitazone	
Canagliflozin 100mg	0.18 (-0.19 to 0.56)
Gliclazide	0.18 (-0.16 to 0.53)
Empagliflozin 25mg	0.26 (-0.11 to 0.63)
Sitagliptin 100mg	0.37 (0.00 to 0.75)
Empagliflozin 10mg	0.38 (0.01 to 0.75)
Vildagliptin 50mg	0.42 (0.05 to 0.77)
Linagliptin 5mg	0.53 (0.16 to 0.89)
Dapagliflozin 10mg	0.55 (0.18 to 0.91)
Compared with Canagliflozin 100mg	
Gliclazide	-0.00 (-0.33 to 0.34)
Empagliflozin 25mg	0.07 (-0.08 to 0.23)
Sitagliptin 100mg	0.19 (0.03 to 0.35)
Empagliflozin 10mg	0.19 (0.04 to 0.35)
Vildagliptin 50mg	0.23 (-0.05 to 0.52)
Linagliptin 5mg	0.34 (0.19 to 0.50)
Dapagliflozin 10mg	0.36 (0.21 to 0.52)
Compared with Gliclazide	
Empagliflozin 25mg	0.08 (-0.26 to 0.40)
Sitagliptin 100mg	0.19 (-0.14 to 0.52)
Empagliflozin 10mg	0.20 (-0.14 to 0.52)
Vildagliptin 50mg	0.24 (0.01 to 0.47)

Pairwise comparison	**Mean difference (95% Credible Intervals)**
Linagliptin 5mg	0.35 (0.01 to 0.68)
Dapagliflozin 10mg	0.37 (0.03 to 0.70)
Compared with Empagliflozin 25mg	
Sitagliptin 100mg	0.12 (-0.01 to 0.24)
Empagliflozin 10mg	0.12 (0.02 to 0.22)
Vildagliptin 50mg	0.16 (-0.12 to 0.44)
Linagliptin 5mg	0.27 (0.16 to 0.38)
Dapagliflozin 10mg	0.29 (0.13 to 0.45)
Compared with Sitagliptin 100mg	
Empagliflozin 10mg	0.00 (-0.12 to 0.12)
Vildagliptin 50mg	0.04 (-0.24 to 0.32)
Linagliptin 5mg	0.15 (0.02 to 0.28)
Dapagliflozin 10mg	0.17 (0.01 to 0.33)
Compared with Empagliflozin 10mg	
Vildagliptin 50mg	0.04 (-0.24 to 0.31)
Linagliptin 5mg	0.15 (0.04 to 0.26)
Dapagliflozin 10mg	0.17 (0.01 to 0.33)
Compared with Vildagliptin 50mg	
Linagliptin 5mg	0.11 (-0.16 to 0.39)
Dapagliflozin 10mg	0.13 (-0.15 to 0.41)
Compared with Linagliptin 5mg	
Dapagliflozin 10mg	0.02 (-0.13 to 0.17)

Weight gain

Networks of eligible comparisons for the weight gain are shown in Figure 6**,** showing predominantly pairwise comparisons of drugs with placebo. There were eleven comparisons (ten active drugs plus placebo).

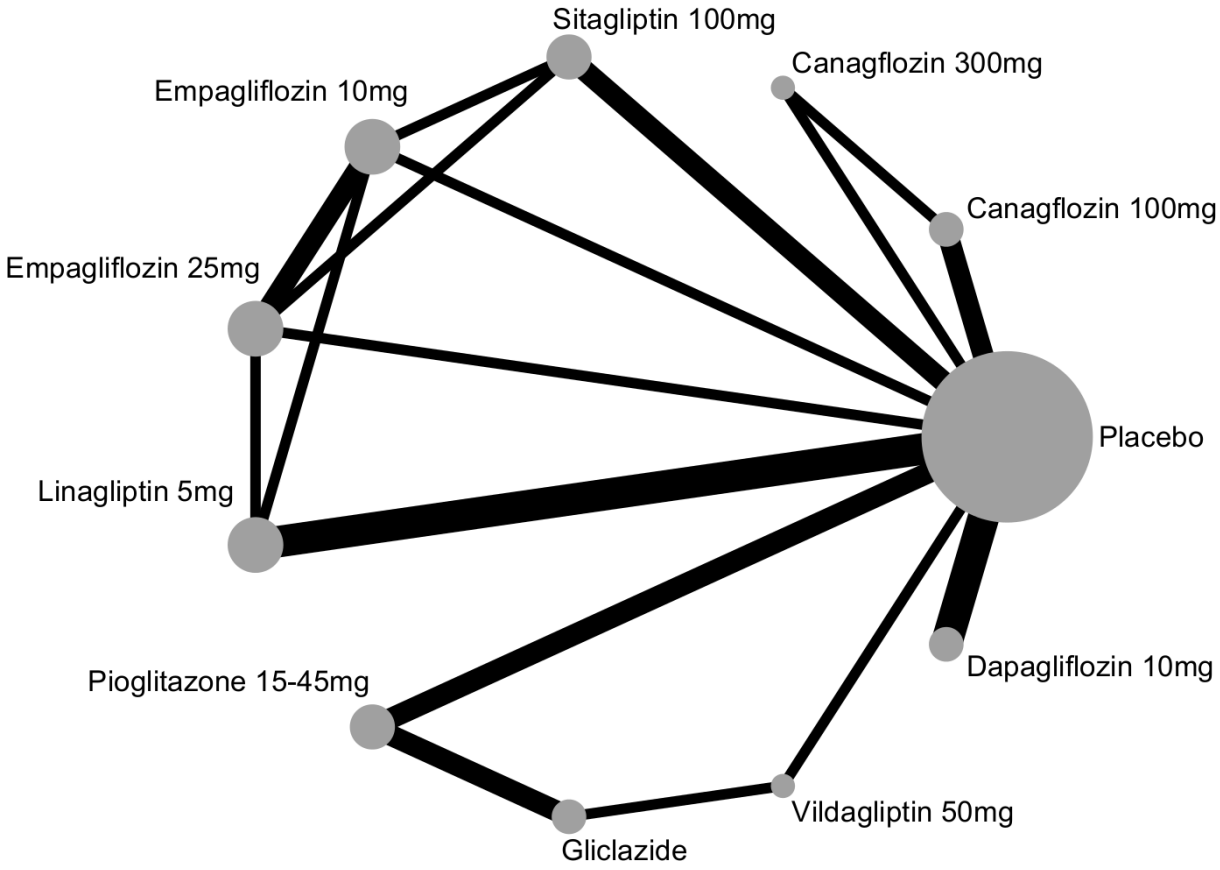

Figure 6 Network plot – weight gain

Figure 7 and Table 10 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in weight gain from baseline. Sitagliptin 100mg, vildagliptin 50mg, gliclazide and pioglitazone were associated with significant weight gain compared with placebo, with the weight gain ranging from 0.74kg to as much as 3.79kg. Compared with placebo, canagliflozin 300mg, canagliflozin 100mg, empagliflozin 25mg, empagliflozin 10mg and dapagliflozin 10mg were associated with significant weight loss, ranging from -2.91kg to -1.58kg. Compared with all other drugs in the network, canagliflozin 300mg was associated with significant weight reduction. The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for weight gain.

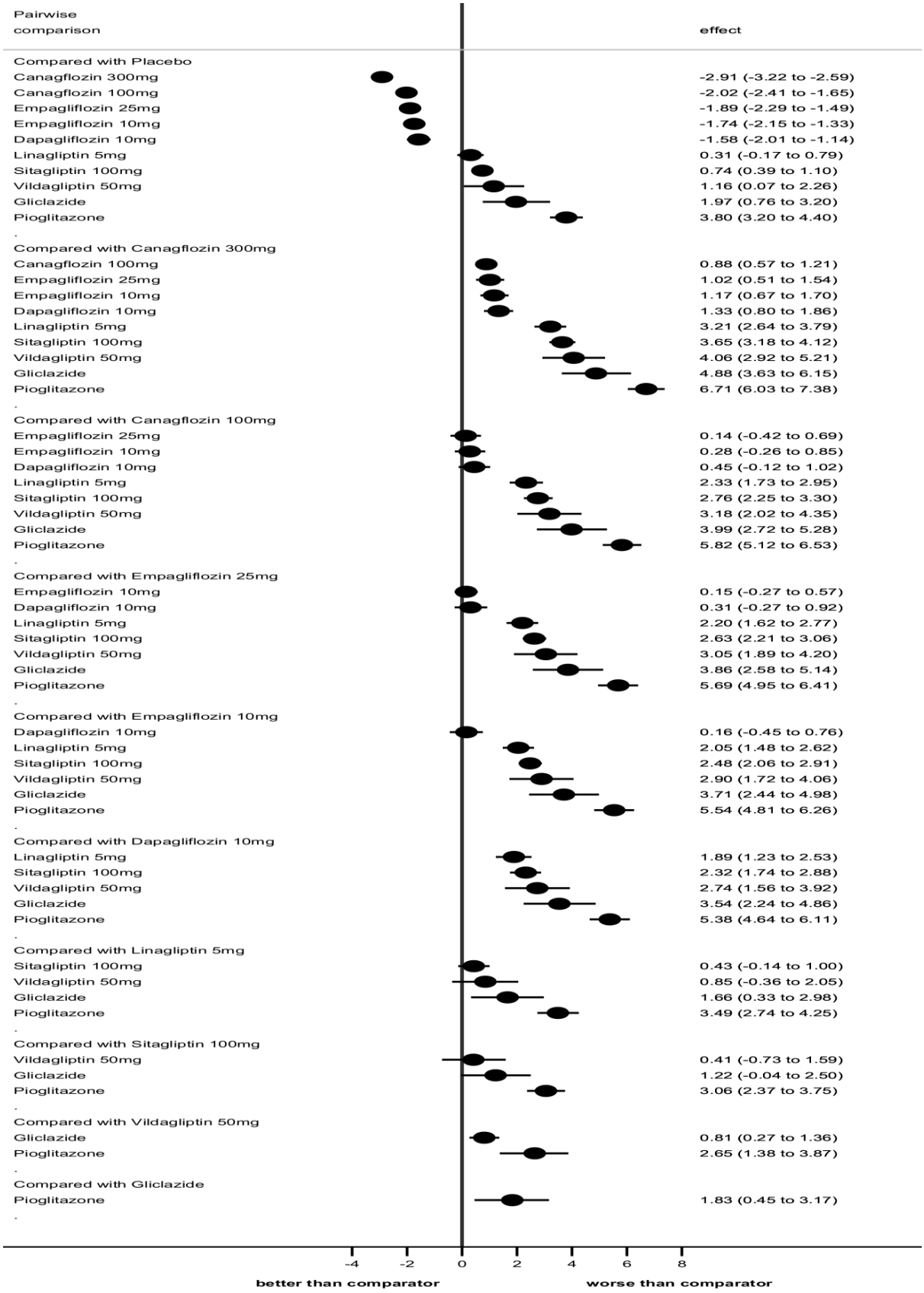

Figure 7 Pairwise comparisons for weight gain

Table 10 Pairwise comparisons of all different flozins for weight gain

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagliflozin 300mg	-2.91 (-3.22 to -2.59)
Canagliflozin 100mg	-2.02 (-2.41 to -1.65)
Empagliflozin 25mg	-1.89 (-2.29 to -1.49)
Empagliflozin 10mg	-1.74 (-2.15 to -1.33)
Dapagliflozin 10mg	-1.58 (-2.01 to -1.14)
Linagliptin 5mg	0.31 (-0.17 to 0.79)
Sitagliptin 100mg	0.74 (0.39 to 1.10)
Vildagliptin 50mg	1.16 (0.07 to 2.26)
Gliclazide	1.97 (0.76 to 3.20)
Pioglitazone	3.80 (3.20 to 4.40)
Compared with Canagliflozin 300mg	
Canagliflozin 100mg	0.88 (0.57 to 1.21)
Empagliflozin 25mg	1.02 (0.51 to 1.54)
Empagliflozin 10mg	1.17 (0.67 to 1.70)
Dapagliflozin 10mg	1.33 (0.80 to 1.86)
Linagliptin 5mg	3.21 (2.64 to 3.79)
Sitagliptin 100mg	3.65 (3.18 to 4.12)
Vildagliptin 50mg	4.06 (2.92 to 5.21)
Gliclazide	4.88 (3.63 to 6.15)
Pioglitazone	6.71 (6.03 to 7.38)
Compared with Canagliflozin 100mg	
Empagliflozin 25mg	0.14 (-0.42 to 0.69)
Empagliflozin 10mg	0.28 (-0.26 to 0.85)
Dapagliflozin 10mg	0.45 (-0.12 to 1.02)
Linagliptin 5mg	2.33 (1.73 to 2.95)
Sitagliptin 100mg	2.76 (2.25 to 3.30)
Vildagliptin 50mg	3.18 (2.02 to 4.35)
Gliclazide	3.99 (2.72 to 5.28)
Pioglitazone	5.82 (5.12 to 6.53)
Compared with Empagliflozin 25mg	
Empagliflozin 10mg	0.15 (-0.27 to 0.57)
Dapagliflozin 10mg	0.31 (-0.27 to 0.92)
Linagliptin 5mg	2.20 (1.62 to 2.77)
Sitagliptin 100mg	2.63 (2.21 to 3.06)
Vildagliptin 50mg	3.05 (1.89 to 4.20)
Gliclazide	3.86 (2.58 to 5.14)
Pioglitazone	5.69 (4.95 to 6.41)
Compared with Empagliflozin 10mg	
Dapagliflozin 10mg	0.16 (-0.45 to 0.76)
Linagliptin 5mg	2.05 (1.48 to 2.62)
Sitagliptin 100mg	2.48 (2.06 to 2.91)
Vildagliptin 50mg	2.90 (1.72 to 4.06)

Pairwise comparison	**Mean difference (95% Credible Intervals)**
Gliclazide	3.71 (2.44 to 4.98)
Pioglitazone	5.54 (4.81 to 6.26)
Compared with Dapagliflozin 10mg	
Linagliptin 5mg	1.89 (1.23 to 2.53)
Sitagliptin 100mg	2.32 (1.74 to 2.88)
Vildagliptin 50mg	2.74 (1.56 to 3.92)
Gliclazide	3.54 (2.24 to 4.86)
Pioglitazone	5.38 (4.64 to 6.11)
Compared with Linagliptin 5mg	
Sitagliptin 100mg	0.43 (-0.14 to 1.00)
Vildagliptin 50mg	0.85 (-0.36 to 2.05)
Gliclazide	1.66 (0.33 to 2.98)
Pioglitazone	3.49 (2.74 to 4.25)
Compared with Sitagliptin 100mg	
Vildagliptin 50mg	0.41 (-0.73 to 1.59)
Gliclazide	1.22 (-0.04 to 2.50)
Pioglitazone	3.06 (2.37 to 3.75)
Compared with Vildagliptin 50mg	
Gliclazide	0.81 (0.27 to 1.36)
Pioglitazone	2.65 (1.38 to 3.87)
Compared with Gliclazide	
Pioglitazone	1.83 (0.45 to 3.17)

Systolic blood pressure

Networks of eligible comparisons for the systolic blood pressure are shown in Figure 8, showing predominantly pairwise comparisons of drugs with placebo. There were seven comparisons.

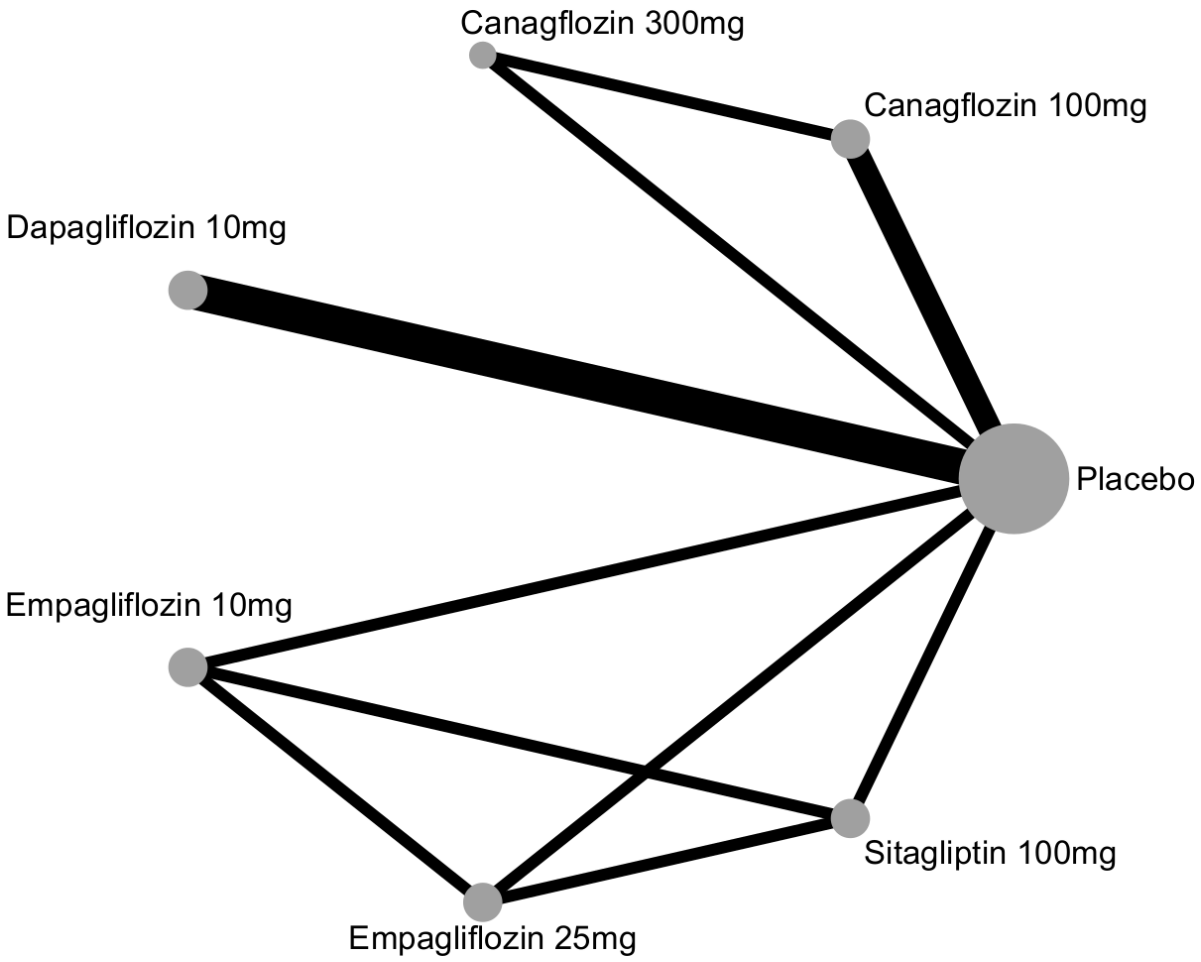

Figure 8 Network plot – systolic blood pressure

Figure 9 and Table 11 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in systolic blood pressure from baseline. Canagliflozin 100mg, empagliflozin 25mg, dapagliflozin 10mg and empagliflozin 10mg were significantly effective in reducing mean change in systolic blood pressure from baseline compared to placebo and sitagliptin 100mg. Canagliflozin 100mg gave the largest reduction in mean change in systolic blood pressure from baseline compared with placebo (-4.22 mmHG). The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for systolic blood pressure.

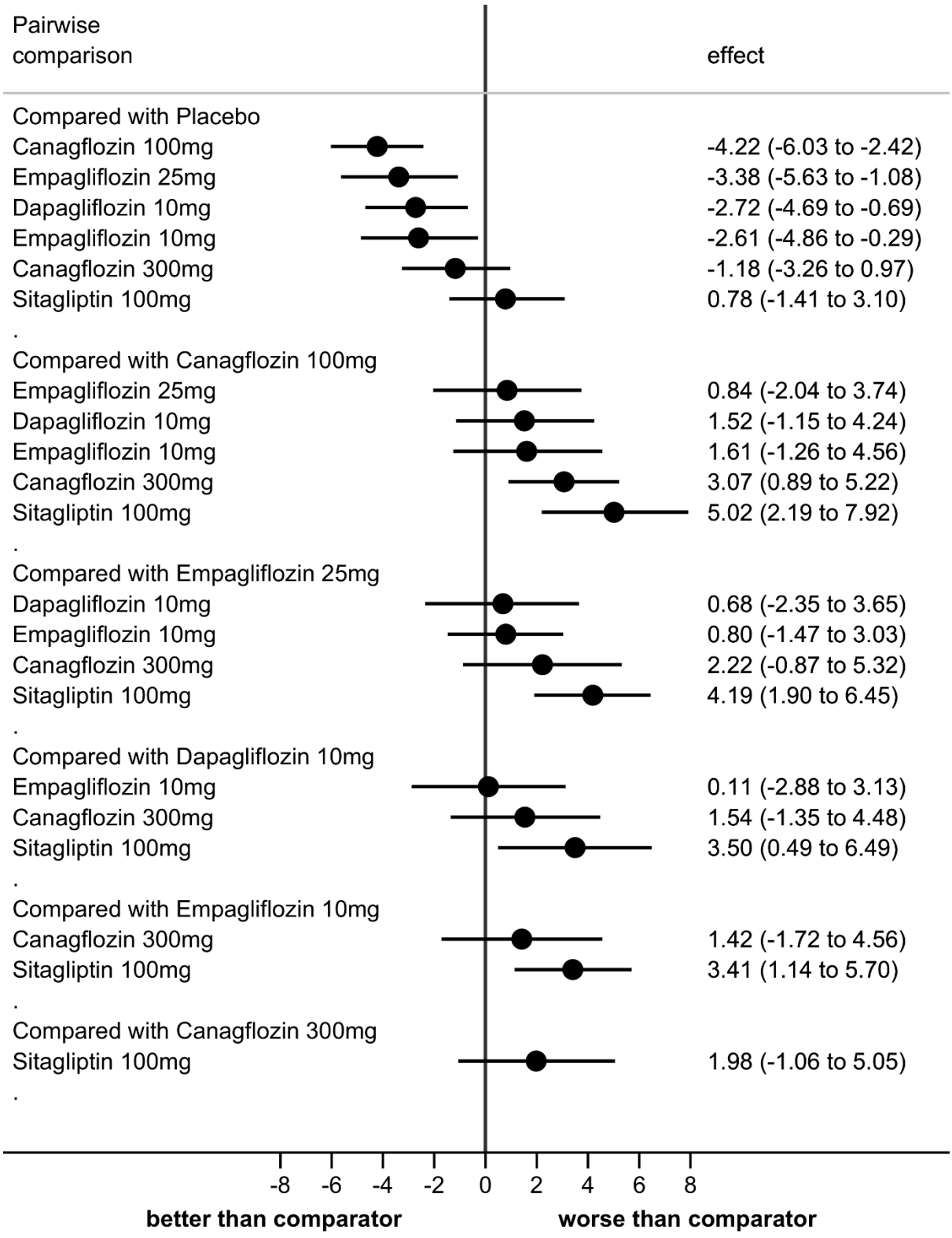

Figure 9 Pairwise comparisons for systolic blood pressure

Table 11 Pairwise comparisons for systolic blood pressure

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagflozin 100mg	-4.22 (-6.03 to -2.42)
Empagliflozin 25mg	-3.38 (-5.63 to -1.08)
Dapagliflozin 10mg	-2.72 (-4.69 to -0.69)
Empagliflozin 10mg	-2.61 (-4.86 to -0.29)
Canagflozin 300mg	-1.18 (-3.26 to 0.97)
Sitagliptin 100mg	0.78 (-1.41 to 3.10)
Compared with Canagflozin 100mg	
Empagliflozin 25mg	0.84 (-2.04 to 3.74)
Dapagliflozin 10mg	1.52 (-1.15 to 4.24)
Empagliflozin 10mg	1.61 (-1.26 to 4.56)
Canagflozin 300mg	3.07 (0.89 to 5.22)
Sitagliptin 100mg	5.02 (2.19 to 7.92)
Compared with Empagliflozin 25mg	
Dapagliflozin 10mg	0.68 (-2.35 to 3.65)
Empagliflozin 10mg	0.80 (-1.47 to 3.03)
Canagflozin 300mg	2.22 (-0.87 to 5.32)
Sitagliptin 100mg	4.19 (1.90 to 6.45)
Compared with Dapagliflozin 10mg	
Empagliflozin 10mg	0.11 (-2.88 to 3.13)
Canagflozin 300mg	1.54 (-1.35 to 4.48)
Sitagliptin 100mg	3.50 (0.49 to 6.49)
Compared with Empagliflozin 10mg	
Canagflozin 300mg	1.42 (-1.72 to 4.56)
Sitagliptin 100mg	3.41 (1.14 to 5.70)
Compared with Canagflozin 300mg	
Sitagliptin 100mg	1.98 (-1.06 to 5.05)

One question was whether canagliflozin is more potent than other SGLT-2 inhibitors, due to its dual effect on SGLT-2 and SGLT-1 receptors. In monotherapy, both doses of canagliflozin lowered HbA1c slightly more than both doses of empagliflozin, which does not have a significant effect on SGLT-1 receptors. Nor does canagliflozin 100mg. This suggests that the SGLT-1 effect does not explain all the differences in HbA1c results. It may explain some of the difference between the two doses of canagliflozin, or it may not be clinically significant.

However, irrespective of the mechanism, one finding is that canagliflozin 300mg does have a greater effect on HbA1c than dapagliflozin and empagliflozin. Indeed, the 100mg dose also has a clinically significantly greater reduction in HbA1c than dapagliflozin 10mg (but see caveats to follow).

Table 12 compares the effects and adverse effects of the two doses of canagliflozin, with effects taken from our NMA and AEs from the published studies. Effects are compared to placebo. However, we do not know whether the reduction seen with canagliflozin 300mg in the trials would be as great in patients who responded insufficiently to the 100mg dose.

Table 12 Effects of canagliflozin dosages

	Canagliflozin 100	Canagliflozin 300mg	difference
HbA1c reduction	0.95%	1.19%	0.26%
Weight reduction	2.02kg	2.91kg	0.89kg
SBP reduction	4.2mmHg	1.2 mmHg	3 mmHg
UTIs by 12 months	8.2%	7.1%	No sig diff
GTIs by 12 months	9.2%	9.1%	
Volume depletion AEs	1.5%	2.0%	
Diuresis AEs	4.6%	7.6%	
Reported hypos by 12 months	5.1%	3.6%	Placebo rate 2.6%

If in patients in whom an SGLT2 inhibitor is considered the appropriate choice, it is considered worth trying canagliflozin 300 mg if the 100mg dose does not have enough effect, it would be logical to also try canagliflozin 300mg if dapagliflozin or empagliflozin are insufficiently effective. The licence implies that they would have to switch to canagliflozin 100mg first, if only briefly. However the same caveat would apply – the HbA1c reduction seen with canagliflozin 300mg might be less amongst patients who have not responded sufficiently to starting doses.

Table 13 shows that the differences in effects of the two empagliflozin doses are slight, using figures from the Roden and Lewin trials.[78-80]

Table 13 Effects of empagliflozin dosages

	Empagliflozin 10mg		Empagliflozin 25mg	difference
HbA1c reduction	0.66 and 0.83		0.78 and 0.95	0.12
Weight reduction	2.2 and 2.3		2.4 and 2.5	0.2kg
SBP reduction	2.1mm HG		3.7	1.6
UTIs by 12 months	16.3%		10.4%	5.9% in favour of 25mg
GTIs by 12 months	5.2%		4.4%	0.8%

Again, a caveat is required. Those who do not respond to empagliflozin 10mg may not achieve as great a reduction in HbA1c after increasing to 25mg daily, as in the table above. The differences are in any case, mostly not clinically meaningful.

In the NMA reported here, dapagliflozin reduced HbA1c significantly less than canagliflozin 100mg, but it should be noted that the Kaku 2014 trial[77] of dapagliflozin recruited patients with mean baseline HbA1c of 7.5%**,** whereas most trials had baseline HbA1c of around 8%.To summarise, the placebo adjusted HbA1c reductions in the trials at 24-26 weeks were, for the starting dosages;

Canagliflozin 100mg

CANTATA[72] 0.91%

Inagaki[73] 1.03%

Dapagliflozin 10mg

Ferrannini[74, 75] 0.66%

Ji[76] 0.82%

Kaku[77] 0.39%

Empagliflozin

Roden[79, 80] 10mg 0.74%

Hence the Kaku trial, while qualifying for our NMA based on the baseline HbA1c of 7.5%, will be reducing the mean effect of dapagliflozin.
When interpreting weight changes, the baseline BMIs need to be considered. The trials in China and Japan recruited people with BMIs in the 25-26 range, whereas the European trials had mean BMIs ranging from 28 to almost 34. The pattern of type 2 diabetes differs in East Asians, with lower BMI and a more insulin-secretory defect.[162] This does not apply to South Asians (Indian subcontinent) in whom insulin-resistance is more important.

Another factor to be considered in interpretation is that in the dapagliflozin trials, HbA1c fell in the placebo groups, by 0.29% and 0.23% in the Ji and Ferrannini trials. In the Ferranni trial, weight fell significantly, by 2.2kg. In the placebo groups in the canagliflozin trials, HbA1c rose by 0.29% (Inagaki) and 0.14% (Stenlof CANTATA-M). Ferranini and colleagues[74] (and the AstraZeneca submission, which talks of a "motivated placebo group" on page 58) suggested that the reduction in HbA1c in the placebo group might have been due to improved adherence to lifestyle advice in that group, but since the placebo tablets matched the dapagliflozin ones, this seems unlikely.

Problems with evidence and effect sizes for modelling.

This review has encountered a number of problems.

Many trials provided data on only some of the variables which are used in the UKPDS Outcomes model. For example, SBP changes were often not reported. This applied more to older trials of comparators than to the more recent trials of the SGLT2 inhibitors.

Some trials provided no data with which to calculate TC:HDL ratio. However a more important problem is that when TC levels were reported, they were often high, giving quite high TC:HDL-C ratios. It is likely that greater use of statins renders such data obsolete. For our modelling, we will assume that all GPs and diabetologists follow NICE guidance and are using atorvastatin 20mg for primary prevention in all people with type 2 diabetes. This will produce a TC:HDL ratio of about 3.0.

Another problem is with effect sizes after intensifications. For example, there are reviews of the effects on HbA1c and weight of sulfonylureas when added to monotherapy, but the bulk of evidence is addition to metformin monotherapy. The weight gain after adding gliclazide to a SGLT2 inhibitor may be different – it may only restore weight to the baseline before weight loss on the flozin. And the weight gain after adding gliclazide to pioglitazone may be less because pioglitazone itself causes weight gain.

In passing, it is worth noting that the weight gains in trials may be greater than in routine primary care. De Fine Olivarius and colleagues[163] reported that 330 patients did not gain weight after starting sulfonylureas. They make the point that most patients with type 2 diabetes are treated in primary care and are seldom recruited to trials. And that trials may therefore not be generalizable to all patients.

As regards reductions in adding sulfonylurea to monotherapy, some reviews report that adding a sulfonylurea to metformin results in a reduction in HbA1c of around 1%. However the size of the reduction will depend on the HbA1c level on metformin alone. Genuth quotes a reduction of 1% from a baseline of 8.3%.[164] This may be a bigger reduction than would be seen in people who have just crept over the NICE switching threshold of 7.5%.

In the same review, Genuth reports that pioglitazone added to metformin reduces HbA1c by 1.0%, and a DPP4 inhibitor does so by 0.7%.

Hirst et al produced a good quality systematic review and meta-analysis in which they examined reductions in HbA1c after starting sulfonylureas in dual therapy.[165] Sulfonylureas (glibenclamide, glipizide and glimepiride) reduced HbA1c by 0.95% on average but with considerable heterogeneity – reductions ranged from 0.47% to1.3%. They found little variation in HbA1c reductions by baseline HbA1c but most of those baselines were well above 8%, ranging from 7.5% to 9.5%. The only trial with baseline HbA1c under 8.4%, had starting HbA1c of 7.5%, and that was the trial by Feinglos and colleagues[166] which showed a reduction of only 0.47%. This trial is closest to what we would expect in care as recommended by the NICE guideline, and with baseline HbA1c of 7.5%, the reduction in HbA1c of 0.47% would be sufficient to improve HbA1c to around 7.0% and would be seen as a reasonable result.

One problem with the review by Hirst et al was that most trials were short term. A very useful observational study by Cook and colleagues[167] used data on 2,220 patients from the UK General Practice Research Database (GPRD) to study glycaemic control over time after a sulfonylurea was added to metformin, because of poor glycaemic control, with median HbA1c 8.8%. There was a prompt reduction to median of 7.3% after six months of sulfonylurea, but thereafter, HbA1c started rising again, by 0.32% between months 6 and 12. Half the patients had HbA1c of 8.0% or over by one year of starting sulfonylureas.

Cook and colleagues also noted that intensification of treatment was often delayed till HbA1c is over 9%. However their data were from 1998 to 2004 and may no longer apply. Neverthless the large drops often reported after sulfonylureas are started may be because of very poor control, and we should not expect such large reductions in HbA1c in carefully monitored patients who have only recently gone above the NICE switching threshold of 7.5%.

In a trial comparing dapagliflozin with glipizide as add-ons to metformin, and with baseline HbA1c of about 7.7%, the reductions in HbA1c by week 52 were 0.50% on dapagliflozin and 0.48% on glipizide.[168]

The durability issue with sulfonylureas has been reported by several studies, of which the best known may be the ADOPT trial[169] in which time to monotherapy failure was longer with rosiglitazone and metformin than with glibenclamide, with 34% of the glibenclamide patients needing additional treatment by 5 years compared to only 15% of those on rosiglitazone.

Del Prato and colleagues[168] looked at duration of effect of dapagliflozin and glipizide in dual therapy when added to metformin. HbA1c fell more rapidly, and further on glipizide, but then rose again more quickly. So at about 12 weeks, the falls were (from graph) about 0.8% on glipizide and 0.5% on

dapagliflozin, but by 52 weeks the curves had met at reductions of about 0.5%, though about 20% of patients were absent by that time point. After 52 weeks, HbA1c rose on both drugs, but more on glipizide, with a gap of 0.30% by 208 months. However the numbers by that time-point were low – 20% of the dapagliflozin group and 18% of the glipizide group. The reductions were due to patients starting rescue therapy after HbA1c rose. Rescue was mandatory once HbA1c reached 8.0% or more, and was at the investigators discretion between 7.0 and 8.0%. So similar proportions in each group had to move to rescue therapy, implying no difference in durability.

There is a 2015 abstract by Bacon et al[170] from Janssen comparing time until insulin is started between canagliflozin and dapagliflozin, when used in dual or triple therapy. It also used the ECHO-T2DM model. In triple therapy, the authors report insulin being started on average at 5.1 years with canagliflozin (starting with 100mg daily and increasing as required to 300 mg) compared to 3.3 years with dapagliflozin. Insulin was started when HbA1c exceeded 7.5%.

For the effects of adding sitagliptin we have two useful trials with HbA1c baseline 7.7 and 7.8% which reported reductions in HbA1c of 0.67% and 0.79% (Scott 2007, Nauck 2007) giving a mean of 0.73%.

A recent report from CADTH (Appendix of CADTH report)[171] concludes that pioglitazone added to monotherapy reduces HbA1c by 0.78%. It also gives the reduction with DPP4 inhibitors as a mean of 0.7% .

At intensification to triple therapy, one option would be to introduce a long-acting GLP-1 analogue. NICE has so far only approved exenatide LA for this purpose, but there are now other drugs in this group, including dulaglutide and albiglutide.

In the DURATION 1 trial[172], Drucker and colleagues compared exenatide LA with the short-acting twice daily form. Patients were on a mixture of baseline treatments with only 38% on dual therapy. However reductions in HbA1c were reported to be similar across baseline treatment groups. On exenatide LA, HbA1c fell by 1.9% from a baseline of 8.3%, with 60% of patients getting HbA1c under 6.5%. The advantages of using a GLP-1 analogue, compared to insulin, are the once weekly injection, weight loss (in DURATION 1 weight fell by 3.7kg on exenatide LA), a low risk of hypoglycaemia (there were no severe hypos in DURATION 1 and minor hypos were seen only in patients on sulfonylurea), and some reduction in SBP (4.7mmHg). Another advantage of adding a GLP-1 analogue to treatment with an SGLT2 inhibitor is that the latter increases plasma glucagon levels which would be suppressed by the former, though if triple therapy includes a sulfonylurea such as gliclazide, glucagon secretion may already be suppressed.[173]

Chapter 4. Clinical effectiveness aspects of the submissions from the manufacturers.

Three submissions were received, from;

- Janssen for canagliflozin
- AstraZeneca for dapagliflozin
- Boehringer Ingelheim for empagliflozin

The submissions had three main sections;

- A review of the evidence on clinical effectiveness and safety
- A network meta-analysis comparing SGLT2 inhibitors with comparators
- Cost-effectiveness analysis

Clinical effectiveness

As regards clinical effectiveness, the evidence provided by the manufacturers was very similar to that presented earlier in this report. The same trials were presented. The submissions were good quality and we have very few comments.

The Janssen submission included 52-week results from an extension to the CANTATA-M study[87], which we omitted because there was no comparison group. In brief, the 52-week data showed that the reductions in HbA1c were largely maintained (reductions on 100mg 0.91% at 26 weeks and 0.81% at 52 weeks; reductions on 300mg 1.16% at 26 weeks and 1.11% at 52 weeks). However a little more weight was lost by 52 weeks.

The Boehringer submission included data from a 76 week extension study which had been published in abstract form only.[79] Almost 40% of patients dropped out leading to extensive use of last observation carried forwards, which is not a reliable method because people do not drop out at random. It is likely that those who stayed in were doing better than those who dropped out.

The Boehringer submission make a useful point about adherence to therapy. This would apply not just to diabetes medications. People with diabetes tend to have co-morbidities such as hypertension and osteoarthritis (due to excess weight) and so may be on other medications for other conditions. Donnan and colleagues reported that the more medications were prescribed and the more complex the regiment, the poorer the compliance.[174]. Lilly now market a combination tablet with empagliflozin and linagliptin.

One omission from the AstraZeneca submission was any mention of cancer risk. The FDA were concerned about imbalance of breast, prostate and bladder cancer even though in none of these cases was the risk statistically significantly raised.[175] In the trials, there were 9 cases of bladder cancer amongst 5501 subjects in the dapagliflozin group versus one amongst 3516 in the placebo arms. Some of these cancers appeared too soon after the patients started dapagliflozin for credible causality and all but one of the patients had had microscopic haematuria, suggestive of bladder pathology, before starting the drug or within six months of doing so.[176] One hypothesis is that an increased UTI rate in patients on dapagliflozin leads to increased testing or urine and hence of detection of bladder tumours, but 7 of the 10 patients diagnosed with bladder cancer had not had UTIs.[176]

Breast cancer was observed in 9 patients (0.04% of female patients) in the dapagliflozin arms but in none of the placebo groups. However two cases were diagnosed within 6 weeks of starting dapagliflozin so were certainly not due to the drug.

There were 10 cases of prostate cancer in the dapagliflozin arms (0.34%) versus 3 in the placebo arms (0.16%).

Some cancers, albeit less common ones, were less common (though 95% CIs overlapped with no difference) in the dapagliflozin groups, and overall there was no difference in rates for all cancers.
It is difficult to explain the differences in bladder and breast cancer, but it seems unlikely that dapagliflozin is the cause.

Network meta-analyses

There were marked differences amongst the NMAs. For example, the AstraZeneca one included 7 trials of sulfonylureas, with five involving glibenclamide. The Janssen one included 9 trials of sulfonylureas, with 5 trials comparing glibenclamide with other sulfonylureas and two of glibenclamide against pioglitazone. Only one trial was in both NMAs.
The Boehringer NMA included 22 trials involving sulfonylureas: glibenclamide 7, glimepiride 6, gliclazide 6, glipizide 3 and tolbutamide one.
Of the 7 sulfonylurea trials in the AstraZeneca NMA, 4 were also in the Boehringer NMA. Of the 9 sulfonylurea trials in the Janssen NMA three were also in the Boehringer NMA. Only one trial was in all three of the manufacturers' NMAs.

AstraZeneca

The Astrazeneca NMA starts with a major assumption with which the Assessment Group disagrees, which is that the classes of drugs (sulfonylureas, thiazolidinediones, DPP4 inhibitors and SLT2

inhibitors) can be grouped. In the case of the thiazolidinediones (TZDs), this does not matter because all the trials cited include pioglitazone. However our view is that the sulfonylureas have different effects, and that gliclazide is the sulfonylurea of choice, as explained in chapter 1.

We also disagree with the assumption by AstraZeneca that when monotherapy fails, NPH insulin would be started. This seems strange when there is such a range of oral medications that can be tried. We note that a recommendation to introduce insulin as second drug was one option in the consensus statement by a group on behalf of the American Diabetes Association and the European Association for the Study of Diabetes in 2006.[177] However this consensus was strongly critised by a larger group of experts as being based more on opinion that evidence.[178]

One problem with the AstraZeneca NMA is the data reported in the forest plot (Figure 4.6) for the pooled sulfonylureas, which include glibenclamide, glimepride, glipizide and one gliclazide trial. The net effect size in HbA1c lowering is 0.12% which is unusually low. Two trials provide 85% of the weight in this meta-analysis, Rosenstock 2013[179] and Shihara 2011.[180] In the forest plot the Shihara trial, glimepiride is shown as reducing HbA1c by 0.10%, and in the Rosenstock trial glipizide is shown as increasing HbA1c by 0.03%. These results are not credible.

In the Rosenstock trial[179], about half the patients left the trial before conclusion, with 21.5% of the glipizide group doing so because they needed additional "rescue" treatment because of hyperglycaemia. About half the recruits had been on glucose-lowering drugs before entry, and had a 4-week washout period. However the primary analysis included the rescued patients and this is reflected in the one of the analyses, which reported a 0.09% reduction in HbA1c. (It is not clear where the rise of 0.03% in the AstraZeneca forest plot comes from.) The baseline HbA1c in the glipizide group was 7.45%, and 33% had baseline HbA1c of 7.0% or less. So a large reduction in HbA1c would not be expected. However if the rescue group is removed, those completing the trial had mean reduction in HbA1c of 0.31% (from text) or about 0.5% (from graph).

The Shihara 2011 trial[180] compared glimepiride and pioglitazone monotherapy in drug-naïve Japanese patients. Basline HbA1c was 7.8% in the glimepiride group and it fell to 6.8% by 6 months (from graph – reduction of 6.9% in text at 3 months). It is not clear where the 0.1% figure used in the AstraZeneca meta-analysis comes from, though we note that the HbA1c difference between glimepiride and pioglitazone at 3 months as 0.1%.

One other sulfonylurea trial in the forest plot is shown as having a very small reduction in HbA1c. This is Erem 2014[152], which was used in the Assessment Group NMA. The AstraZeneca forest plot reports a reduction in HbA1c of 0.14% compared to placebo. There was no placebo group in Erem

2014 which compared gliclazide with pioglitazone and metformin. The HbA1c was reduced from 8.26% at baseline in the gliclazide group to 6.92% at 6 months, so a more credible reduction against placebo might have been to use the 1.34% before and after figure.

Given that these Rosenstock and Shihara trials dominate the meta-analysis, the sulfonylurea section of it is not credible. It contains 8 trials but the others are smaller and carry less weight. Apart from the Erem trial, their HbA1c results in the other five are as expected from sulfonylureas, showing reductions ranging from 0.6% to 1.8%.

However, these problems may just affect the forest plot. In appendix 8.9, the reduction attributed to glipizide in the Rosenstock trial is 0.23%, still smaller than usual but more credible. The reduction stated in this table for glimepiride in the Shihara trial is 1.0%. In addition, the caterpillar figure 8.9 in the appendices looks reasonable and is followed by a reported difference for sulfonylureas versus placebo of 0.80% in Table 8.21.

Table 4.4 in the AstraZeneca NMA gives a reduction in HbA1c of 0.99% with sulfonylureas, compared to placebo. In the modelling a figure of -0.95% is used, which corresponds with both of the submitted AstraZeneca models and table 5.3 of their submission. So the forest plot figures are a minor mishap which does not affect the AZ modelling.

Review of statistical methods

Model type: The MS estimated both fixed- and random-effects meta-analyses for the continuous and count based outcome measures. It used the Deviance Information Criterion (DIC) to assess model fit, with at least a 3 point change signifying an improved model. Also, the MS compared the posterior distribution of between study standard deviations with the prior distributions to assess whether it was updated by the available evidence (i.e. the additional information had had an effect). Random-effects models were fitted first, as they were considered *a priori* as the appropriate model. Fixed–effects models were only selected if they significantly improved model fit as demonstrated by DIC and changes to the posterior distribution of between study standard deviations. Clinical and statistical heterogeneity were assessed through an evaluation of sources and the I^2 statistic for pairwise comparisons respectively. Heterogeneity was examined through a sensitivity analysis using meta-regression to adjust for the effects of baseline HbA_{1c}. Consistency was also assessed through a comparison of the direct and indirect evidence using pairwise meta-analyses of the active treatments versus placebo for the outcome of HbA_{1c} only. The overall modelling strategy used in the MS seemed appropriate.

Distributions & Priors: The MS undertook Bayesian Markov Chain Monte Carlo (MCMC) network meta-analyses for continuous and count based outcome measures. It specifies that vague priors were used for unknown parameters, however no details were provided as to the distributions or link functions used in the models. Vague priors are usually specified, however there are occasions when other priors should be assessed to establish the possible effects on the posterior estimates (e.g. binomial model with a logit link function or a rate model with log link function (where a uniform prior is used for the standard deviation) or where data are sparse and the model fails to converge (where vague gamma priors are used for precision)). No sensitivity analyses assessing the effects of different distributions, link functions or priors were presented. As the treatments considered in the network meta-analyses were assessed by class, this may be less of a concern. The MS reports that MCMC models were run using 3 chains starting from different values of the unknown parameters, used a burn in of ≥20,000 iterations, an update of ≥100,000 iterations and a parameter thin of 10. Convergence was assessed using history plots of the chains for the relevant parameters (overlapping histories indicating convergence) and a Monte Carlo error for each parameter (error of ≤5% of posterior standard deviation indicating convergence). No assessment is reported regarding the influence of autocorrelation. The approach taken in the MS to MCMC models appears appropriate.

Interventions: The MS performed network meta-analyses on classes of treatments (i.e. SGLT2s, DPP4s, SUs, TZDs), rather than comparing individual treatments. Such 'lumping' of evidence is a concern as regards the assumption of consistency, leading to heterogeneity, difficulties in interpreting results and potential conflict between the direct and indirect evidence. The MS states that the rationale for considering the treatments as a class was due to the limited evidence base for some treatments, that previous NICE clinical guidelines had indicated that they could be considered as a class and that heterogeneity among some individual studies in terms of study characteristics within a class of treatments meant that comparison of individual studies may be affected by a risk of bias. The MS should have considered a network meta-analysis of individual treatments as well as presenting one of class effects. This would have shown results similar to the Assessment Group NMA, where dapagliflozin has slightly less effect than empagliflozin 10mg and canagliflozin 100mg, the other starting doses. Although it is not clear which treatment was the reference treatment in the network meta-analyses, results are presented for comparisons of the treatment classes with both placebo and SGLT2 only.

Outcomes: Continuous outcomes of mean change from baseline in HbA_{1c}, weight and SBP (mean difference scale) and count based outcomes of proportion of patients experiencing hypoglycaemia (odds ratios) were used in the network meta-analysis. Although data for the continuous outcomes was for ITT population using LOCF, any missing data were based on estimates from the primary study. Data time points ranged from 18 to 30 weeks.

Participants: Comparison of the baseline characteristics of the 32 studies showed variability. Although the MS stated that the trials were generally similar in baseline characteristics, it identified that 9 RCTs were conducted only in Asian patients, 1 RCT had a higher mean age, 1 RCT had a higher mean baseline HbA_{1c}, 8 RCTs had higher mean baseline weights and that average duration of diabetes and baseline BMI varied. It should be noted that the included studies were conducted between 1994 and 2014 with study duration ranged from 18 to 102 weeks. Although the effects of baseline HbA_{1c} was assessed through meta-regression and those associated with the Asian only studies through exclusion of the studies in a sensitivity analysis, possible heterogeneity associated with the other factors was not considered further.

Evidence networks: The MS presents network diagrams of the decision space for the classes of treatment. It is not clear the number of RCTs linking each treatment class and subsequent Forrest plots are presented for comparisons with placebo only. It is difficult to judge whether sparse evidence networks or zero values were a concern, although the 'lumping' of evidence into treatment classes may well have overcome this issue. It is also unclear which treatment was used as the reference treatment.

Summary: The MS clearly specified the approach it had taken to the majority of the elements of its network meta-analyses. It lacked details concerning the prior distributions and link functions used, its assessment of autocorrelation in MCMC models and sensitivity analyses concerning the elements of the models themselves (e.g. prior distributions, link functions and priors for parameters). Although it assessed some possible causes of heterogeneity, others were not considered (e.g. participant characteristics, length of study follow-up). It appropriately examined consistency of the outcomes from the network meta-analyses. The MS identified several limitations underlying its analysis, including high placebo effects associated with the assessment of body weight in a dapagliflozin monotherapy study and a study focusing on Asian patients, a lack of evidence on specific patient groups (i.e. metformin intolerant), limited duration of follow-up, different definitions of hypoglycaemia and inconsistent reporting of safety outcomes. However, the key limitation that affects the network meta-analysis is the lack of evidence on individual treatments. As a result, the MS 'lumps' together the evidence by treatment class. This can cause concerns with regards to the assumption of consistency, lead to heterogeneity, difficulties in interpreting results and potential conflict between the direct and indirect evidence.

Boehringer Ingelheim

The Boehringer NMA is shaded as confidential. It was very complex and included 37 studies, including some which the Assessment Group rejected for our NMA. All the sulfonylureas trials were

pooled into one node, which we think is undesirable given the mix of drugs from tolbutamide to gliclazide. The NMA includes both the Saleem 2011 and Jibran 2006 trials with their striking similarities.

Review of statistical methods for NMA for Empagliflozin (Jardiance) – Boehringer Ingelheim

Model type: The MS correctly used both fixed- and random- effects meta-analyses to assess the continuous and count based outcome variables. It also used hierarchical Bayesian regression modelling for analysing the continuous outcomes, assumed to be due to the different ways in which the continuous outcomes are reported (e.g. change from baseline per treatment (arm level data) and change from baseline compared to a reference treatment (study level data)), although this was not clearly stated. Meta-regression models were fitted to explore the influence of possible effect modifiers in terms of explaining any heterogeneity, specifically baseline values of continuous variables at the trial level. These effect modifiers were centred on the average baseline value and any effects were assumed to affect all treatments linearly. Decisions regarding the fit of the different models (i.e. which was the most appropriate) were made using both Deviance Information Criterion (DIC) (differences of between 3 to 5 points being statistically significant) and the residual deviance (comparison with the number of data points with a ratio of 1 considered a good model). A parsimonious approach appeared to be adopted. Fixed-effects models were fitted initially with random-effects and/or meta-regression models adopted only if they reduced the DIC significantly and suggested a good model through the residual deviance. Heterogeneity and consistency were not specifically assessed, although heterogeneity was examined through sensitivity analyses. The overall modelling strategy used in the MS seemed appropriate.

Distributions & Priors: The MS produced network meta-analyses for both continuous and count based outcome measures. It appropriately made the assumption that the continuous outcomes should be normally distributed and used an identity link function. Also, that the outcomes measuring counts should use a binomial model with a logit link function. The MS stated that vague priors were used for random-effects models. Vague priors tend to be recommended for trial specific baselines (μ_i), trial specific treatment effects (d_{1k}) and for the between-study variance (where appropriate), unless the model is either binomial with a logit link function or a rate model with log link function (where a uniform prior is used for the standard deviation) or where data are sparse and the model fails to converge (where vague gamma priors are used for precision). Although the MS used vague priors for both the count based outcome measures and when there were sparse networks, it undertook some sensitivity analyses. These focused on examining different prior distributions when the random-effects models failed to converge, although limited information is provided on the specific distributions used. The MS also provided limited information concerning model convergence such as burn-in simulations, iterations used for the modelling or the diagnostic statistics and plots. It only identified the number of iterations on the occasions that model convergence was not achieved.

Interventions: The MS appropriately selected placebo as the reference treatment for all the network meta-analyses undertaken, presenting all comparisons of treatments against placebo. No comparisons were made between the different active treatments and it is assumed that the evidence network was insufficient to support such analyses.

Outcome measures: Continuous outcome measures included changes in HbA_{1c} and weight from baseline. These outcomes were reported in different forms as change from baseline per treatment, change from baseline compared with a reference treatment and as baseline and endpoints. To ensure comparability the outcome of mean change from baseline was calculated for each trial, using specific steps to derive the outcome and common measures of variability around the point estimates. The steps taken in the MS appeared appropriate. Count based outcomes included measures of the incidence of hypoglycaemia, UTI and GTI. The outcome measures were reported as being assessed at 24 weeks and 52 weeks, however as noted in the MS the 24 week time-point varied by 6 weeks and the 52 week time-point by 4 weeks. Such heterogeneity may have affected the outcomes reported and these differences were not encompassed in any sensitivity analysis.

Participants: The systematic review that underlies the network meta-analysis included 5 studies that had patients who were elderly and/or had a renal impairment. These studies differed from the other included studies and may have had some influence on the outcomes of the network meta-analyses, although their effects were not considered in sensitivity analyses.

Evidence network: The MS identified concerns about sparsely populated networks and zero events, both of which were evident in the current network meta-analyses. Where trial evidence is limited, the posterior distribution of the standard deviation will be poorly identified and likely to include extreme values (i.e. unexpectedly wide credible intervals). It is also possible that models, particularly random-effects models, will not converge. The MS identified that the networks may be sparse and, where random-effects models did not converge, estimated fixed-effects models only. Inevitably fixed-effects models assume that all studies are estimating exactly the same underlying effect size, which may be unrealistic. As such, the sparse evidence network and the fixed-effects models may be affected by uncertainty around the point estimate and credible intervals. Given the sparse network, it was likely that there may be zero values in the categorical variables. Although the Bayesian Markov Chain Monte Carlo network meta-analyses can accommodate zero values, if the data are too sparse and/or several trials have zero values, then the model may fail to converge or produce high standard deviations. The MS correctly employed a continuity correction, although it did not specify the actual correction used.

Summary: Although the MS undertook many of the steps in conducting an appropriate network meta-analysis, its reporting was not completely transparent. It lacked some clarity as regards: the use of hierarchical regression models; the rationale for not exploring other underlying study characteristics (i.e. participants and outcomes) as causes of heterogeneity; the sensitivity analyses around prior distributions and priors; and, the reasoning behind only presenting comparative results against placebo rather than the active treatments. Also, the

analysis did not present information concerning the convergence of the different models. However, the key issue underlying the network meta-analysis is the sparsity of the evidence in the network itself. Although numerous different active treatment options are included, limited evidence is available for many of the comparisons made. The lack of an evidence base prevented many of the random-effects and meta-regression models from converging, limiting the analyses to the less conservative fixed-effects models. As such, there remains uncertainty around the outcomes of the network meta-analyses and the variance in the treatment effects.

Janssen

The Janssen NMA included 40 studies, including some which the AG did not think relevant, such as dapagliflozin 5mg. It included four DPP4 inhibitors and 4 sulfonylureas. It did not include repaglinide but this was included in a sensitivity analysis.

Review of statistical methods

A Bayesian hierarchical model was used for the network meta-analysis. Although not explicitly stated, it is evident that both fixed-effects and random-effects models were estimated. No analysis was undertaken of possible effect modifiers using meta-regression, instead sensitivity analyses excluded trials with different characteristics. The MS used Deviance Information Criterion (DIC) to assess the goodness of fit of the models, selecting the model with the lowest DIC as the most appropriate. A threshold of 3 points on the DIC is used to judge significant change. Where a random-effects model was selected as the base case analysis, a fixed-effects model was estimated in a sensitivity analysis. Given other statements in the MS, it is assumed that random-effects models may have also been estimated as a sensitivity analysis when a fixed-effects model was the base case. Where trials had multiple arms, the MS correctly made adjustments to the statistical approach to account for the correlation between treatment effects from the same trials. The approach taken was based on a conditional distribution formulation of the multivariate normal distribution. The influence of heterogeneity was assessed through an analysis of the direct pairwise comparison of treatments using Cochran's Q test ($p=0.1$), I^2 statistic (threshold >50%), comparisons using forest plots and comparison of the characteristics of the trials. Consistency of the direct and indirect evidence was compared using the difference in the respective point estimates and their p values, testing whether they differed statistically significantly from zero. As well as producing point estimates (and credible intervals) of the mean difference and odds ratios, the MS ranked the probability of the different treatments as being the most effective based on the Surface Under the Cumulative Ranking (SUCRA). SUCRA produces probabilities that range from 100%, showing the treatment ranks first, to 0%, which shows it ranks last. These rankings formed the basis of the comparison of the different treatments, along with an assessment of the probability that canagliflozin performed better than the other treatments. The comparative ranks were interpreted on the basis that a treatment with >70% was judged the best,

between 30% and 70% no difference between treatments, and <30% the alternative treatment was considered best. Although the analysis lacked an assessment of heterogeneity through meta-regression, the overall modelling strategy used in the MS appeared appropriate.

For the network meta-analyses of continuous outcomes, the MS correctly assumed that a Normal distribution and identity link function should be used. Similarly, for binary outcomes, the MS appropriately selected a binomial distribution and logit link function. The MS states that it uses non-informative priors for unknown parameters. Priors for the Normal distributions for treatment effects $(0, 10^4)$ and the uniform distributions for between-trial standard deviations (binary outcomes range (0,2); continuous outcomes range based on outcome scale with assessment of posterior distribution to select prior distribution) were specified. While the priors are considered suitable, issues concerning sparse data may require other priors to be considered, particularly if the model fails to converge. Although not specifically stated in the MS, this issue appears to have considered as a sensitivity analysis on the prior distributions for between-trial precision uses a gamma distribution (0.001, 0.001) for the random-effects model. No other prior distributions appear to have been examined in sensitivity analyses.

The network meta-analyses used Markov Chain Monte Carlo simulation in WinBUGS running 3 chains with different starting values. It assessed convergence through history and Gelman-Rubin plots, although these are not presented. Fixed-effects network meta-analyses used a burn-in of 20,000 iterations, which were discarded, and a further 20,000 iterations to monitor the parameters. Random-effects network meta-analyses used a burn-in of 100,000 iterations (which were discarded) and monitored parameters for a further 100,000 iterations. Where convergence was not achieved, iterations were increased (numbers of iterations used not stated).

Treatments included in the network meta-analysis had to be in common use in the UK. The network meta-analyses assessed both treatment- and dose-specific outcomes in the classes of SGLT-2, thiazolidinedione and DPP-4, with those for sulfonylurea pooled to reflect dose adjustments on a per-patient basis. The MS appropriately selected placebo as the reference treatment for all of the evidence network diagrams, however all results were compared with canagliflozin. No comparisons were made between the other active treatments, which may reflect the sparse nature of the evidence.

Continuous outcomes measured the change from baseline in each treatment arm for $HbA_{1c,}$ FPG, weight, BMI and SBP. If data were missing, values were estimated as the difference between the final value and the value at baseline, with the variance calculated using an approach recommended by the NICE DSU. Sensitivity analyses were conducted on the approach to estimating the variance of the mean change (i.e. within-patient correlation varied from base case of 0.5 to 0.7). Binary outcomes used the number of events and total patients in each treatment arms for calculating the proportion of patients reaching HbA_{1c} <7%, proportion of patients with ≥ 1 hypoglycaemic event and proportion of patients reaching HbA_{1c} <6.5%. Handling of missing data from binary outcomes is not discussed. Outcomes were assessed at 26 weeks ± 4 weeks with a sensitivity analysis of 26 weeks ± 10 weeks.

This variation may have led to heterogeneity in the outcomes reported, although the MS states that these were based on expert clinical opinion. Additional sensitivity analyses were also conducted including studies reporting outcomes from 16 to 21 weeks and/or 31 to 36 weeks.

There appeared to be some heterogeneity in the participant characteristics. Patients in the included studies ranged in age from 48 to 72 years; the proportion of males from 11% to 80%; the proportion who were Caucasian/white from 6% to 80%; and, in duration of their diabetes 1.1 years to 13 years. In many instances studies did not report the characteristics of their participant populations. As a result, heterogeneity was identified in the network meta-analyses and sensitivity analyses were undertaken.

The MS presented evidence networks for the different comparisons undertaken. It was evident from the network diagrams that some of the treatments were in parts of the network that were unconnected and these were excluded from the analyses. Other parts of the evidence networks were sparsely populated with only 1 trial. Such limited data may have resulted in posterior distributions of the standard deviations that included extreme values and the possibility of non-convergence of the model. This increased the uncertainty around the outcome of the network meta-analyses. Trials including binary outcomes were affected by zero events. Where this occurred, the MS appropriately used a continuity correction (0.5 added to all cells counts of studies with at least one arm with a zero). Trials with no event in any arm or that were considered to affect convergence (basis of exclusion not stated) were excluded from the analysis.

The trials included in the evidence network were assessed through sensitivity analyses that excluded trials considered a source of heterogeneity or inconsistency, identified as lower quality (not double blind), where it was unclear if it assessed monotherapies, assessed a single ethnic group, or published in a non-peer reviewed journal or as part of a regulatory process. Further sensitivity analyses were conducted that included an unpublished trial (DIA3011) assessing canagliflozin 100mg and canagliflozin 300mg and repaglinide trials that included metformin and sulfonylurea.

The MS clearly outlined the key aspects of the network meta-analyses. It estimated fixed- and random-effects Bayesian hierarchical models using MCMC simulation in WinBUGS, evaluating the fit of the models through DIC. Prior distributions and values were correctly assumed, with an alternative assessed through sensitivity analysis to examine the effects of sparse data. The MS discussed the simulation process in terms of chains run, iterations for burn-in and monitoring parameters, and the process for assessing convergence. The analysis also assessed heterogeneity, inconsistency between direct and indirect meta-analyses and made adjustments for multiple treatment arms. The network meta-analyses presented point estimates and credible intervals for outcomes and ranked treatments as to which performed the best. Treatments were compared to canagliflozin, with no comparisons of the other active treatments. Missing data were appropriately estimated for continuous measures, however there is no discussion of missing data for binary outcomes. Outcomes were assessed at 26 weeks ± 4 weeks with a sensitivity analysis at 26 weeks ± 10 weeks, which may have resulted in some heterogeneity. It was evident that the network was sparsely populated in certain

comparisons and that there were zero values for binary outcomes. Although the zero values were handled appropriately through a continuity correction, the effects of sparse data for the continuous variables may lead to increased uncertainty around the estimates. The MS produced a range of sensitivity analyses to explore the robustness of the models. Overall the methods used in the network meta-analyses appeared appropriate and identified most limitations in the evidence. The sparse evidence base may influence the outcomes produced.

Comments

Despite the different approaches and inclusions, some findings from the different meta-analyses were similar. For example, the differences in effect sizes of HbA1c of canagliflozin 100mg and dapagliflozin 10mg were reported as 0.33% (Janssen), 0.365% (Boehringer) and 0.36% (Assessment group).

There appears to be a systematic difference between results of the Assessment Group NMA and the Boehringer NMA, with effects on HbA1c being higher in the latter one, with the AG results being closer to the trial results. The Janssen figures are similar to the AG ones. This is shown in Table 14.

Table 14 Reductions in HbA1c at 24 weeks compared to placebo

	Reduction in HbA1c %			
Drug	Boehringer NMA	Janssen*	Assessment group	Trial
Dapaglifozin 10mg	[redacted]	0.64	0.59	0.66 (Ferrannini[74])
Empagliflozin 10mg	[redacted]	0.74	0.76	0.74 (Roden[79])
Empagliflozin 25mg	[redacted]	0.85	0.88	0.86 (Roden[79])
Canagliflozin 100mg	[redacted]	0.97	0.95	0.91 (CANTATA-M[72])
Canagliflozin 300mg	[redacted]	1.20	1.19	1.17 (CANTATA-M[72])

Janssen figures derived from their Figure 8.
However the relative differences between drugs are similar, and those are what matter in the modelling.

Chapter 5 Cost effectiveness

Approach to modelling

There are several issues to consider in choosing sequences, including;

- The assumption that in most patients, the condition will progress, requiring intensification of therapy by adding a second glucose-lowering agent – dual therapy – and later one or more others
- Whether the second drug should vary according to what the first was. For example, after a flozin as first drug, the choice of second drug includes sulfonylureas, gliptins, and pioglitazone
- Whether these drugs could also come in at later stages. For example, if dual therapy with canagliflozin and gliclazide is failing, one option might be to add sitagliptin. Others include pioglitazone, insulin and a GLP-1 analogue
- We assume that if intensification to dual therapy is required, the doses of empagliflozin and canagliflozin will already have been raised to 25mg and 300mg respectively.

These options could create a need for a very large number of pathways which is beyond the scope of this report. We also need to keep regimens after monotherapy as similar as possible in order to focus on the differences arising from the initial monotherapy.

Dual therapy

The draft NICE guideline on type 2 diabetes, for patients who cannot take metformin, has been reproduced earlier in this report. It envisages dual therapy with one of the following combinations;

- Pioglitazone and a sulfonylurea
- Pioglitazone and a gliptin
- Sulfonylurea and a gliptin

In the interest of simplicity, we have chosen the sulfonylurea as the second drug, except after gliclazide monotherapy, when we use pioglitazone. The sulfonylurea was preferred to pioglitazone because of the latter's safety record. Pioglitazone is preferred to a DPP4 inhibitor only on cost grounds.

We have assumed that patients are at the maximum tolerated dose of each monotherapy drug before moving to dual therapy.

Triple therapy

Moving to triple therapy is more complicated, since after some of the dual regimens, pioglitazone and a gliptin are still available, and the GLP-1 analogues and insulin enter the frame. It is not possible to review all options.

At this stage, the draft NICE guideline recommends that insulin-based treatment should be considered.

In the interests of simplicity, our base case is therefore to bring in NPH insulin for triple therapy. We therefore have sequences as follow;

- Empagliflozin 25mg > empagliflozin + gliclazide > empagliflozin + gliclazide + NPH insulin
- Canagliflozin 300mg > canagliflozin + gliclazide > canagliflozin + gliclazide + NPH
- Dapagliflozin 10mg > dapagliflozin + gliclazide > dapagliflozin + gliclazide + NPH
- Sitagliptin 100mg > sitagliptin + gliclazide > sitagliptin + gliclazide + NPH
- Pioglitazone 45mg > pioglitazone + gliclazide > pioglitazone + gliclazide + NPH
- Glic> glic + pio > glic + pioglitazone + NPH

Some patients will progress to needing short-acting insulin to control blood glucose after meals. We assume that once patients move to a basal-bolus insulin regimen, the sulfonylurea will be stopped. Note that we have not introduced any of the flozins beyond monotherapy since those situations were dealt with in the three STAs.

An alternative to bringing in insulin as third drug, is to consider the GLP-1 analogues. These are simpler for patients to manage, involving a once a week injection, and a low risk of hypoglycaemia.

NICE has adopted a very restrictive position on the GLP-1 analogues, based on a minimum BMI, and stopping rules requiring both a 1% reduction in HbA1c and 3% weight loss, but that was not based on any cost-effectiveness analysis and is due for review.

Only one long-acting GLP-1 analogue has been appraised by NICE – long-acting exenatide. If we bring that in as 3rd drug, basal insulin would be the fourth drug, with sequences as follow;

Empa 25mg > empa + gliclazide > empa + glic + exenatide LA > empa + glic + exen + NPH insulin

Cana 300mg > cana + gliclazide > cana + glic + exenatide LA> cana+ glic + exen +NPH

Dapa > dapa + gliclazide > dapa + glic + exenatide LA > dapa + glic+ exen +NPH

Sita 100mg > sita + glic > sita + glic + exenatide LA > sita+ glic+ exen+ NPH

Pio 45mg > pio+ glic > pio + glic + exenatide LA > pio + glic + exen + NPH

One problem with deriving effect sizes for modelling, is that most trials recruit patients with rather poorer control than would be expected amongst patients who are being followed up according to NICE guidelines which state (draft 2)

> *1.6.1 In adults with type 2 diabetes, measure HbA1c levels at 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy*

So if the above guideline is being followed, patients whose HbA1c rises above the 7.5% intensification threshold, should have that detected within a few months, before it has gone much higher. Their HbA1c levels might be in the 7.5% to 8.0% range. Whereas most trials of intensification to dual or triple therapy recruit patients with much higher HbA1c, often in the 8.7-9.05 range, but sometimes well over 9%.

The importance of this is that reductions in HbA1c tend to be larger when baseline HbA1c is higher. So the effect sizes in HbA1c seen in most trials will be larger than expected in management of type 2 diabetes according to the NICE guideline, with close monitoring and prompt intensification.

So we need to be selective in the trials from which we extract data, rather than using effect sizes from broad-spectrum meta-analysis.

The generalisability of trials to routine care has been examined by Thomsen and colleagues in Denmark.[7] They looked at the effects of adding a second drug to metformin in a large population-based cohort, and concluded that the results were similar to those seen in the trials. The mean HbA1c at intensification was 8.0%. They observed reductions in median HbA1c of 1.2% with sulfonylureas, 0.8% with DPP4 inhibitors, 1.3% with GLP-1 receptor agonists and 2.4% with insulin. However, these differences reflect different baseline HbA1cs, notably 9.5% to 10% amongst those who started insulin. Despite intensification, 41% had not achieved HbA1c <7.5% six months later.

Thomsen and colleagues[7] also noted that the threshold for intensification had fallen over the years, from about 8.8% in 2000-2003 to about 8.1% in 2010-2012 (estimated from graph in supplementary material figure 3). If this has also occurred in the UK, it reinforces the need to be selective in extracting effect sizes for modelling. In past studies, patients with type 2 diabetes were often left poorly controlled for several years before intensification[181, 182] but this may be happening less nowadays, with improved control promoted by the Quality Outcomes Framework of payments to general practices for demonstrating performance against HbA1c control indicator s[183], including DM007 for the HbA1c indicator. The three bands are now 59, 64 and 75 mmol/mol. All of them (not just the tightest) probably encourage initiation of insulin in practice.

AG cost effectiveness literature review

Only one paper was identified that addressed the cost effectiveness of flozin monotherapy in the patient group under consideration. Neslusan et al[184], available only in abstract, used the ECHO-T2DM model to compare the cost effectiveness of monotherapy canagliflozin 100mg and canagliflozin 300mg with lifestyle management within the US. Patients could intensify to sulfonylurea and then on to insulin, both apparently with an 8.0% intensification threshold. By the 10th year the use of canagliflozin had delayed the intensification to insulin such that 27% of the canagliflozin 100mg and 19% of the canagliflozin 300mg group were receiving insulin, compared to 66% of those who started with lifestyle management. Canagliflozin was reported to lower total costs and result in improved quality of life over a 30 year time horizon, and so dominated lifestyle management.

The UKPDS and the UKPDS OM models

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.[185] 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 was used by Oxford University to develop an electronic cost effectiveness model, the OM1.

The UKPDS68 has recently been partially updated by the UKPDS82[186], the latter incorporating longer follow-up data of the UKPDS. This provides an alternative 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. Oxford University is developing an updated electronic model, the OM2. As far as the AG is aware, this currently relies upon the UKPDS68 for the evolution of the risk factors and the UKPDS82 for the probabilities of events and deaths. The AG has not had access to the OM2 during the course of the assessment.

The UKPDS82 provides the following table (Table 15) to outline the differences in the predicted number of events at 10 years for patients of different ages.

Table 15 Table 2 of UKPDS82: Ten year event rates (%): OM1 vs OM2

	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

IHD includes angina and consequences of procedures to relieve it such as angioplasty and coronary artery bypass grafting.

The OM1 predicts roughly double the number of myocardial infarctions over ten years, and the rates of IHD are also noticeably higher. Possibly mainly as a consequence of the higher rate of myocardial infarction predicted by the OM1, the ten year death rate predicted by the OM1 is also noticeably higher. The OM1 will tend to over predict event rates compared to the OM2. The OM1 is now likely to overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment.

It is anticipated that the longer follow-up data of the UKPDS associated with the UKPDS82[186] will result in additional publications, one of which will update the evolution of the risk factors. The costs associated with events have already been updated, the UKPDS84[187] being an update of the UKPDS65.[188] The quality of life estimates have also been updated in Alva et al.[189] But the format of the analysis of Alva et al is less closely aligned with the events of the UKPDS84 when compared with the alignment of the quality of life estimates of the UKPDS62[190] with the events of the UKPDS68.[185]

Company submissions

There are three company submissions.

- Boehringer Ingelheim for empagliflozin
- Astrazeneca for dapagliflozin
- Janssen for canagliflozin

An overarching summary of the companies' and the AG's modelling assumptions, inputs and results is presented at the end of the economics, permitting an easy read across. Readers may wish to work through this overarching summary first, before turning to the more detailed summaries presented below for more clarity around specific points of the individual modelling exercises.

All the submissions contain modelling exercises with long term time horizons of around 40 years, which for the majority of patients will be a lifetime horizon. They all undertake a cost utility analysis using the appropriate perspectives of the NHS and PSS for costs and the patient for benefits, and discount costs and benefits at 3.5%.

Boehringer Ingelheim designed a front end to the UKPDS OM1 model. The Boehringer Ingelheim submission has a great deal in common with the modelling of recent NICE clinical guidelines for T2DM and the AG modelling for the current assessment, both of which design a front end to the UKPDS OM1.

Astrazeneca uses the CARDIFF diabetes model (CDM) which uses many of the UKPDS68[185] equations and so has much in common with the UKPDS OM1 model, but updates the calculation of the probabilities of having an event to use the UKPDS82[186] which is the basis of the OM2.

Janssen differs from Astrazeneca and Boehringer Ingelheim in using the ECHO-T2DM model. Its base case has assumptions which differ quite noticeably from those of the other two submissions. There is also relatively little detail in the Janssen submission, with most of the detail being contained in the appendices to the submission and the submitted electronic copy of the model.

In the light of the above, the review of the company submissions below provides a reasonably in depth review of the Janssen modelling. This is followed by shorter reviews of the Boehringer Ingelheim the Astrazeneca modelling, which are more in line with the AG modelling.

Janssen economic modelling

The ECHO-T2DM model is an individual patient simulation model developed by staff of the Swedish Institute for Health Economics. It has been routinely submitted to the Mt. Hood challenges. The Mt. Hood challenges are intermittent events at which the main diabetes models are challenged to use a set of real world clinical inputs to predict the longer term incidences of the various complications of diabetes without having access to the actual longer term incidences of the various complications. Their predictions are then compared with the actuals. But the ECHO-T2DM submissions to the Mt.

Hood challenges were probably with different assumptions than those used for the Janssen submission, in particular with regards the evolution of HbA1c.

The model was run with a 40 year time horizon and a cycle length of 1 year. Costs and benefits were discounted at 3.5%. The perspective was that of the patient for health impacts and of the NHS/PSS for costs.

1,000 PSA iterations were run for the base case, with each PSA iteration modelling 2,000 patients. It appears that each patient was run through the model only once, with no internal loops to reduce Monte-Carlo error. For the scenario analyses the number of patients was reduced to 1,500. The submission did not present any analysis of model convergence over the number of patients modelled. It appears that only results of analyses performing the 1,000 PSA iterations were presented and that no deterministic analyses, i.e. analyses with no sampling of second order uncertainty, were undertaken. This could have permitted more than 2,000 patients to be simulated and some analysis of convergence of results as patient numbers were increased to be presented. Note also that it appears that only pairwise comparisons are permitted in the ECHO-T2DM model. Consequently, it is unclear whether the characterisation of uncertainty within the PSAs across all the comparators is correct; i.e. whether each PSA iteration used the same sampled parameter values across the various pairwise comparisons. This should not affect the central estimates of the probabilistic analysis but the characterisation of the uncertainty around it would be affected.

The model simulates the evolution of the severity of the micro-vascular complications of diabetes, based mainly upon WESDR data:

- Retinopathy
- Chronic kidney disease (CKD)
- Neuropathy, this also encompassing peripheral vascular disease

CKD health states range from stage 1 with an eGFR > 90ml/min/1.73m^2 to end stage renal disease with an eGFR < 15ml/min/1.73m^2 for over one year.

The appendices to the Janssen submission state that four macro-vascular complications are included:

- Ischaemic Heart Disease (IHD)
- Myocardial infarction (MI)
- Stroke; and
- Congestive heart failure (CHF).

The model also incorporates:

- Patient weight;
- Severe hypoglycaemia;
- Non-severe hypoglycaemia;
- UTIs;
- GTIs;
- Peripheral oedema; and,
- Discontinuations.

Patient characteristics

Patient characteristics at baseline were drawn from a pooled analysis of the CANTATA-M [72, 87] and Japanese canagliflozin [73] studies, resulting in baseline estimates of 56 years of age, 52% male, 8.016% HbA1c, 128mmHg SBP, 29.7 BMI, 200mg/dl total cholesterol, 118mg/dl LDL, 48mg/dl HDL, 175mg/dl triglycerides and a mean eGFR of 86ml/min/1.73m^2. Note that the inclusion of the Japanese study pulls down the mean BMI because the mean BMI was 25.6 kg/m^2. Those in CANTATA-M had a higher BMI, mean 31.6 kg/m^2.

Based upon the submitted electronic model input sheets, the mean disease duration was 4.6 years and was assumed to range uniformly between 0 years and 9.2 years. The proportion of patients with background diabetic retinopathy was 0.7%, with micro-albuminuria was 0.1% and with symptomatic neuropathy was 1.5%. The proportion of patients with IHD was 1.2%, MI 0.8%, stroke 0.1% and amputation 0.1%. The other complication rates were zero.

Sequences modelled and treatment effectiveness

The Janssen submission modelled the following treatment sequences (see Table **16**).

Table 16 Janssen model treatment sequences

Monotherapy	1st intensification	2nd intensification	3rd intensification	4th intensification
Flozin	Flozin + SU	NPH insulin	NPH + Aspart	None
Pioglitazone	Pioglitazone + SU	NPH insulin	NPH + Aspart	None
Gliclazide	Sitagliptin + SU	NPH insulin	NPH + Aspart	None
Sitagliptin	Sitagliptin + SU	NPH insulin	NPH + Aspart	None
Repaglinide	Pioglitazone	Pioglitazone + SU	NPH insulin	NPH + Aspart

Repaglinide was only included as a scenario analysis. For canagliflozin 100mg it appears that two arms were modelled: one that intensified by adding gliclazide and another that permitted a dose increase to canagliflozin 300mg [redacted].
But the Janssen submission is slightly ambiguous about this.

Clinical effectiveness estimates for the monotherapies were mainly drawn from the 26 week NMA, though infection rates were drawn from the canagliflozin trials with the flozins being assumed to have the same rate as canagliflozin 100mg and the other comparators the same rate as the placebo arm. Based upon the electronic input sheets submitted by Janssen and the model having an annual cycle, the 26 week estimates were assumed to apply at the end of the first cycle. Note also that the estimates of the electronic input sheets are stated as being relative to placebo, and that there does not appear to be a placebo effect within the electronic input sheets. As a consequence, it appears that the treatment effects relative to placebo rather than the absolute treatment effects have been applied within the Janssen modelling.

The appendices to the submission present two NMAs: with and without repaglinide. The central estimates of these appear to the AG to be virtually identical, with the exception of the rates of severe and non-severe hypoglycaemic events for pioglitazone and sitagliptin. Why these should differ between the two analyses is not clear (see Table 17).

Table 17 Janssen central clinical effectiveness estimates including repaglinide

Drug	Cana		Dapa	Empa		Glicl.	Pio	Sita	Repa.
Dose	100mg	300mg	10mg	10mg	25mg	160mg	30mg	100mg	2mg
HbA1c	-0.97	-1.2	-0.64	-0.73	-0.85	-0.59	-0.78	-0.72	-1.28
SBP	-3.71	-5.41	-3.21	-2.60	-3.40	0.191	0.880	0.800	0.191
BMI	-0.85	-1.21	-0.57	-0.61	-0.65	0.220	0.833	0.293	0.220
TC	4.512	7.544	4.512	4.512	4.512	..	..	..	..
LDL	1.655	6.156	1.655	1.655	1.655	..	..	..	..
HDL	3.447	3.236	3.447	3.447	3.447	..	..	..	..
Triglycerides	-25.0	-24.0	-25.0	-25.0	-25.0	..	..	..	..
AEs									
Female GMI	0.208	0.161	0.208	0.208	0.208	0.065	0.065	0.065	0.065
Male GMI	0.047	0.165	0.047	0.047	0.047	0.015	0.015	0.015	0.015
Upper UTI	0.008	0.000	0.008	0.008	0.008	0.000	0.000	0.000	0.000
Lower UTI	0.107	0.109	0.107	0.107	0.107	0.071	0.071	0.071	0.071
Severe hypo	0.008	0.000	0.003	0.008	0.008	0.034	0.002	0.002	0.010
Non-severe hypo	0.046	0.065	0.057	0.046	0.046	0.508	0.027	0.031	0.156
1st year disc.	0.025	0.020	0.025	0.025	0.025	0.011	0.011	0.011	0.011
Periph. oedema									
Year 1	0.119	0.119	0.119	0.119	0.119	0.119	0.254	0.119	0.119
Subsequent	0.058	0.058	0.058	0.058	0.058	0.058	0.085	0.058	0.058

As already noted, the definition of hypoglycaemia used a cut-off of below 4.0mmol/l, which is above the foot of the normal range of 3.5mmol/l.

The submission appears to state that when a patient intensified by adding another therapy that the clinical effectiveness estimates of that therapy were applied. When a patient intensified therapy by switching to another therapy, rebound was assumed with the clinical effectiveness estimates of the initial therapy being removed prior to applying the clinical effectiveness estimates of the therapy that was being switched to. Rebound consequently appears to be to take the patients back to their baseline values for the risk factors. And the clinical effectiveness of a treatment was assumed to be the same whether it was being used as a monotherapy or was being added to other therapies.

At the progression to insulin the following clinical effectiveness estimates were applied, the values being taken from the copy of the electronic model input sheet that was submitted. The source of these estimates (see Table 18) was not clear to the AG

Table 18 Janssen central clinical effectiveness estimates for insulin

Drug	NPH	Aspart
HbA1c	-0.9	-1.509
SBP	..	..
BMI	0.496	1.009
TC	..	..
LDL	..	..
HDL	..	..
Triglycerides	..	..
AEs		
Severe hypo	0.0049	0.04
Non-severe hypo	0.67	44.95

Treatment intensification and discontinuation

Treatment intensification occurred if the patient breaches the 7.5% HbA1c treatment intensification threshold.

[redacted]

[redacted]

[redacted]

[redacted].

Patients could also discontinue their current treatment due to adverse events and contraindications. It is unclear to the AG whether those discontinuing one treatment were assumed to intensify to monotherapy with another agent or to dual therapy with another agent.

The submission states that the treatment effects associated with discontinuations were immediately reversed at discontinuation. If treatment effects were limited to; e.g. one off reductions in HbA1c it is easy to see how this treatment effect could be reversed and rebound occur. But treatment effects are not limited to one-off effects. The evolution of HbA1c after the initial one-off effect is also treatment specific so has to be counted as a treatment effect. The AG assumption is that rebound was to baseline values, but this is not unambiguous and may have been treated differently for different risk factors; e.g. HbA1c and weight.

The Janssen submission is ambiguous about whether the model handles treatment intensifications and treatment discontinuations in the same manner. It is important to know whether rebound also occurs when treatments are withdrawn at treatment intensification, particularly for the intensification from repaglinide to pioglitazone, and for the intensification to insulin when patients are assumed to discontinue their oral therapies. Appendix 4 to the main submission states that:

> *Treatment intensification algorithms triggered when biomarker threshold levels are exceeded determine AHA and concomitant medication use (i.e. anti-hypertensive, dyslipidaemia) over time. Each drug (or drug combination) is described by a profile that includes price, initial treatment effects, bio-marker evolution, "rebound" effects applied upon discontinuation, AE rates, non-compliance rates, contraindications, and disutility (if any). A treatment sequence of rescue medications can be specified by the user, including at least one line of rescue insulin therapy. Agents can be continued or discontinued at bio-marker failure (HbA1c for AHA, SBP for anti-hypertensive agents, and any of the cholesterol components for anti-dyslipidaemia agents).*

To the AG this suggests the intensifications, or discontinuation at biomarker failure of HbA1c in the above, may be treated in the same manner as discontinuations and treatment switches and have rebound applied if specified by the user.

This raises the possibility of repaglinide rebounding at treatment failure, so adding 1.28% to the then current 7.5% patient HbA1c. Intensifications to pioglitazone with its -0.78% effect and then the subsequent intensification to add gliclazide and its effect of -0.59% may not reverse this rebound, given the incorporation of annual drift. If this applied, patients on repaglinide could spend little to no time on subsequent oral intensifications before intensifying to insulin. But the AG assumption is that rebound is to the baseline value rather than to the baseline value plus annual drift, and that this rebound applies to all the risk factors and not just HbA1c.

It is not obviously reasonable to assume that there will be rebound when patients start insulin. The clinical effectiveness estimates for insulin may reflect the overall effect of a switch to insulin including any discontinuations of existing therapy.

HbA1c evolution

A major difference in assumptions in the Janssen submission compared to the other submissions and the AG modelling is that rather than apply the UKPDS68[185] equation to evolve HbA1c, treatment specific linear evolutions were assumed. The argument for this is that though most NICE assessments in diabetes have used the UKPDS68 equations to evolve HbA1c these evolutions encompass treatment intensifications. As a consequence, if treatment effects are being associated with treatment intensifications in the modelling, using the UKPDS68 evolution will tend to double count these treatment effects.

The values of these for the monotherapies were based upon values taken from the ADOPT trial as reported in Kahn et al.[169] The majority of the monotherapies under consideration were not used in the ADOPT trial, which used rosiglitazone, metformin and glyburide (the Amrican name for glibenclamide). Janssen assumes that values from treatments within the ADOPT trial apply to the monotherapies under consideration as below (Table 19).

Table 19 Janssen annual rates of HbA1c drift by monotherapy

Monotherapy	ADOPT equivalent	Annual HbA1c drift
Flozin	Metformin	0.14%
DPP IV: Sitagliptin	Metformin	0.14%
SU: Gliclazide	SU: Glyburide	0.24%
Repaglinide	SU: Glyburide	0.24%
Pioglitazone	Rosiglitazone	0.07%

Applying the glibenclamide progression rate to gliclazide may be pessimistic given the 6-year difference in start of insulin on gliclazide and glibenclamide, in favour of gliclazide.[13]

Given the annual rates of drift and the initial HbA1c treatment effects estimated in the NMA, it is apparent that the annual rates of drift are likely to be as, if not more, important than the HbA1c treatment effects estimated in the NMA. Due to the NMA estimating HbA1c from 24 week data, half the annual drift is added to the estimated treatment effect to provide the 52 week estimate.

At intensification, if another treatment is added the annual rate of HbA1c drift is assumed to be the average of the HbA1c annual drifts of the two treatments being used as dual therapy (Table 20).

Table 20 Janssen annual rates of HbA1c drift by dual therapy

Dual therapy	Annual HbA1c drift
Flozin + Sulfonylurea	0.19%
DPP IV + Sulphonylurea	0.19%
Pioglitazone + Sulphonylurea	0.16%

For those intensifying to insulin, Janssen derive an annual rate of drift of 0.15% from the UKPDS82.[186]

The impact of these different annual drifts in HbA1c is applied in tandem with the initial treatment effects. For instance, at the central Janssen treatment effect estimates and a baseline value for HbA1c of 8.0% it appears that for those who do not discontinue for other reasons the following evolutions are implied up to the point at which HbA1c rises above 7.5% and treatment is intensified (see Figure 10).

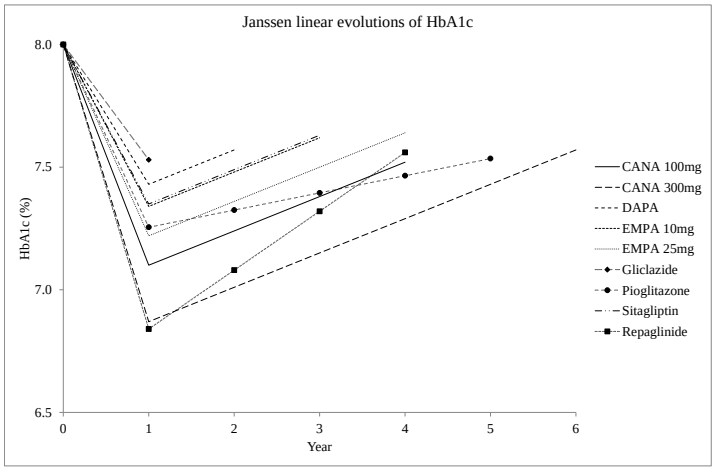

Figure 10 Janssen modelled HbA1c drift by treatment at central values

Immediately apparent is that for gliclazide (the topmost line) the treatment effect of -0.59% when coupled with half of the annual drift; i.e. an increase of 0.12%, means that the patient is above 7.5% at the end of the first cycle.

Turning to canagliflozin 100mg (the solid line) despite its initial treatment effect of -0.97% being somewhat less than the -1.28% of repaglinide they both breach the 7.5% HbA1c intensification threshold at the fourth year due to the differences in annual drift. The slower drift for canagliflozin 300mg also means that despite an initial treatment effect of -1.20% it breaches the 7.5% HbA1c intensification threshold two years later.

Thereafter, it should be borne in mind that repaglinide is assumed to be replaced by pioglitazone. Due to the withdrawal of treatment the current AG reading of the Janssen submission is that in the model this causes the HbA1c to rebound to the original baseline value of 8.016%, and not to have the full rebound of the repaglinide 1.28% treatment effect applied. The -0.59% pioglitazone effect is then applied with the pioglitazone specific HbA1c rate of drift applied, with a further intensification to pioglitazone + SU after this. In other words, in the repaglinide arm there is the initial repaglinide evolution of HbA1c, in the above example for 4 years, which is then followed by exactly the same HbA1c evolution as in the pioglitazone arm, only with this being lagged by 4 years.

The same annual drifts apply for empagliflozin, dapagliflozin and sitagliptin as for canagliflozin. They also intensify by adding gliclazide, and then on to insulin. Again ignoring discontinuations for other reasons, the linear evolution of HbA1c means that any difference in the timings of the first intensification is also reflect in the timings of the intensification to insulin. It appears that the assumption of a linear evolution of HbA1c will maintain absolute differences in HbA1c between treatments, at least until the patient intensifies to insulin. Upon intensification to insulin it appears that the ECHO-T2DM model applies the linear evolution for HbA1c, but then permits the patient to increase their insulin dose in order to stabilise their HbA1c. The Janssen submission is not particularly clear on this point, but it appears that this means that HbA1c may eventually converge between treatments once the patient has started insulin.

Pioglitazone benefits from a slower annual rate of drift, and continues to derive some benefit from this source even after the intensification of adding gliclazide. At central parameter values and again ignoring discontinuations it will have a permanent HbA1c benefit over all the other comparators with the possible exception of canagliflozin 300mg.

Reconciling the above with the evolutions of HbA1c reported in the Janssen submission is difficult, given the annual cycle of the model. But it should be borne in mind that the Janssen curves are

averaged over a large number of patients and PSA iterations, and include the effects of discontinuations for other reasons (see Figure 11).

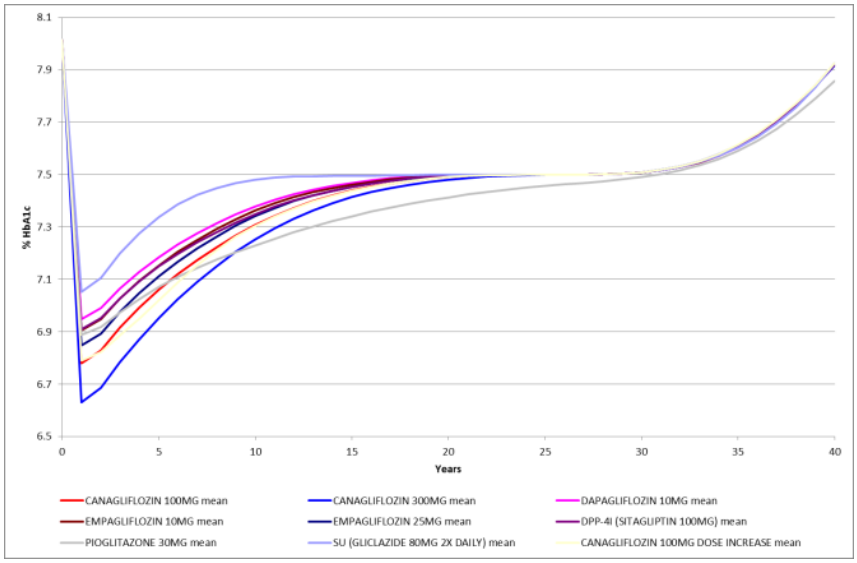

Figure 11 Janssen Figure 13: submission reported evolutions of HbA1c

For instance, the mean first year effect for the gliclazide arm as shown by the topmost curve is around a 0.95% reduction in HbA1c, which is somewhat greater than the -0.59% mean estimate for gliclazide. Those discontinuing for reasons other than HbA1c apparently in effect switch to pioglitazone, the estimate for which is -0.78%. Similarly, the reduction of around 1.4% in HbA1c for canagliflozin 300mg as shown by the bottom curve is also difficult to reconcile with its central estimate of -1.20%. Perhaps both discontinuations and their treatment effects and intensifications and their treatment effects are included in the year 1 estimates, though this timing could be questionable given the annual cycle of the model. It remains difficult to reconcile the above with the central estimates for treatment effectiveness.

At central estimates around a third of the canagliflozin 300mg patients would be required to not to receive a boost of the -0.59% estimate for the intensification to gliclazide to achieve the reduction of 1.4% shown in the above figure. This also requires that none discontinue, rebound and receive a lesser treatment effect from whatever alternative they switch to. Any discontinuations in the canagliflozin 300mg arm would seem to require an even larger boost to the 1.2% canagliflozin 300mg treatment effect among those not discontinuing if the reduction of around 1.4% is to be arrived at.

Even with the effects of 2nd order sampling, it is not clear to the AG how the above central estimates for the evolutions of HbA1c have been arrived at. Perhaps there are additional placebo treatment effects in addition to the treatment effects relative to placebo and the AG has not managed to identify these. In the light of the above, while having read the Janssen submission and its appendices, the AG does not really understand how the model is implementing the changes in HbA1c and how the central

estimate for canagliflozin 300mg is to on average reduce the patient HBA1c from 8.016% at baseline to around 6.63% at one year: a reduction of around 1.4%.

The above figure also sees the HbA1c values converge between the arms. Janssen states that this is "*Because of differences in the timing of requirements for rescue medication, HbA1c, SBP, and lipid curves tend to converge as patients with higher values benefit from treatment-related improvements earlier*". To the AG this does not obviously explain the convergence, or why the curve for gliclazide converges by essentially having zero increase from the 10th to the 30th year. A possible explanation might be the intensification to insulin with patients then being permitted to increase their insulin dose in order to stabilise their HbA1c.

The argument that the UKPDS68 equation 11 includes the effects of treatment intensifications does have some force. But it should be borne in mind that the UKPDS68 equation 11 explicitly includes a parameter for whether the patient is in their second year of diagnosis. This could be viewed as a proxy for the clinical effectiveness of the first treatment for diabetes being introduced, though the second year of diagnosis might be a little early for some patients. As a consequence, modelling could as an alternative apply treatment specific effects and still apply the UKPDS68 equation 11 thereafter, only ignoring the parameter related to whether the patient is in their second year or not. For the patient baseline characteristics outlined in the Janssen submission the annual increases implied by the UKPDS68 equation 11 in the years shortly after the second year are around 0.18% which is broadly central to the rates Janssen takes from theADOPT study as reported in Kahn et al.[169] This may be preferable to extrapolating linear rates from the ADOPT trial, particularly since these rates are being applied to treatments which were not used in the ADOPT trial, and to periods beyond the 5 year follow up of the ADOPT trial, and with some distinctly ad hoc averaging for the rates for dual therapy.

The AG has some sympathy with the argument that HbA1c drift may initially be treatment specific. A linear evolution might even be the most reasonable functional form, particularly given the coefficients reported by Kahn et al.[169] But the AG does not view it as reasonable to assume a linear evolution of HbA1c throughout and that there will be no convergence between treatments, or at least none until a patient starts insulin therapy. This may artificially preserve differences between treatments, when the UKPDS68 evolution clearly implies a convergence. The AG is also uncomfortable with the assumed linear rates of drift that have been imputed from Kahn et al, given that none of the monotherapies under consideration were studied by Kahn et al.

A scenario analysis where the model applies the UKPDS68 evolution of HbA1c was presented.

Evolution of other risk factors

Linear drifts were also assumed for the other biomarkers but these were not differentiated by treatment: 0.30mmHg for SBP, 0.03mg/dl for lipids resulting in a flat TC:HDL evolution. These annual rates of drift were apparently derived from the UKPDS. The UKPDS was conducted largely before the use of statins, and it can be argued that alternative evolutions to those of the UKPDS are now appropriate. But given that the annual rates of drift were apparently derived from the UKPDS, it is unclear to the AG why the equations of the UKPDS68 were not applied.

For a patient's SBP, the common annual rate of drift will tend to maintain the absolute differences between the arms. As far as the AG can ascertain, it also appears that unlike HbA1c this absolute difference for SBP will be maintained even after insulin therapy has been started.

Weight was associated with an annual gain of 0.1kg. Table 12 of the submission states that weight drifts upwards but there is no suggestion of a base case assumption of convergence. Table 13 goes on to suggest that for the base case the patient's weight was assumed to converge at treatment discontinuation with this being in line with figure 26 of the appendix. If this convergence applied, it is unclear whether it was at the 1st intensification or was when the oral therapies were being discontinued and the patient switched to insulin. A scenario analysis of a slower convergence over two years after treatment discontinuation was also presented.

Treatment discontinuation: Renal impairment

In accordance with the canagliflozin SmPC, canagliflozin 100mg was modelled as being discontinued if the eGFR fell below 45ml/min/1.73m^2. Canagliflozin 300mg was modelled as being discontinued if the eGFR fell below 60ml/min/1.73m^2. The SmPC states that if the eGFR falls below 60ml/min/1.73m^2 the patient should have their dose adjusted to 100mg. Those intensifying from canagliflozin 100mg to canagliflozin 300mg would have already failed on canagliflozin 100mg. The license states that canagliflozin 100mg should always be used before canagliflozin 300mg. So dose reduction may be of limited relevance and discontinuation of canagliflozin 300mg may be the appropriate assumption.

Empagliflozin has similar restrictions in its SmPC, with it being possible to increase the dose from 10mg to 25mg if the eGFR is more than 60ml/min/1.73m^2. If the eGFR falls below 60ml/min/1.73m^2 the patient should have their dose adjusted to 10mg, and if the eGFR falls below 45ml/min/1.73m^2 the patient should discontinue empagliflozin.

The dapagliflozin SmPC has slightly different restrictions and is not recommended for patients with an eGFR of less than 60ml/min/1.73m^2.

The sitagliptin SmPC does make the administered dose depend on renal impairment, requiring it to be reduced to 50mg in those with moderate renal impairment and to 25mg in those with severe renal impairment. But discontinuation does not appear to be required.

As far as the AG can see the submission does not state what assumptions if any have been made about discontinuing empagliflozin and dapagliflozin based upon the patient's eGFR. Table 12 of the submission is explicit in its consideration of the canagliflozin SmPC for discontinuations related to renal impairment and to the pioglitazone SmPC for discontinuations related to CHF, but makes no reference to the empagliflozin SmPC or the dapagliflozin SmPC. Appendix 4 of the submission mentions that empagliflozin and dapagliflozin also have treatment rules based upon eGFR. The input sheets to the electronic model suggest that empagliflozin 10mg, empagliflozin 25mg and dapagliflozin are assumed to be discontinued as per canagliflozin: if the eGFR drops below 60ml/min/1.73m^2. This appears to be incorrect for empagliflozin 10mg, and illogical for empagliflozin 25mg.

The use of the ECHO-T2DM model was in part justified by Janssen on grounds of the need to properly account for discontinuations due to renal impairment. In the light of this, a scenario analysis that does not apply these discontinuations would have been useful in order to assess the importance of attempting to model this.

Treatment discontinuations: Adverse events

Patients could discontinue treatments due to adverse events. It is not clear to the AG what was assumed to happen to these patients. They may have discontinued their current treatment and switched to whatever is next in the sequence; e.g. from flozins to SU and then on to NPH insulin, or they may switch to an alternative monotherapy, or they may have switched to an alternative dual therapy.

Hypoglycaemic events

Hypoglycaemia event rates were derived from the pooled 26 week data of the two canagliflozin trials. The NMA 26 week data provided the estimates for the other comparators with the exception of gliclazide. No hypoglycaemia rates were available for gliclazide, and as a consequence rates for glimepiride were adjusted by relative risks of 0.43 for symptomatic and 0.45 for severe hypoglycaemia. The AG is unclear whether these rates were adjusted to be annual rates and so to be in line with the annual model cycle.

Hypoglycaemia event rates were further modified by increasing the risk of hypoglycaemia for low HbA1c values. The relationship underlying this was based upon a large data set of the DCCT study among patients with type 1 diabetes. A 1% drop in HbA1c below the mean value of the clinical study was associated with an increased hazard of hypoglycaemia of 1.43. However patients in the DCCT

intensive arm were on either multiple daily injections or continuous subcutaneous insulin infusion via insulin pumps.

Adverse events

UTI and GTI event rates were derived from the pooled 26 week data of the two canagliflozin trials. The AG is unclear whether these rates were adjusted to be annual rates and so to be in line with the annual model cycle. The other flozins were assumed to have the same rates as canagliflozin 100mg, with the other comparators being assumed to have the same rate as the pooled placebo arms of the canagliflozin trials.

Quality of life

A systematic literature review was conducted with Janssen preferring the CODE-2 data of Baghust and Beale[191] over the UKPDS62[190] due to it providing greater richness for the micro-vascular complications. Baghust and Beale is also the source for quality of life coefficient for BMI.

Janssen report that no appropriate studies were identified for adverse events, and as a consequence a time trade-off study (TTO) among 100 members of the UK general public was conducted to determine the quality of life impacts from UTIs and GTIs. This TTO study also explored hypoglycaemia, GI symptoms and hypovolaemic events, but the estimates for these were disregarded (see Table **21**).

Table 21 Janssen TTO AE quality of life report mean values

	Mean	s.d.	Disutility
T2DM	0.92	0.10	..
and Mild/ moderate UTIs	0.83	0.14	0.09
and Severe UTIs	0.73	0.20	0.19
and Mycotic infection	0.67	0.26	0.25
and Moderate hypoglycaemia	0.81	0.19	0.11
and Severe hypoglycaemia	0.77	0.21	0.15
and Fear of hypoglycaemia	0.77	0.17	0.15
and GI symptoms	0.68	0.24	0.24
and Hypovolaemic events	0.84	0.14	0.08

Based upon the references cited, these values apparently contributed to a regression analysis which arrived at the final QALY decrements. Unfortunately, the AG has not been able to source this regression analysis.

The health state descriptors suggest that the estimates relate to ongoing infection and are not time limited as is appropriate in a TTO study, but this implies that event health states need to be adjusted by the average duration of UTIs and GMIs as occurs in the Janssen submission. The method of this adjustment does not appear to have been presented. At mean values 1 week of a moderate UTI would roughly correspond with a -0.0012 QALY decrement, 2 weeks of a severe UTI would roughly correspond with a -0.0073 QALY decrement and 1 week of a mycotic infection would roughly correspond with a -0.0046 QALY decrement.

The quality of life values applied for the baseline characteristics and micro-vascular complications are presented below. Those for macro-vascular complications, obesity, hypoglycaemic events and adverse events are presented in the overarching summary comparison of the companies' and AG's inputs (see Table **22**).

Table 22 Janssen QoL values: Baseline and micro-vascular

State	QoL	Source
Baseline	1.027	CODE 2
Patient Characteristics		
Age (per 10 Years)	-0.0235	CODE 2
Female	-0.0930	CODE 2
Duration of T2DM (per 10 Years)	-0.0163	CODE 2
Micro-vascular Complications		
Retinopathy (BDR, MO, PDR, and combinations)	0.000	CODE 2
Blindness (one or both eyes, incl. combinations)	-0.057	CODE 2
Gross Proteinuria	-0.048	CODE 2
ESRD	-0.175	CODE 2
Symptomatic Neuropathy	-0.084	CODE 2
Peripheral Vascular Disease (PVD)	-0.061	CODE 2
Symptomatic Neuropathy & PVD	-0.085	CODE 2
Diabetic Foot Ulcer	-0.170	CODE 2
One lower extremity amputation	-0.272	CODE 2
Two lower extremity amputations	-0.272	CODE 2

Costs

Direct drug costs were sourced from the BNF69 and are not presented here for reasons of space. Note that the Janssen analysis in common with the other company analyses applies the £608 cost for canagliflozin 300mg, due to the submission predating the equalisation of the canagliflozin list prices at the canagliflozin 100mg list price of £477.

The costs of blindness, IHD, MI, CHF and stroke were derived from the UKPDS84[187] but are not presented here again for reasons of space. Similar costs are presented within the section on the AG modelling. A variety of other costs are sourced from a variety of NICE guidelines and other sources. Again for reasons of space and because they have very little impact upon the modelling these are not presented here. A full table of event costs is presented in the appendices of the Janssen submission in table 33 starting on page 69. Costs are also summarised in the overarching comparison of the companies and AG modelling exercises.

Adverse events costs were based upon the following (see Table 23).

Table 23 Janssen adverse event costs

Adverse event	Cost	Description and Reference
Non-severe hypoglycaemic event	£0.00	Assumption
Severe hypoglycaemic event	£380.00	Value taken from NICE draft CG
lower UTIs (male)	£93.01	2 GP visits plus trimethoprin 200mg twice daily
lower UTIs (female)	£47.01	1 GP visits plus trimethoprin 200mg twice daily
upper UTIs (male)	£94.02	2 GP visits plus trimethoprin 200mg twice daily
upper UTIs (female)	£94.02	2 GP visits plus trimethoprin 200mg twice daily
GMI (male)	£52.86	1 GP visit plus fluconazole for 7 days
GMI (female)	£49.45	1 GP visit plus 1 500mg clotrimazole pessary

Some additional costs for GTIs might be anticipated if a patient's partner is also treated.

Results

The QALY losses in the model are presented in tables 42 and 43 of the appendices which is summarised below (see Table 24). The AG interpretation of this is that canagliflozin 100mg has been taken as the reference for survival with the absolute QALY losses associated with the various events also being presented. The net absolute QALY difference between canagliflozin 100mg and each of the comparators is then presented, with the percentage contribution of the various events to this net QALY effect being presented alongside. Since the complications of diabetes other than neuropathy make little contribution to this, they have been grouped together for reasons of space.

Table 24 Janssen base case sources of QALY differences

	Loss	Survival	Hypo	AEs	Weight	Neurop.	Other
Cana. 100	1.258	..	0.213	0.015	0.553	0.358	0.119
Absolute QALY differences relative to canagliflozin 100mg, and proportionate contribution by source							
Cana. 300	+0.044	38%	11%	1%	42%	5%	3%
Cana. 100/300	+0.012	49%	12%	1%	36%	2%	0%
Dapa.	-0.033	26%	7%	1%	51%	9%	6%
Empa. 10mg	-0.029	28%	6%	1%	49%	10%	6%
Empa. 25mg	-0.015	7%	8%	1%	70%	8%	6%
Pioglitazone	-0.041	27%	33%	0%	36%	1%	4%
Gliclazide	-0.090	27%	19%	2%	40%	8%	5%
Sitagliptin	-0.058	23%	2%	3%	62%	4%	5%

The AG considers it odd that neuropathy should be so different between gliclazide and pioglitazone, but it is not possible to see how this is handled within the model.

The above shows that within the modelling survival differences account for a reasonable proportion of the estimated differences in mean QALYs between the comparators: about one quarter for the non-canagliflozin comparators. But the direct quality of life impacts of weight, hypoglycaemia and to a lesser extent neuropathy account for the majority of the differences. The QALY losses from the other complications of diabetes are relatively insignificant. A similar analysis can be presented for the cost differences (see Table 25).

Table 25 Janssen base case sources of cost differences

	Total	Oral Tx	Insulin	Hypo	AEs	Neurop.	Other
Cana. 100	£23,525	£3,190	£5,604	£142	£179	£6,350	£8,060
Absolute cost differences relative to canagliflozin 100mg, and proportionate contribution by source							
Cana. 300	£777	73%	21%	1%	0%	2%	3%
Cana. 100/300	£144	61%	33%	0%	0%	0%	4%
Dapa.	£69	46%	45%	1%	0%	2%	5%
Empa. 10mg	£55	47%	44%	0%	0%	3%	6%
Empa. 25mg	£3	49%	43%	0%	1%	3%	5%
Pioglitazone	-£3,261	68%	23%	1%	1%	1%	7%
Gliclazide	-£305	53%	39%	0%	1%	2%	4%
Sitagliptin	-£82	49%	30%	1%	3%	2%	14%

As can be seen from the above, the main differences in cost arise from difference treatment costs for both the oral drugs and insulin, with these being in part driven by the survival differences alluded to

above. The only real exceptions to this are for the comparison with pioglitazone, where an additional £156 treatment cost for CHF is anticipated compared to canagliflozin 100mg.

Ranking treatments in order of increasing total costs, the Janssen base case cost effectiveness results are as below. Note that the following table presents the ICERs relative to the cheapest comparator among those being considered. Not all these ICERs are presented by Janssen, with some having been derived be the AG, so are subject to rounding errors (see Table **26**).

Table 26 Janssen base case cost effectiveness estimates

			vs Pioglitazone			vs Gliclazide			vs Sitagliptin		
	Cost	QALY	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER
Pioglitazone	£20,264	9.998									
Gliclazide	£23,220	9.949	£2,956	-0.049	Dom						
Sitagliptin	£23,443	9.981	£3,179	-0.017	Dom	£223	0.032	£6,969			
Cana. 100	£23,525	10.039	£3,261	0.041	£79,537	£305	0.090	£3,377	£82	0.058	£1,414
Empa. 25mg	£23,528	10.024	£3,264	0.026	£125,538	£308	0.075	£4,107	£85	0.043	£1,977
Empa.10mg	£23,580	10.010	£3,316	0.012	£276,333	£360	0.061	£5,902	£137	0.029	£4,724
Dapa.	£23,594	10.006	£3,330	0.008	£416,250	£374	0.057	£6,561	£151	0.025	£6,040
Cana. 100/300	£23,669	10.051	£3,405	0.053	£64,245	£449	0.102	£4,402	£226	0.070	£3,229
Cana. 300	£24,302	10.083	£4,038	0.085	£47,456	£1,082	0.134	£8,075	£859	0.102	£8,422
Dom: dominated by pioglitzone.											

Pioglitazone is the cheapest due to its acquisition cost. As a consequence, while other treatments are estimated to be more effective compared to pioglitazone their cost effectiveness is poor. Both gliclazide and sitagliptin are estimated to be dominated by it. Sitagliptin being dominated by pioglitazone may be due to its assumed faster rate of HbA1c drift. Canagliflozin 100mg is estimated to have an ICER of £79,537 per QALY compared to pioglitazone. Canagliflozin 100mg also provides more QALYs at a cheaper cost than empagliflozin and dapagliflozin, so dominating them. Canagliflozin 100mg followed by canagliflozin 300mg has a better cost effectiveness against pioglitazone than canagliflozin 100mg, so extendedly dominates canagliflozin 100mg. But it is in turn extendedly dominated by canagliflozin 300mg which is estimated to have a cost effectiveness compared to pioglitazone of £47,456 per QALY.

The cost effectiveness of sitagliptin and the flozins is estimated to be more reasonable when compared to gliclazide. But canagliflozin 100mg extendedly dominates sitagliptin and dominates empagliflozin and dapagliflozin.

Across the nine comparators, the probabilistic modelling suggested that if the willingness to pay is zero, pioglitazone has a 100% probability of being the most cost effective treatment. This probability declined as the willingness to pay increased, until at around a willingness to pay of £55k it ceased to have the highest probability of being the most cost effective treatment. At this point canagliflozin 300mg overtook it, with a probability of being the most cost effective of around 25%.

At high willingness to pay values of £200k per QALY it appears that the probabilities of being the most cost effective have stabilised. Canagliflozin 300mg remains the highest with a probability of around 33%.

The others increase their probabilities as the willingness to pay rises, but still only converge to values under 20%, with the values for empagliflozin 10mg, dapagliflozin 10mg, sitagliptin 100mg and gliclazide never rising above 10%.

Sensitivity analyses

The univariate sensitivity analyses presented by Janssen vary parameters by an arbitrary ±20% and are consequently of limited interest. Full results of these are presented in tables 46 to 48 of the appendices to the submission. The main result of interest is that the modelling is sensitive to the annual rate of HbA1c drift that is assumed for canagliflozin: deterministic sensitivity analyses (DSA) number 6 lower value and upper value (6L and 6U) which respectively decrease and increase the base case 0.14% annual rate of drift by 20%. The cost effectiveness estimates under DSA 6L and DSA 6U for canagliflozin 100mg compared to:

- pioglitazone are £45,862 per QALY and £211k per QALY respectively
- gliclazide are £593 per QALY and £8,751 per QALY respectively
- sitagliptin are dominance and £8,528 per QALY respectively

In the opinion of the AG these changes are likely to be due more to the time spent on therapy and its immediate effects upon treatment cost, weight, adverse events and hypoglycaemia than to any changes in the modelled complications of diabetes. An exception to this might be the modelled rates of neuropathy.

Scenario analyses

A range of scenario analyses as summarised in table 13 on page 52 of the Janssen submission is presented, with summary results for all of these in tables 19 and 20 of the Janssen submission. The main points of interest identified by the AG are summarised below.

For the comparison with empagliflozin and dapagliflozin the main scenario analyses of interest are those that:

- revise the patient characteristics at baseline from those that Janssen pools from its trials to those of the THIN database, which is the database that underlies the patient characteristics of the modelling for the draft NICE CG: Sc5;
- apply the UKPDS68 HbA1c evolution equation and UKPDS62 quality of life values, while also assuming that patients can intensify to NPH insulin but not to basal-bolus insulin: Sc6; and,
- apply the UKPDS68 HbA1c evolution equation: Sc14.

These scenario analyses remove the dominance of canagliflozin 100mg over empagliflozin and dapagliflozin with the costs effectiveness estimates typically changing to lie between £5k and £10k per QALY.

Scenario analysis 14 is rather more dramatic in terms of the cost effectiveness estimates. But it would probably be more accurate to describe it as showing broad clinical equivalence but additional costs from canagliflozin compared to dapagliflozin, empagliflozin 10mg and empagliflozin 25mg of £198, £150 and £65 respectively.

Including repaglinide: Sc1

The analysis which includes repaglinide differs little from the base case analysis, but with repaglinide being estimated to have total costs of £22,170 and total QALYs of 9.967. As a consequence it is dominated by pioglitazone. If pioglitazone is excluded from this analysis gliclazide is still dominated, only now by sitagliptin. Sitagliptin with a cost effectiveness of £79,400 per QALY compared to repaglinide is in turn extendedly dominated by canagliflozin 100mg, which has a cost effectiveness of £21,050 per QALY compared to repaglinide. Empagliflozin and dapagliflozin remain dominated by canagliflozin 100mg. Canagliflozin 100mg followed by canagliflozin 300mg has a cost effectiveness estimate compared to repaglinide of £20,816 per QALY, which is again extendedly dominated by canagliflozin 300mg which has a cost effectiveness of £20,200 per QALY compared to repaglinide.

Same annual HbA1c drift across the monotherapies: Sc2

Unfortunately table 50 of the Janssen submission appendices does not provide the estimates for the canagliflozin 300mg arm. But the estimates for canagliflozin 100mg and canagliflozin 100 / 300 mg are extremely similar to those of the base case, and as a consequence the AG has used the estimates of the base case for canagliflozin 300mg for the following table. The reported ICERs are all compared to repaglinide (see Table **27**).

Table 27 Janssen scenario analysis: common HbA1c annual drift

	Cost	QALY	ICER
Repaglinide	£20,982	10.03	
Pioglitazone	£21,485	9.95	Dom
Gliclazide	£22,589	10.01	Dom
Sitagliptin	£23,615	9.99	Dom
Cana. 100	£23,732	10.05	£137,500
Empa. 25mg	£23,732	10.03	Dom
Emap. 10mg	£23,739	10.02	Dom
Dapagliflozin	£23,786	10.02	Dom
Cana. 100/300	£23,853	10.06	£95,700
Cana. 300	£24,594	10.09	£63,368
Dom: dominated by repaglinide			

If the annual HbA1c drift across the monotherapies is set equal to that of canagliflozin 100mg, this somewhat worsens the cost effectiveness of pioglitazone to the extent that it is now dominated by repaglinide. The cost effectiveness estimate for canagliflozin 100mg compared to pioglitazone improves to £24,233 per QALY

Assuming the same annual rate of HbA1c drift across the comparators improves the cost effectiveness of repaglinide and somewhat worsens the costs effectiveness estimates for canagliflozin compared to repaglinide. But the cost effectiveness estimate for canagliflozin compared to pioglitazone improves.

Lower BMI disutility: Sc4

Revising the disutility per BMI point from 0.0061 to 0.0038 has quite a large impact upon some results, as would be anticipated. The cost effectiveness estimate for canagliflozin 100mg compared to pioglitazone worsens to £146k per QALY and compared to repaglinide to £26,378 per QALY. The other costs effectiveness estimates are not particularly affected. Canagliflozin 100mg is still estimated to dominate the other flozins.

UKPDS68 HbA1c evolution coupled with UKPDS62 QoL: Sc6

This scenario applied the UKPDS68 HbA1c evolution and some of the UKPDS62 quality of life values.[185] It also assumed that there was no intensification to basal bolus insulin. The rationale for these grouped changes is not obvious, and as a consequence the AG prefers scenario analysis 14.

UKPDS HbA1c evolution: Sc14

Applying the UKPDS HbA1c evolution isolates the effects of this compared to scenario 6. The full results for this scenario do not appear to be reported in the Janssen appendices. As already reported above, for the comparisons with the other flozins there is broad clinical equivalence but additional costs from canagliflozin 100mg compared to dapagliflozin, empagliflozin 10mg and empagliflozin 25mg of £198, £150 and £65 respectively. Similarly there is broad clinical equivalence with gliclazide but a rather larger incremental cost of £744. The cost effectiveness of canagliflozin 100mg compared to pioglitazone improves somewhat to £31,945 per QALY.

The assumptions around the evolution of HbA1c are clearly central to the Janssen modelling. In the opinion of the AG this is not due to the complications of diabetes being modelled as changing. In the opinion of the AG it is likely to be mainly due to the amount of time a patient is modelled as spending on the various oral therapies changing. This primarily affects the direct drug costs of treatment, patients' weights, hypoglycaemia and adverse events.

Astrazeneca economic modelling

The CARDIFF Diabetes Model (CDM) is an individual patient level model that has been used for previous NICE assessments. It has been routinely submitted to the Mt. Hood challenges. But these submissions to the Mt. Hood challenges were with different assumptions than those used for the AstraZeneca submission.

The modelling of the complications of diabetes within the CDM was previously largely based upon the UKPDS68 risk equations, these being the basis of the UKPDS OM1 model. For the Astrazeneca submission, the CDM modelling of the complications of diabetes has been updated to use the UKPDS82 risk equations, these being the basis of the UKPDS OM2 model. Note that for the probabilistic modelling the UKPDS researchers have made available the 1,000 bootstraps of the equations underlying the UKPDS OM1 model to the Mt Hood challenge modellers. As far as the AG is aware the corollary of these has not been made available for the equations underlying the UKPDS OM2 model. As a consequence, it is not clear how the CDM of the Astrazeneca submission has implemented the probabilistic modelling.

During the STA of dapagliflozin the ERG noted various errors in the CDM implementation formulae for the evolution of the risk factors, which were subsequently corrected during the course of the STA. The AG assumption is that within the Astrazeneca submission these errors have been corrected.

The model was run with a 40 year time horizon and a cycle length of 6 months. Costs and benefits were discounted at 3.5%. The perspective was that of the patient for health impacts and of the NHS/PSS for costs.

It appears that for a deterministic model run 30,000 patients were run. It appears that each patient was run through the model only once, with no internal loops to reduce Monte-Carlo error. Probabilistic modelling was based upon 1000 PSA iterations, each with 30,000 patients being simulated. The submission did not present any analysis of model convergence over the number of patients modelled. The CDM only permits pairwise comparisons. As a consequence, the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion.

The AstraZeneca submission notes that among those receiving monotherapy, among the comparators within the NICE scope sulfonylurea has the largest market share of [redacted]. The gliptins share is stated as being [redacted] followed by [redacted] for the glitazones. Astrazeneca argue that the main comparator for the flozins will be the gliptins, which if true would justify the concentration upon pairwise comparisons.

The CDM models the incidence of the following micro-vascular complications:

- Amputation
- Nephropathy
- Blindness

Four macro-vascular complications are included:

- Ishaemic Heart Disease (IHD)
- Myocardial infarction (MI)
- Stroke; and
- Congestive heart failure (CHF).

The model also incorporates:

- Patient weight;
- Severe hypoglycaemia;
- UTIs;
- GTI; and,
- Discontinuations.

Patient characteristics

Patient characteristics at baseline were mainly drawn from the NMA, resulting in baseline estimates of 55 years of age, 54.6% male, 7.5% HbA1c due to NICE clinical guidelines though the NMA mean of 8.2% was used as a scenario analysis, 128.3mmHg SBP, 195mg/dl total cholesterol, 46mg/dl HDL and a weight of 80kg.

The submission does not appear to state what the baseline prevalence of the complications of diabetes was. The submitted electronic model sets these to zero.

Sequences modelled and treatment effectiveness

The comparators were grouped into their class as per the AstraZeneca NMA, e.g. the cost effectiveness of flozins as a group was estimated compared to the gliptins as a group. Note that of the glitazones only pioglitazone was considered, rather than a class effect being applied. Repaglinide was not considered as a comparator due to a lack of evidence.

Astrazeneca argues that allowing the intensifications to differ between the arms would not permit a fair assessment of the cost effectiveness of alternative monotherapies, but would rather be a comparison of the cost effectiveness of alternative treatment sequences. Consequently, the Astrazeneca submission modelled the following treatment sequences despite this not reflecting UK clinical practice (see Table **28**).

Table 28 Astrazeneca model treatment sequences

Monotherapy	1st intensification	2nd intensification
Flozin	NPH insulin	Intensified NPH
Gliptin	NPH insulin	Intensified NPH
Pioglitazone	NPH insulin	Intensified NPH
Sulfonylurea	NPH insulin	Intensified NPH

Intensified insulin was assumed to involve a 50% dose escalation.

Clinical effectiveness estimates for the monotherapies were drawn mainly from the 24 week NMA. Infection rates were not meta-analysed but were drawn from a weighted pooled mean of incidence data at 24 weeks from the papers included in the NMA. Clinical effectiveness estimates for insulin were drawn from Monami et al[192] for NPH and from Waugh et al[193] for intensified NPH (see

Table **29**). (The AG does not know how these figures for "intensified NPH" were obtained. Usually if NPH was insufficient, short-acting insulin would be added at meal-times.)

Table 29 Astrazeneca central clinical effectiveness estimates

Drug	Flozin	Glitpin	Pio	SU	NPH	Int. NPH
HbA1c	-0.74	-0.64	-0.90	-0.95	-1.10	-1.11
SBP	-5.87	-1.53	-1.31	-0.65	..	..
Weight (kg)	-2.81	-0.13	2.61	0.07	1.08	1.90
AEs						
UTI	0.092	0.022	0.153	..	..	..
GTI	0.074	0.002	..	..	..	..
Severe hypo	0.010	0.016	0.024	0.055	0.0004	0.0136
Non-severe hypo	..	..	..	..	0.0104	0.6024
1st cycle disc.	0.034	0.039	0.177	0.061	..	..

Treatment intensifications and discontinuations

A patient is modelled as intensifying treatment, first to NPH and then to intensified NPH, when their HbA1c breaches the 7.5% intensification threshold. The AG assumption is that the monotherapies are withdrawn at treatment intensification, but this is not explicit within the Astrazeneca submission.

Patients may also discontinue due to adverse events. The AG was unable to identify what was assumed for these patients: whether they switched to an alternative monotherapy and if so which, or whether they intensified to NPH insulin.

HbA1c evolution

In common with the AG modelling, the evolution of HbA1c is based upon equation 11 of the UKPDS68. Treatment intensification occurs if a patient's HbA1c breaches the 7.5% intensification threshold. This leads to a sawtooth evolution of HbA1c, as described in more detail in the section on the AG modelling.

Evolution of other risk factors

The evolution of SBP and the TC:HDL ratio was also based upon equations 12 and 13 of the UKPDS68. The section on the AG modelling describes this in some detail so it is not further described here.

Weight loss with the flozins is assumed to be maintained for two years after which it is assumed that patients rebound to their starting weight. A similar assumption appears to have been made for the gliptins, though the weight loss is only maintained for one year. The weight increases associated with the other treatments are assumed to be retained. Weight is also assumed to increase by 0.1kg annually.

Quality of life

The quality of life for a patient without any complications is a function of patient age, as drawn from analysis of EQ-5D data from the Health Survey for England 2003[194]:

$$QoL = 1.2066 - 0.0184 * Age + 0.0004 * Age^2 - 0.0000026 * Age^3$$

This results in a baseline quality of life of 0.882, with this slowly declining over time.

Quality of life decrements associated with the complications of diabetes were drawn from the UKPDS62[190] with the exception of that for End Stage Renal Disease (ESRD) which was drawn from the standard UKPDS OM1 source . Quality of life decrements for hypoglycaemic events were drawn from Currie et al[195], but note that it appears that the coefficient for symptomatic event was applied to the number of symptomatic events rather than to their logarithm. The quality of life impacts of increasing BMI was drawn from Baghust and Beale.[191] These sources and values are all as per the AG modelling so are not tabulated here for reasons of space.

Note that the submission suggests that the BMI disutility is applied for all BMI changes and is not limited in its effects to changes in BMI when the patient BMI is greater than $25kgm^{-2}$. If this applies it may have biased the analysis in favour of the flozins by valuing reductions on patients' BMI among those with a BMI of less than $25kgm^{-2}$. But given the mean BMI at baseline of $29.2kgm^{-2}$ this may not be a particular concern.

A systematic literature review was conducted for UTI and GTI QoL decrements. For UTIs the average of the values of Barry et al[196] 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.

Costs

The direct drug costs were sourced from the British National Formulary (BNF) 69. For both the flozins and the gliptins weighted average costs based upon their UK market share were used. This resulted in a mean annual flozin cost of £482 and a mean annual gliptin cost of £429. The annual cost of pioglitazone was £19 and the annual sulfonylurea cost was based upon gliclazide at an annual cost of £66. The cost of gliclazide suggests to the AG that modified release gliclazide has been assumed, as the standard version would be around half the cost that was applied.

The costs of the complications of diabetes in the first year and for subsequent years for blindness and amputation were based upon the UKPDS84.[187] This is the same source as the AG though the AG arrives at somewhat lower values. There may be a suggestion that indexation by AstraZeneca was

based on 2007 prices, when the UKPDS84 is in 2012 prices. But the source of the discrepancies is unclear.

AG calculations suggest that the UKPDS84 average inpatient costs and outpatient costs for those without any of the modelled complications have not been included within the AstraZeneca modelling. If this is the case it would be a quite serious omission, and would tend to bias the analysis in favour of the more effective treatment.

Astrazeneca may have used the UKPDS84 bespoke costing template to derive costs for a representative baseline patient, but this seems to be unlikely to be the source of the discrepancies between Astrazeneca and the AG. The Astrazeneca mean age at baseline is 55, while the AG has in order to be able to implement the costs probabilistically taken the costs example of the UKPDS82[186] for a 60 year old man. Costs are typically increasing in age in the UKPDS84.[187]

Table 5.10 of the AstraZeneca submission also does not include a cost for fatal IHD events despite these being within the UKPDS84 and seeming to be associated with deaths in the UKPDS82 and the UKPDS OM2. The UKPDS65 that goes along with the UKPDS68 and the UKPDS OM1 does not itemise a cost for fatal IHD events. But the AG understanding is that the AstraZeneca CDM modelling is based upon the UKPDS82 and as a consequence does not understand why fatal IHD events have had a zero cost assigned.

For reasons that are unclear, AstraZeneca chose to revert to the costs of the UKPDS65 for the ongoing costs among those with a history of IHD, CHF and stroke, and probably MI as well. This seems peculiar to the AG, given that the UKPDS82 and the UKPDS65 are very similar in their format with the UKPDS82 also presenting cost estimates for those with a history of IHD, CHF, stroke and MI.

ESRD was costed using the estimate of Baboolal et al.[197] for continuous ambulatory peritoneal dialysis. Previous NICE assessments have also used this reference, though have also tended to use the higher cost estimates within Baboolal et al for hospital haemodialysis. Astrazeneca argued that the use of the peritoneal dialysis cost was conservative.

Severe hypoglycaemia was costed using the Hammer et al (2009) reference, which is the reference used for the AG modelling. UTIs and GTIs were assumed to involve one GP appointment, costed at £46 using the PSSRU Unit Costs of Health and Social Care 2014.[198]See Table **30**.

Table 30 Astrazeneca costs of complications and adverse events.

	1st year		
Event	Fatal	Non-fatal	Subs. Years
Ischaemic Heart Disease		£12,762	£1,395
Myocardial Infarction	£2,605	£7,938	£2,177
Congestive Heart Failure		£5,180	£1,656
Stroke	£5,188	£11,450	£1,378
Amputation		£13,499	£4,618
Blindness		£6,502	£2,307
ESRD (including dialysis)		£18,776	£18,776
Severe hypoglycaemia		£424	£424
UTI		£46	£46
GTI		£46	£46

Results

The CDM modelling for the base case results in the following (see Table **31**). The AG assumption is that this is based upon deterministic modelling; i.e. with no second order sampling.

Table 31 Astrazeneca base case results: pairwise comparisons

	Flozins	Gliptins	net	Pioglitazone	net	SU	net
Drug costs	£5,638	£5,449	£190	£4,066	£1,572	£4,128	£1,510
Macro. compl.	£9,179	£9,251	-£72	£9,319	-£140	£9,226	-£47
Micro. compl.	£12,924	£12,938	-£14	£12,433	£491	£12,935	-£11
Hypoglycaemia	£175	£184	-£9	£197	-£22	£244	-£69
Other AE costs	£63	£51	£12	£53	£10	£49	£14
Total costs	£27,979	£27,873	£106	£26,067	£1,912	£26,582	£1,397
QALYs	13.206	13.188	0.018	13.111	0.095	13.179	0.027
ICER			£5,904		£20,089		£52,047

Within the pairwise comparisons, compared to the sulfonylureas the flozins offer some additional benefit of 0.027 QALYs but there are reasonable additional costs of £1,397 associated with this resulting in a cost effectiveness estimate of £52,047 per QALY.

The gains from the flozins compared to pioglitazone are larger at 0.095 QALYs which may be sufficient to justify the additional cost of £1,912 which results in a cost effectiveness estimate of £20,089 per QALY.

When compared with the gliptins, the flozins provide only a small additional gain of 0.018 QALYs but this is also at a relatively modest additional £106 cost which results in a cost effectiveness estimate of £5,904 per QALY.

The probabilistic pairwise modelling suggests that the flozins have a probability of being cost effective compared to the gliptin of 66%, compared to pioglitazone of 51% and compared to the sulfonylureas of 13%.

Ranking results in order of increasing cost sees the following (Table **32**).

Table 32 Astrazeneca base case results

	Cost	net	QALY	net	ICER
Pioglitazone	£26,067		13.111		
SU	£26,582	£515	13.179	0.068	£7,574
Gliptins	£27,873	£1,291	13.188	0.009	£143,444
Flozins	£27,979	£106	13.206	0.018	£5,904

As would be anticipated from the pairwise comparisons, it appears that the sulfonylureas have an acceptable cost effectiveness compared to pioglitazone of £7,574 per QALY. The gliptins offer minimal patient benefit compared to the sulfonylureas, 0.009 QALYs or the equivalent of around an additional 4 days survival, but with a reasonable increase in costs of £1,291 and a cost effectiveness estimate of £143k per QALY. As already noted, the flozins cost effectiveness estimate compared to the gliptins is good at £5,904 per QALY, but is poor against the sulfonylureas at £52,047 per QALY.

A variety of univariate sensitivity analyses were presented which varied the clinical effectiveness estimates to their upper and lower confidence interval limits, the disutilities for BMI changes to their upper and lower confidence interval limits, varied the disutilities for complications by ±10% and varied the total non-drug costs by ±25%.

Only the changes to the BMI disutility had any marked impact, with these impacts being mainly for the comparisons with pioglitazone and sulfonylurea. The lower confidence limit for the disutility of weight gains improved the cost effectiveness estimate compared to pioglitazone from £20,089 per QALY to £14,626 per QALY, while the upper confidence limit worsened it to £32,065 per QALY. The lower confidence limit for the utility of weight losses worsened the cost effectiveness compared to the sulfonylureas from £52,047 per QALY to £62,810 per QALY, while the upper confidence limit improved it to £4,434 per QALY.

Due to the CDM of AstraZeneca only modelling pairwise comparisons, the probabilistic modelling is only presented for the pairwise comparisons.

Compared to the gliptins, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 42%, 65% and 68% with the CEAC converging to a little over 70% at high willingness to pay values.

Compared to pioglitazone, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 0%, 50% and 80% with the CEAC converging to a little over 95% at high willingness to pay values.

Compared to sulfonylurea, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 0%, 12% and 26% with the CEAC still slowly increasing to a little over 60% at a willingness to pay of £100k per QALY.

Scenario analyses

A range of scenario analyses were undertaken, mainly varying the HbA1c values at baseline and HbA1c thresholds for intensifying treatment, altering the assumptions around maintenance of weight effects and the drug costs that were applied (see Table **33**).

Table 33 Astrazeneca scenario analyses: cost effectiveness estimates for the flozins

	vs Gliptins			vs Pioglitazone			vs SUs		
	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER
HbA1c base. 7.5%, thresh. 8.0%	£225	0.021	£10,799	£3,059	0.106	£28,970	£2,335	0.037	£63,783
HbA1c base. 8.19%, thresh. 8.19%	£198	0.023	£8,694	£3,327	0.101	£32,982	£1,846	0.021	£88,934
HbA1c base. 7.5%, thresh 7.5, 8.0%	£100	0.020	£4,977	£1,902	0.101	£18,884	£1,382	0.026	£53,057
Flozin wgt maintain 1 year	£22	0.014	£1,583	£1,828	0.091	£20,077	£1,313	0.023	£57,839
Comparator wgt maintain 2 year	£115	0.014	£8,137	£1,913	0.101	£19,032	£1,435	0.028	£51,166
Flozin & Pio wgt conv. final int.	..	..	..	£1,818	0.048	£38,199	..	..	..
No discontinuations	£69	0.023	£3,035	n.a.	n.a.	n.a.	£1,431	0.028	£51,718
No AE disutility	£106	0.019	£5,685	n.a.	n.a.	n.a.	£1,397	0.028	£50,456
Cana 100 and 300 mkt share [redacted]	£137	0.018	£7,585	£1,943	0.095	£20,407	£1,427	0.027	£53,176
Sitagliptin price	£90	0.018	£4,996	..	..	..	..	..	..
Alogliptin price	£410	0.018	£22,756	..	..	..	..	..	..
20 year time horizon	£100	0.020	£5,093	£1,841	0.089	£20,611	£1,399	0.028	£49,275

The scenario analyses around adverse events and discontinuations for the comparison with pioglitazone were reported as having the same values as the corresponding analyses for sitagliptin, so appear to be typos.

Less stringent thresholds for intensification of therapy tended to worsen the cost effectiveness estimates. This seems likely to be mainly due to patients remaining on their monotherapy for longer and the associated increase in the direct drug costs, and not due to differences in the modelled complications of diabetes.

Weight convergence between the flozins and pioglitazone somewhat worsens the cost effectiveness estimate, due to this removing the weight gains associated with pioglitazone. Not that this convergence is only imposed at around the seventh or eighth year of the modelling.

Results compared to the gliptins are not particularly sensitive to whether the sitagliptin price is applied rather than the gliptins' prices weighted by their market shares, due to Astrazeneca estimating sitagliptin to have a market share of the gliptin monotherapy of [redacted] with the similarly prices saxagliptin and linagliptin having market shares of [redacted] and [redacted] respectively. Alogliptin is notably cheaper but is estimated to have less than a [redacted] market share.

Boehringer Ingelheim economic modelling

Boehringer Ingelheim presented the results of two modelling exercises: model A and model B.

Model A simulated the effects of one year of treatment. Thereafter the path of the patient was determined by the UKPDS OM1. This appears to have limited the direct treatment effects for elements such as treatment cost and the direct treatment effects upon adverse events and the quality of life impact of weight changes to one year's duration. At the end of the first year the AG assumption is that the treatment effects upon HbA1c, SBP, the TC:HDL ratio and weight were fed into the UKPDS OM1 to model the lifetime impact of the monotherapy. But the AG has not been able to identify how the model A does this and this assumption is based upon the written Boehringer Ingelheim submission which states that "*Model A… approach… patients undergo different comparator therapies for a year… the UKPDS model then undergoes a full 40 year … run*".

The AG understanding, which may not be correct, is that in effect this assumed that the patient remained on the monotherapy for the patient lifetime. And that it also assumed that the direct treatment costs, adverse events and direct quality of life impacts from weight changes would only apply during the first year.

Model B was somewhat more involved, and took a similar modelling approach to that of the modelling for the draft NICE CG for T2DM and the AG modelling for the current assessment. An excel front end was designed for the UKPDS OM1, which modelled the initial treatment effects and then used the UKPDS risk equations to model the evolution of the risk factors and the complications of diabetes. When patients' HbA1c breached the 7.5% intensification threshold they could first intensify by adding another oral drug, with a second intensification to NPH insulin also being possible. The survival curve of the OM1 coupled with the timing of intensifications permitted model B to calculate treatment specific treatment costs, adverse event rates and quality of life impacts from weight changes to add to the outputs of the OM1 model.

Boehringer Ingelheim noted that the model B ran the OM1 one year at a time, and that this can lead to an underestimation of the total costs and total QALYs over the 40 year time horizon. Boehringer Ingelheim suggested that this will tend to have underestimated the cost effectiveness of empagliflozin. Note that the AG approach was to run the OM1 model over the 40 year time horizon for each patient simulated.

Patient characteristics

Patient characteristics were drawn from patients within the Clinical Practice Research Datalink (CPRD). This identified 9,211 UK patients with who started their first oral antidiabetic treatment in 2014. While not all of the codes used for the search appear to have been specific to T2DM; e.g. diabetes mellitus, the minimum age at diagnosis was 23 with a mean of 60 and a standard deviation of 12 and the requirement to be starting an oral therapy should have restricted the sample to T2DM patients.

The average duration of diabetes was 2.9 years, 57% being male. The mean HbA1c was 8.49%, SBP 134mmHg, HDL 1.2mmol/l and LDL 4.0mmol/l. The mean BMI was 31kgm^{-2}.

The presence of existing complications was included: 6.63% for atrial fibrillation, 3.18% for PVD, 2.21% for MI, 1.92% for CHF, 1.62% for stroke, 6.13% for IHD, 0.29% for amputation, 0.23% for blindness, and 0.05% for renal failure.

Sequences modelled and treatment effectiveness

Model A only considers the first year of treatment with monotherapy and then adds the UKPDS costs and complications to this.

Model B considers the following treatment sequences, with patients intensifying to the next line of therapy when their HbA1c breaches the 7.5% intensification threshold (see Table **34** and Table **35**).

Table 34 Boehringer Ingelheim sequences modelled: 52 week data

Monotherapy	1st intensification	2nd intensification
Repaglinide 1mg	+Gliclazide	+ NPH insulin
Gliclazide	+Sitagliptin	
Pioglitazone 45mg	+Gliclazide	
Sitagliptin 100mg	+Gliclazide	
Empagliflozin 10mg	+Gliclazide	
Empagliflozin 25mg	+Gliclazide	

Pioglitazone 45mg was chosen due to it being the most commonly prescribed dose. The differences in cost between pioglitazone 30mg and pioglitazone 45mg are minimal.

AG comment. If repaglinide was insufficient, it would be replaced since for dual use, it is licensed only with metformin. So it would not be logical to add gliclazide to repaglinide since they act largely on the same receptors. Note also that 1mg is a small dose of repaglinide.

Table 35 Boehringer Ingelheim sequences modelled: 24 week data

Monotherapy	1st intensification	2nd intensification
Dapagliflozin 5mg	+Gliclazide	+ NPH insulin
Dapagliflozin 10mg	+Gliclazide	
Canagliflozin 100mg	+Gliclazide	
Canagliflozin 300mg	+Gliclazide	
Empagliflozin 10mg	+Gliclazide	
Empagliflozin 25mg	+Gliclazide	

Clinical effectiveness data was based upon 52 week data where available though this was apparently not available for canagliflozin or dapagliflozin. Sitagliptin clinical effectiveness estimates were apparently based upon 24 week data, though the submission does not state that 52 weeks data was not available. The effect upon SBP and rates of UTIs were also based upon 24 week data due to 52 week data not being available.

Hypoglycaemia rates were based upon sulfonylurea 16.4% annual rate of the NMA (for pooled sulfonylureas) coupled with odds ratios for each of the comparators against sulfonylurea. A ratio of non-severe to severe hypoglycaemia event rate of 17.2 was based upon the 0.009 annual rate of severe hypoglycaemia event rates of Leese et al (2003) coupled with the overall rates of hypoglycaemia in the NMA.

UTI event rates were based upon the annual placebo rates of 3.5% from the NMA coupled with odds ratios for each of the comparators.

Table 36 Boehringer Ingelheim monotherapies effectiveness: 24 week data

	Cana		Dapa		Empa	
	100mg	300mg	5mg	10mg	10mg	25mg
HbA1c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..	..	..	..
Hypos OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSHypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37 Boehringer Ingelheim monotherapies effectiveness: 52 week data

	Empa		Pio	Repa	Sita	Gliclazide
	10mg	25mg	45mg	1mg	100mg	
HBA1c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..	..	..	..
Hypos OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSHypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The above table (Table **36** and Table **37**) reports the SBP effects and hypoglycaemia odds ratios from the written submission, and the hypoglycaemia event rates of the electronic model B.

Based upon a comparison of the written submission with the electronic model B it appears that the values relative to placebo have been inputted to the model. It appears that the placebo effects have not been included which may tend to have underestimated the absolute treatment effects from baseline to 24 or 52 weeks. This is with the exception of the hypoglycaemia and UTI rates.

Table 38 Boehringer Ingelheim intensification effectiveness data

	1st		2nd
	+SU	+Glitpin	NPH
HBA1c	[redacted]	[redacted]	[redacted]

SBP	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..
Hypos OR	[redacted]	[redacted]	..
NSHypos	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	..
UTIs	[redacted]	[redacted]	[redacted]

Note that for the intensifications the hypoglycaemia event odds ratios are apparently relative to placebo, while the UTI odds ratio is relative to the sulfonylurea. The UTI rate of NPH insulin was taken from the placebo arm of the NMA of the submission for empagliflozin combination therapy (see Table **38**).

Treatment intensifications and discontinuations

Within model A there are no treatment intensifications. Treatment with the monotherapies is for one year only, after which it appears that the UKPDS OM1 model is appended to this.

Within model B treatment is intensified when a patient is modelled as breaching the 7.5% HbA1c threshold.

It appears that discontinuations of therapy for reasons other than breaching the HbA1c threshold of 7.5% have not been modelled.

HbA1c evolution

The evolution of HbA1c is based upon equation 11 of the UKPDS68.

Within model A it appears that the patient's baseline HbA1c has the treatment effect of the initial monotherapy applied, with the UKPDS OM1 and hence relevant equation of the UKPDS68 being used to model its evolution thereafter. But as stated in the introduction, the AG has not been able to identify how model A interacts with the UKPDS OM1.

Within model B it appears that the patient's baseline HbA1c has the treatment effect of the initial monotherapy applied. Equation 11 of the UKPDS68 is then used to model the evolution of the patient's HbA1c until it breaches the 7.5% intensification threshold, at which point the treatment effect of the 1st intensification is applied. Equation 11 of the UKPDS68 is then applied until the 2nd intensification occurs with the associated treatment effect. HbA1c is then modelled as progressing as per equation 11 of the UKPDS68.

Evolution of the other risk factors

The evolution of SBP and the TC:HDL is based the UKPDS OM1 and hence relevant equation of the UKPDS68.

Within model A, it appears that the patient's baseline SBP had the treatment effect of the initial therapy applied, with equation 12 of the UKPDS68 being used to model its evolution thereafter. For the TC:HDL ratio due to there being no treatment effects estimated, it appears that equation 13 of the UKPDS68 was used to model the evolution throughout. But again, as stated in the introduction, the AG has not been able to identify how model A interacts with the UKPDS OM1.

Within model A the direct impacts of weight changes upon quality of life were only evaluated during the first year. For the UKPDS modelling it appears that weight losses were assumed to rebound to baseline after one year, while weight gains were assumed to remain indefinitely.

Within model B it appears that the patient's baseline SBP had the treatment effect of the initial therapy applied, with equation 12 of the UKPDS68 being used to model its evolution except for when a treatment intensification took place at which point the treatment effect of the intensification was applied. For the TC:HDL ratio due to there being no treatment effects estimated, it appears that equation 13 of the UKPDS68 was used to model the evolution throughout.

Within model B, weight losses from treatment were assumed to apply at 52 weeks and then to rebound to baseline at 104 weeks. Weight gains from treatment were assumed to be maintained indefinitely. A 0.1kg annual weight gain from natural history was also applied.

Quality of life

The quality of life at baseline and the quality of life decrements associated with the complications of diabetes were drawn from the recent paper by Alva et al[189] which reanalysed the updated UKPDS data set and in some sense updated the values of the UKPDS62 which is the paper that the AG modelling relies upon. The values and a commentary upon this are presented later in the comparison of modelling inputs used by the companies and the AG.

In common with the other companies, the quality of life impact of hypoglycaemic events was drawn from Currie et al.[195] Similarly, the quality of life decrement of -0.0061 per BMI point above 25kgm^{-2} was drawn from Baghust and Beale.[191]

The quality of life decrement of -0.00283 per UTI was based upon the estimates of Barry et al.[196]

Costs

Treatment costs were based upon the March 2015 MIMs.

The costs of diabetes without complications and the costs of the complications of diabetes were taken from the UKPDS84. Boehringer Ingelheim appears to have only applied the inpatient costs of the UKPDS84, and to have ignored the outpatient costs.

A cost of £380 per severe hypoglycaemic event was drawn from the draft NICE CG for T2DM, which is similar to that of the other company submissions and AG value.

UTIs were associated with a £36 cost, based upon the ERG report[199] for the previous STA of dapagliflozin for T2DM combination therapy.

Results

For model A, table 65 of the Boehringer Ingelheim submission presents the disaggregate costs and QALYs. Tables 66 and 67 present net quantities for the 52 week analyses relative to empagliflozin 25mg and empagliflozin 10mg respectively. Tables 68 and 69 present net quantities for the 24 week analyses relative to empagliflozin 25mg and empagliflozin 10mg respectively. The following presents a summary of these. For clarity:

- Model A is the one year decision tree model with the UKPDS OM1 tacked onto the end of it
- Model B is the Boehringer Ingelheim designed front and back end to the UKPDS OM1
- The 52 week analysis compares empagliflozin with the non-flozin comparators
- The 24 week analysis compares the flozins with one another

The combination of the above yields four sets of results.

Table 39 Boehringer Ingelheim results: Model A: 52 weeks analysis

			vs. pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Gliclazide	[redacted]	[redacted]	£4	0.008	£500
Repag. 1mg	[redacted]	[redacted]	£30	0.009	£3,333
Empa. 25mg	[redacted]	[redacted]	£283	0.050	£5,634
Empa. 10mg	[redacted]	[redacted]	£304	0.043	£7,070
Sita. 100mg	[redacted]	[redacted]	£363	0.014	£25,929

Table 40 Boehringer Ingelheim results: Model A: 24 weeks analysis

			vs. canagliflozin 100mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Cana. 100mg	[redacted]	[redacted]			
Empa. 25mg	[redacted]	[redacted]	£26	-0.008	Dominated
Empa. 10mg	[redacted]	[redacted]	£43	-0.015	Dominated
Dapa. 10mg	[redacted]	[redacted]	£44	-0.018	Dominated
Dapa. 5mg	[redacted]	[redacted]	£55	-0.020	Dominated
Cana.300mg	[redacted]	[redacted]	£64	0.021	£3,048

The tables above (Table **39** and Table **40**) may have some rounding errors due to the AG constructing the ICERs versus pioglitazone.

In model A, empagliflozin 25 mg is estimated to dominate both empagliflozin 10mg and sitagliptin. Its cost effectiveness compared to pioglitazone is estimated to be £5,364 per QALY, compared to gliclazide is estimated to be £6,643 per QALY, and compared to repaglinide is estimated to be £6,171 per QALY. Pioglitazone, gliclazide and repaglinide are essentially estimated to all involve the same costs and patient benefits. Among the flozins, canagliflozin 100mg is estimated to dominate the other flozins with the exception of canagliflozin 300mg.

For Model B, table 71 of the submission presents the disaggregated results with tables 72 and 73 presenting the aggregate results. The AG has not managed to reconcile these to sources, so the results of both are presented below (Table **41**).

Table 41 Boehringer Ingelheim results: Model B costs: 52 week analysis

	Table 71					Table 72
	UKPDS	Tx	S Hypo	UTI	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa.10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pio 45mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sita. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that the UKPDS costs of Model B that are reported in table 71 are around half those of Model A that are reported in table 65. This is a cause of some concern, and the reason for these discrepancies is far from obvious.

Table 42 Boehringer Ingelheim results: Model B QALYs: 52 week analysis

	Table 71						Table 72
	UKPDS	BMI	NSHypo	S Hypo	UTIs	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa.10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pio 45mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sita 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The UKPDS QALYs of Model B are much more in line with those of Model A, the values in table 71 being around 90% of those in table 65 (Table **42**).

Table 43 Boehringer Ingelheim results: Model B: Table 71 : 52 week analysis

			vs pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	£57,416
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	£35,223
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,987
Sita. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom

Pioglitazone is estimated to be the cheapest comparator, and to dominate both gliclazide and sitagliptin. Repaglinide costs an additional [redacted] than pioglitazone and yields an additional [redacted] QALYs, resulting in a cost effectiveness estimate of £57,416 per QALY compared to pioglitazone. But repaglinide is extendedly dominated by empagliflozin 25mg which while costing [redacted] more than pioglitazone results in an additional [redacted] QALYs, hence a cost effectiveness estimate of £35,223 per QALY. Empagliflozin 25mg is estimated to dominated empagliflozin 10mg and sitagliptin 100mg.

But the AG assumption is that the correct cost effectiveness estimates are those of table 72, as reported below (Table **44**) since it is these that Boehringer Ingelheim has chosen to concentrate upon.

Table 44 Boehringer Ingelheim results: Model B: Table 72 : 52 week analysis

			vs pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Repa 1mg	[redacted]	[redacted]	£635	0.025	£25,349
Gliclazide	[redacted]	[redacted]	£1,527	0.013	£122k
Sita. 100mg	[redacted]	[redacted]	£2,504	0.015	£164k
Empa. 25mg	[redacted]	[redacted]	£2,834	0.061	£46,480
Empa. 10mg	[redacted]	[redacted]	£2,837	0.056	£50,892

With the exception of repaglinide, none the other comparators appear to be cost effective compared to pioglitazone at conventional thresholds. But empagliflozin 25mg is estimated to cost an additional [redacted] when compared to sitagliptin 100mg and to cause an additional [redacted] QALYs, so have a cost effectiveness of £7,228 per QALY (Table 45, Table 46 and Table **47**).

Table 45 Boehringer Ingelheim results: Model B Costs: 24 week analysis

	Table 71					Table 72
	UKPDS	Tx	S Hypo	UTI	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 46 Boehringer Ingelheim results: Model B QALYs: 24 week analysis

	Table 71						Table 73
	UKPDS	BMI	NSHypo	S Hypo	UTIs	Total	Total

Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 47 Boehringer Ingelheim results: Model B: table 71: 24 weeks

			vs empagliflozin 25mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Empa. 25mg	[redacted]	[redacted]			
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Cana.100mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	£62,442

Based upon table 71, empagliflozin 25mg is estimated to be the cheapest of the flozins and to dominate the other flozins with the exception of canagliflozin 300mg. Canagliflozin 300mg is estimated to cost an additional [redacted] compared to empagliflozin 25mg but also yield an additional [redacted] QALYs so have a cost effectiveness estimate of £62,442 per QALY.

But the AG assumption is that the correct cost effectiveness estimates are those implied by table 73, as reported below (Table **48**).

Table 48 Boehringer Ingelheim results: Model B: table 73: 24 weeks

			vs dapagliflozin 10mg			vs canagliflozin 100mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Dapa. 10mg	[redacted]	[redacted]						
Cana. 100mg	[redacted]	[redacted]	£1	0.033	£39			
Dapa. 5mg	[redacted]	[redacted]	£43	0.001	£31,840	£42	-0.032	Dom
Empa. 25mg	[redacted]	[redacted]	£46	0.021	£2,172	£45	-0.012	Dom
Empa. 10mg	[redacted]	[redacted]	£68	0.007	£9,835	£67	-0.026	Dom
Cana. 300mg	[redacted]	[redacted]	£970	0.056	£17,363	£969	0.023	£42,951

While dapagliflozin 10mg is technically the cheapest, being only £1 less than canagliflozin 100mg it is essentially the same cost but inferior to it. Canagliflozin 100mg is the more natural baseline. This dominated the other comparators, with the exception of canagliflozin 300mg. Canagliflozin 300mg

costs £969 more than canagliflozin 100mg but yield an additional 0.023 QALYs, resulting in a cost effectiveness estimate of £42,951 per QALY.

Sensitivity analyses

Boehringer Ingelheim did not present any sensitivity analyses.

Assessment group economic modelling

The model

The protocol specified that either the UKPDS outcomes model 1 (OM1) or the UKPDS outcomes model 2 (OM2) would be used by the AG. For some of its outputs the OM1 is quite different from the OM2 in its predictions. But the OM2 was not made available to the AG in time for the assessment and so as specified in the protocol the OM1 has been used.

As already noted, the OM1 predicts roughly double the number of myocardial infarctions over ten years, and the rates of IHD are also noticeably higher than those of the OM2. The ten year mortality is also higher with the OM1. Compared to the OM2, the OM1 will tend to over predict event rates and so overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment. Being more recent and more reflective of current practice, the OM2 would consequently have been much preferable had it been available to the AG.

The OM1 was used for the modelling that underlies the current draft NICE CG for diabetes. During its development the GDG reviewed in detail ten T2DM cost effectiveness models. These included the JADE and CORE models, but not the ECHO-T2DM model. Based upon validation and consistency with the NICE reference case the GDG very much preferred the OM1, in no small part due to it being based upon a single RCT rather than drawing a range of modelling inputs from disparate sources.

The AG has developed a front and back end to the OM1. Briefly, for each patient and treatment strategy that is simulated the AG front end models the patient's progression from monotherapy through the various treatment intensifications over a 40 year time horizon in annual cycles. This in turn introduces the patient's evolutions of HbA1c, SBP, TC:HDL, BMI, hypoglycaemia event rates, adverse events and treatment costs. The evolutions of the patient's HbA1c, SBP and TC:HDL are then fed into the OM1 which models the complications of diabetes and patient lifespan, and outputs the costs and quality of life impacts of living with diabetes and the patient's survival curve. The AG back end takes the OM1 survival curve and uses this to condition the evolutions of the patient's BMI, hypoglycaemia event rates, adverse events and treatment costs. The cost and quality of life impacts of these are then summed with the cost and quality of life impacts outputted by the OM1.

In slightly more detail, patients start on monotherapy but intensify their treatment if their HbA1c is modelled as breaching the 7.5% threshold. Intensifications typically add another treatment to a patient's existing treatment(s). This permits treatment sequences to be modelled, starting with monotherapy but with subsequent treatment intensifications, these intensifications eventually leading to first basal insulin and then basal-bolus insulin. Each treatment within a sequence is associated with treatment costs, weight changes, hypoglycaemic events and adverse events. The AG modelling also

permits treatments to be associated with a discontinuation rate in their first year, with patients who discontinue being assumed to switch to another treatment at the same line of therapy.

For each patient that is modelled, the modelled treatment sequences lead to a modelled evolution of HbA1c, SBP and TC:HDL ratio. These, together with the patient's baseline characteristics, are fed into the OM1. The OM1 then models the rates of the complications of diabetes, such as CHF, and the patient survival, which results in estimates for the discounted costs and QALY impacts of the complications of diabetes over the modelled lifetime of the patient. A survival curve is also drawn from the OM1 model. Due to the model being an individual patient simulation any given patient is run through the model many times, say 1,000 inner loops, in order to reduce Mote-Carlo sampling error. In effect this is the same as running a cohort of 1,000 identical patients through the model. The OM1 survival curve is the proportion of this cohort, or 1,000 inner loops, that is modelled as surviving. This survival curve conditions the AG front end evolutions of treatment sequences and the cost and QALY impacts of their treatment costs, weight changes, hypoglycaemic events and adverse events.

For the deterministic model run the OM1 correctly outputs the relevant survival curve. Unfortunately, for the PSA iterations it appears that the OM1 does not output the relevant survival curve. As a consequence, the relevant survival curve has had to be imputed from the OM1 annual discounted QALY estimates by an initial run of the model with the baseline quality of life set equal to unity and the quality of life decrements of the complications all set to zero. The resulting annual discounted QALYs were then undiscounted to arrive at the patient specific survival curve. (For the PSA each patient was run with 100 inner loops, and as a consequence the imputed survival curve had a granularity of 1%) But this also meant that the PSA had to run the OM1 model twice for each strategy for a given patient for a given PSA iteration. This also required that the same random number seed be used for each of these model runs in order for the imputed survival curve to be consistent with the second run of the model that estimated the strategy's costs and benefits. The OM1 only permits the random number seed to be 1 of 100 values. The AG model randomly assigned this value during the PSA, keeping this value constant between the two model runs for a given patient for a given PSA iteration. Having to run the model twice for a given patient for a given PSA iteration also significantly increased the time it took to run the PSA.

An element that the OM1 cannot address is the requirement for patients receiving a flozin to have their dose of it reduced or discontinued based upon renal function and eGFR rates. While the AG has a number of issues with the Janssen modelling, the use of the ECHO-T2DM model did permit this to be explored though the AG has not reviewed the implementation of this in any detail. It would be interesting to know the impact that turning off these discontinuations would have upon the cost effectiveness estimates of the Janssen modelling. If this is significant enough to affect the conclusions

that would be drawn from the Janssen modelling it could suggest additional modelling uncertainty from the AG use of the OM1.

The AG visual basic modelling has the advantage of permitting up to twelve treatment strategies to be simultaneously compared with one another, with the correlation between treatments' effects being properly taken into account. Each PSA iteration also uses the same set of parameter values and random number seed across all the treatment strategies being modelled. This in turn permits the correct characterisation of uncertainty within the probabilistic modelling.

Model runs

The draft NICE CG for diabetes concluded after a number of model runs that with a patient cohort of 35,000 or more there was little to be gained from running more than 100 inner loops to reduce Monte-Carlo sampling error. As a consequence, probabilistic results were based upon 1,000 PSA iterations each with a patient cohort of 50,000 with 100 inner loops. For deterministic model runs, i.e. those without any second order sampling, the modelling for the CG increased the number of inner loops to 1,000 as recommended within the OM1 manual.

The AG has adopted the same approach.

Probabilistic sampling

The risk factor evolution parameters of equations 11, 12 and 13 of the UKPDS68 were received as 1,000 bootstrap samples from the UKPDS group (Personal communication Prof Alastair Gray University of Oxford June 2015). The UKPDS OM1 also only permits 1,000 bootstraps.

The other parameters within the modelling were sampled by the AG. Clinical effectiveness was sampled within the NMA, with this outputting 10,000 lookup values for the various clinical effectiveness parameters. But due to the OM1 only permitting 1,000 bootstraps and the time taken to run the PSA, a subset of 1,000 were sampled from the 10,000 lookup values of the NMA. It was checked that these subsets had means that were similar to the central estimates of the NMA.

Other parameters were sampled by the AG using the distributions outlined below.

Patient characteristics at baseline

The patient characteristics at baseline are taken from the current draft NICE CG for diabetes. This undertook extensive analysis of the THIN data base, supported by some additional data from the Health Survey for England (see Table **49**).

Table 49 NICE CG baseline risk factors and baseline complication rates

Age	59.8	Atrial fibrillation	0.81%
Duration diabetes	2.0	PVD	0.51%
Male	57%	MI	0.80%
BMI	31.9	CHF	0.50%
HbA1c	8.40%	Stroke	0.50%
SBP	137.5	IHD	2.70%
TC	4.96	Amputation	0.10%
HDL	1.18	Blindness	0.40%
Current smoker	18.1%	Renal failure	0.20%
Past smoker	34.0%		

These were sampled once for the modelling using the full variance-covariance between the characteristics, as per the modelling for the current draft NICE CG for diabetes.

The AG has adopted these values with the exception of the baseline the baseline TC:HDL ratio. TC:HDL has been assumed to be 3.0 due to NICE guidelines on atorvastatin use in people with diabetes. This change in therapy may be partly the cause of the differences between the OM1 and the OM2. A scenario analysis applies the values of the NICE CG and evolves these according to the UKPDS 68 equation 13.

Astrazeneca argued that the baseline HbA1c should be 7.5% in order to be in line with NICE guidelines. But the patients modelled are starting their first drug treatment after on average having been diagnosed with diabetes for 2.0 years. The mean HbA1c at diagnosis was estimated to be 8.2%. It seems unlikely that most patients will have successfully controlled their diabetes through diet and exercise and got below 7.5% if they were above it at diagnosis, only to subsequently lose this control. As a consequence, the base case will apply the baseline HbA1c values as estimated within the draft NICE CG. A scenario analysis applies a common 7.5% HbA1c at baseline across the 50,000 patients simulated.

Sequences modelled

As outlined in the assessment protocol, in line with NICE guidelines patients will intensify their treatment if their HbA1c breaches the 7.5% intensification threshold. As a consequence, the modelling needs to take into account the clinical effects and costs of these intensifications. Based upon expert opinion the AG has modelled the following treatment sequences (Table **50**).

Table 50 AG treatment sequences modelled

Monotherapy	1st intensification	2nd intensification	3rd intensification

Repaglinide	-Repaglinide +Pioglitazone +Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Gliclazide	+Pioglitazone	+NPH insulin	-Gliclazide +Bolus insulin
Pioglitazone	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Sitagliptin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Dapagliflozin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Empagliflozin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Canagliflozin100	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin

Clinical effectiveness

The clinical effectiveness estimates are drawn from the Warwick AG NMA as presented in the clinical effectiveness section and from a review of the literature. Events rates are annual unless otherwise stated (Table **51** and Table **52**).

Table 51 AG monotherapy clinical effectiveness estimates: non-flozins

	Gliclazide		Pio.		Repag.		Sita.	
	μ	s.e.	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-1.301	0.014	-1.200	0.011	-1.200	0.360	-0.723	0.019
SBP	-0.600	0.520	-1.400	0.500	-1.000	0.000	0.394	0.048
Weight	1.397	0.013	2.962	0.009	0.100	0.670	-0.003	0.275
Sev. Hypo	0.10%	0.04%	0.00%	0.00%	2.00%	0.70%	0.00%	0.00%
Symp. Hypo	1.30%	0.40%	0.00%	0.00%	13.00%	1.70%	0.00%	0.00%
UTI	4.00%	1.00%	4.00%	1.00%	4.00%	1.00%	4.00%	1.00%
GTI	1.00%	0.49%	1.00%	0.49%	1.00%	0.49%	1.00%	0.49%
Disc.	3.30%	0.82%	9.00%	0.74%	5.00%	3.00%	4.00%	1.30%

Note that in the above the rates of hypoglycaemia, UTIs and GTIs are annual.

Table 52 AG monotherapy clinical effectiveness estimates: flozins

	Dapa. 10		Empa. 25		Cana.300	
	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-0.704	0.016	-0.870	0.016	-1.153	0.032
SBP	-2.931	0.024	-3.743	0.054	-1.338	0.048
Weight	-2.457	0.006	-2.471	0.008	-3.577	0.012
Sev. Hypo	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Symp. Hypo	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
UTI	5.50%	1.97%	5.40%	1.50%	6.60%	1.80%
GTI	4.50%	1.80%	3.60%	0.64%	5.00%	2.00%
Disc.	3.00%	1.50%	1.80%	0.91%	2.00%	1.00%

For the flozins the UTIs rates and GTIs rates are half-yearly.

For the intensifications, due to a lack of data the addition of a treatment is assumed to have the same clinical effectiveness regardless of what it is being added to (see Table **53** and Table **54**).

Table 53 AG 1st intensification clinical effectiveness estimates

	+Pio		+Glicl.		-Repag. +Glicl. +Pio.	
	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-1.200	0.011	-1.010	0.011	-1.200	0.011
SBP	-1.400	0.500	-0.600	0.520	-1.400	0.500
Weight	2.800	0.160	1.300	0.070	2.800	0.160
Sev. Hypo	0.00%	0.00%	0.00%	0.00%	0.10%	0.18%
Symp. Hypo	10.70%	1.80%	11.20%	2.10%	10.70%	1.80%
GMI	4.0%	1.0%	4.0%	1.0%	4.0%	1.0%
UTI	1.0%	0.5%	1.0%	0.5%	1.0%	0.5%

Table 54 AG 2nd and 3rd intensification clinical effectiveness estimates

	+NPH		+Bolus	
	μ	s.e.	μ	s.e.
HbA1c	-1.200	0.300	-0.660	0.060
SBP	-0.500	1.200	0.000	0.000
Weight	3.600	0.500	0.800	0.200
Sev. Hypo	0.40%	0.17%	0.7%	0.5%
Symp. Hypo	14.0%	5.1%	38.0%	2.9%
UTI	0.0%	0.0%	6.0%	1.4%
GTI	0.0%	0.0%	0.0%	0.0%

Adjusting the HbA1c effect for a patient's baseline HbA1c

The NICE CG modelling estimated two alternative models for the change at one year in HbA1c. The first corresponded to the base case approach of the AG, though metformin was the reference treatment in the NICE CG NMA rather than placebo as in the AG NMA.

- estimate a reference treatment's absolute change in HbA1c from baseline, t_0, to the end of the first cycle, t_1: Δ_{abs}
- estimate the difference between the reference treatment and the other treatments at the end of the first cycle: ΔTx_{rel}
- $H_1 = H_0 + \Delta_{abs} + \Delta Tx_{rel}$

For instance, suppose that the change between t_0 and t_1 for metformin $\Delta_{abs} = -1.49$ and that the difference between metformin and canagliflozin at t_1 was $\Delta Tx_{rel} = -0.51$. A patient with a baseline H_0=9.00 would be estimated to have $H_1 = 9.00 – 1.49 – 0.51 = 7.00$, whereas a patient with a baseline H_0=7.00 would be estimated to have H1 = 7.00 – 1.49 – 0.51 = 5.00.

But a strong correlation was observed between the trials' metformin absolute effect between t_0 and t_1 and their mean baseline HbA1c. As a consequence the NICE CG explored adding an additional term to Δ_{abs} to make the change also a function of the baseline HbA1c, H_0. This led to the following adjusted model for the HbA1c at the end of the first cycle:

$$H_1 = H_0 + (\Delta_{abs} + \beta (H_0 - 7.5)) + \Delta Tx_{rel}$$

with ΔTx_{rel} being taken from the NICE CG NMA.

The Δ_{abs} and β were not estimated during the NMA, but were separately estimated using the same data for metformin as was used in the NMA. The adjusted model simplifies to the unadjusted model by setting β=0. This resulted in the following coefficients (see Table **55**):

Table 55 NICE CG adjustment to reference treatment HbA1c effect by baseline HbA1c

	Unadjusted (95% CrI)	Adjusted (95% CrI)
Δ_{abs}	-1.49 (-2.16,-0.90)	-0.78 (-1.65, 0.03)
β	..	-0.50 (-0.78, -0.21)

and the following unadjusted and adjusted treatment effects for metformin (see Figure **12**).

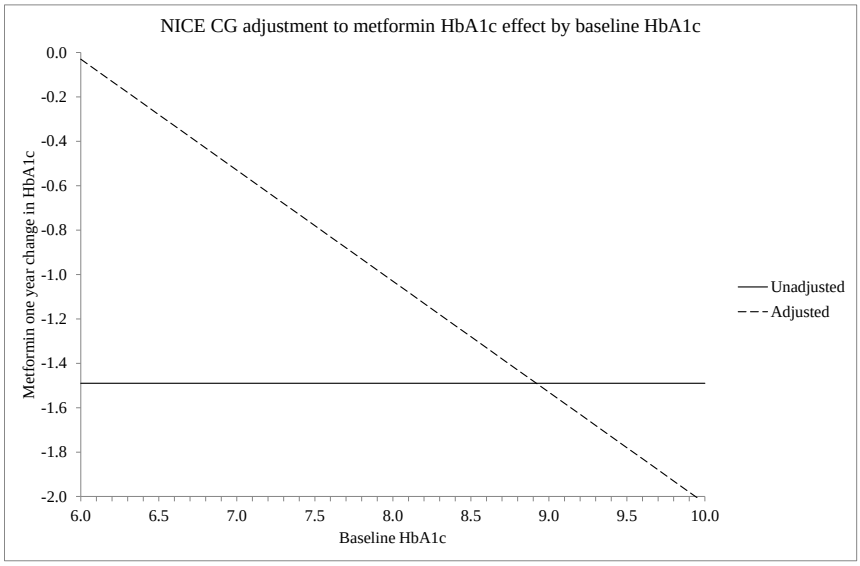

Figure 12 NICE CG adjustment to reference treatment HbA1c effect by baseline HbA1c

In essence, the adjusted function adds the difference between the two intercepts -1.49 and -0.78, or a constant 0.71, and the β (H_0 -7.5) to the unadjusted H_1. In other words for a given baseline H_0 the H_1 of the adjusted function is a constant difference from the H_1 of the unadjusted function, regardless of the treatment effect relative to metformin ΔTx_{rel}. Since β = -0.50 is negative the reduction in HbA1c between t_0 and t_1 is larger for those with a high baseline H_0. The application of the adjusted function means that more patients will see a treatment reduce their HbA1c to below the NICE treatment intensification threshold of 7.5%. It also prevents patients with a low baseline H_0 being modelled as falling to perhaps unrealistically low values of HbA1c.

The adjusted function was preferred for the NICE CG due to a superior information criterion and because the influence of β was judged to be significant with its 95% credible interval all lying below zero.

For the patient with a baseline H_0 = 9.00 the adjusted model estimates that under canagliflozin their H_1 = 9.00 – 0.78 – 0.50 * (9.00 – 7.50) – 0.51 = 6.96 in contrast to the estimate of H_1 = 7.00 of the unadjusted model. Similarly, for the patient with a baseline H_0 = 7. 00 the adjusted model estimates that under canagliflozin their H_1 = 7.00 – 0.78 – 0.50 * (7.00 – 7.50) – 0.51 = 5.96 in contrast to the estimate of H_1 = 5.00 of the unadjusted model.

The NICE CG function is for metformin monotherapy. It was also estimated using a very different data set than the current AG NMA. Any read across from it to the current assessment is consequently almost submerged in caveats. But if a hypothetical placebo in the monotherapy metformin trials would have a reasonably constant relative effect, Tx_{rel}, at t_1 compared to metformin, and this placebo effect could reasonably be read across to the current patient group it would be reasonable to explore the impact of the above relationship in the current assessment. For a deterministic analysis this simply requires 0.71 - 0.50 (H_0 -7.5) to be added to the overall unadjusted H_1 treatment effect estimated for each of the active treatments within the AG NMA. This will be explored as a scenario analysis.

Treatment discontinuations

Those discontinuing in the first year for reasons other than their HbA1c not falling below the 7.5% threshold are assumed to switch to another monotherapy:

- From flozins to gliclazide
- From sitagliptin to gliclazide
- From pioglitazone to gliclazide
- From gliclazide to pioglitazone
- From repaglinide to pioglitazone

Note that those discontinuing are in effect assumed to switch to the alternative monotherapy, and its associated subsequent sequence of treatments. These sequences were retained in part due to data availability and in part due to a desire not to introduce new sequences with a different number of possible intensification steps.

But these subsequent sequences may also contain the treatment that the patient was intolerant of as a monotherapy. This only affects those discontinuing from pioglitazone and those discontinuing from gliclazide. In the light of this, a scenario analysis will be undertaken where among those discontinuing and switching treatment the intensification step to a treatment the patient was intolerant of as a monotherapy is omitted.

The modelling of the evolution of the risk factors

For HbA1c the base case applies the treatment effect in the first year of therapy. HbA1c is then evolved according to the UKPDS68 equation 11. But this is with the proviso of the UKPDS68 equation 11 parameter for a patient being in their second year since diagnosis not being applied. Given the average patient duration of 2 years since diagnosis, the AG is of the opinion that including the UKPDS68 equation 11 parameter for a patient being in their second year since diagnosis would

tend to double count the treatment effect of starting a monotherapy. HbA1c is evolved according to the UKPDS68 equation 11 until the treatment intensification threshold of 7.5% is breached.

At this point, the patient intensifies treatment and receives the associated treatment effect. HbA1c is then once more evolved according to the UKPDS68 equation 11 until the treatment intensification threshold of 7.5% is breached, at which point another treatment intensification occurs. When the patient is on the last line of treatment HbA1c evolves according to the UKPDS68 equation 11 with no further treatment intensifications.

Should a patient discontinue and move onto an alternative treatment at the same line of therapy, the treatment effect of the first line of therapy of the first year is removed, one year's evolution according to the UKPDS68 equation 11 added and the treatment effect of the alternative treatment applied.

The paragraphs that follow are purely for illustration. The data are hypothetical and bear no realtion to the actual inouts used in the AG modelling.
The figure below (Figure **13**) shows how this results in a sawtooth evolution of HbA1c. It applies to a patient aged 40 with a current baseline HbA1c of 7.6%, who at diagnosis was aged 30 and had an HbA1c of 7.0%. It assumes four strategies, with initial reductions in HbA1c of 1.8%, 1.6%, 1.4% and 1.2% for strategies 1, 2, 3 and 4 respectively. It also assumes that two further treatment intensifications are possible, these having the reductions in HbA1c of 2.0% and 1.5% across the four strategies.

The modelled evolution of strategies 2, 3 and 4 are very similar with the first treatment intensification at year 6. The slightly greater initial reduction in HbA1c of strategy 1 is sufficient for HbA1c not to breach the treatment intensification threshold of 7.5% until 1 year later, and as a consequence the first treatment intensification does not occur until year 7.

The other figure below (Figure **13**) illustrates how a discontinuation could affect the modelled evolution of HbA1c for strategy 1. This still assumes a reduction in HbA1c from the original treatment of 1.8% but from the alternative treatment that the patient discontinues to of only 0.5%. As before, this also assumes that two further treatment intensifications are possible, with reductions in HbA1c of -2.0% and -1.5% in the sequence that the patient has discontinued to.

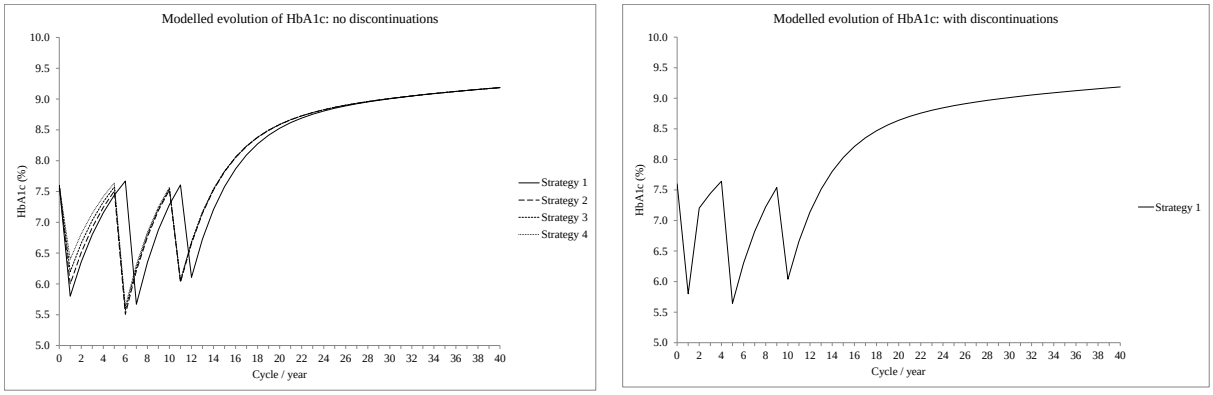

Figure 13 Example of the modelled evolution of HbA1c: UKPDS68

In the light of the Janssen submission, the model has been constructed to permit a scenario analysis of HbA1c having a linear increase and for the annual rate of increase to be treatment specific. The following illustrates the same initial treatment effects for strategies 1, 2, 3 and 4 but for the annual linear increase while on first line treatment to be 0.1%, 0.2%, 0.3% and 0.4% respectively. For those discontinuing from strategy 1, the annual linear increase while on the first line treatment is assumed to be 0.05%. Subsequent to treatment intensification the evolution of HbA1c is assumed to revert to the UKPDS68 equation 11, but the model has the facility to impose treatment specific annual linear increases in HbA1c at any or all treatment lines (see Figure **14**).

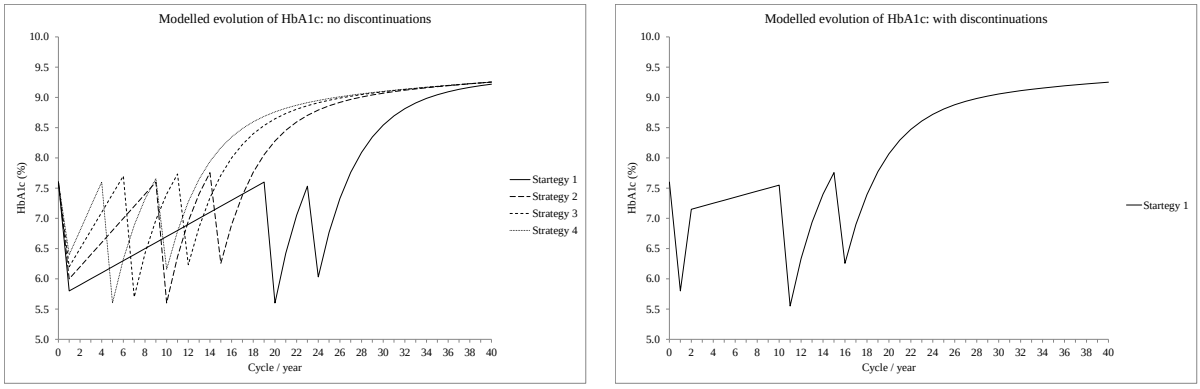

Figure 14 Example of the modelled evolution of HbA1c: Linear evolution

A similar approach is taken for the modelling of the evolution of SBP and can be for the TC:HDL ratio, though the base case holds the TC:HDL ratio constant at 3.0. The UKPDS 68 specifies equation 12 and equation 13 respectively. Treatment intensifications are still determined by the modelled HbA1c.

The figures below (Figure **15**) illustrate the modelled evolution of SBP for the same patient as before with HbA1c being modelled to evolve according to the UKPDS68 equation 11, with an SBP at

baseline of 130mmHg and at diagnosis of 120mmHg. It assumes initial treatment effects of -20mmHg, -15mmHg, -10mmHg and -5mmHg for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of -15mmHg and -10mmHg. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is -5mmHg.

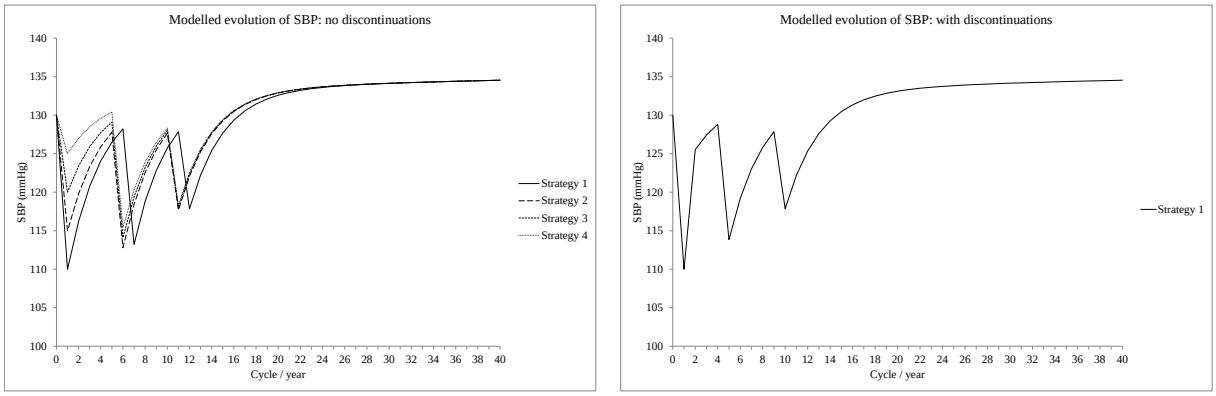

Figure 15 Example of the modelled evolution of SBP

The figures below (Figure **16**) illustrate the UKPDS modelled evolution of the TC:HDL ratio for the same patient as before with HbA1c being modelled to evolve according to the UKPDS68 equation 11, with a TC:HDL ratio at baseline of 4.0 and a ratio at diagnosis of 3.5. It assumes initial treatment effects of -1.0, -0.8, -0.6 and -0.4 for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of -0.8 and -0.6. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is -0.4.

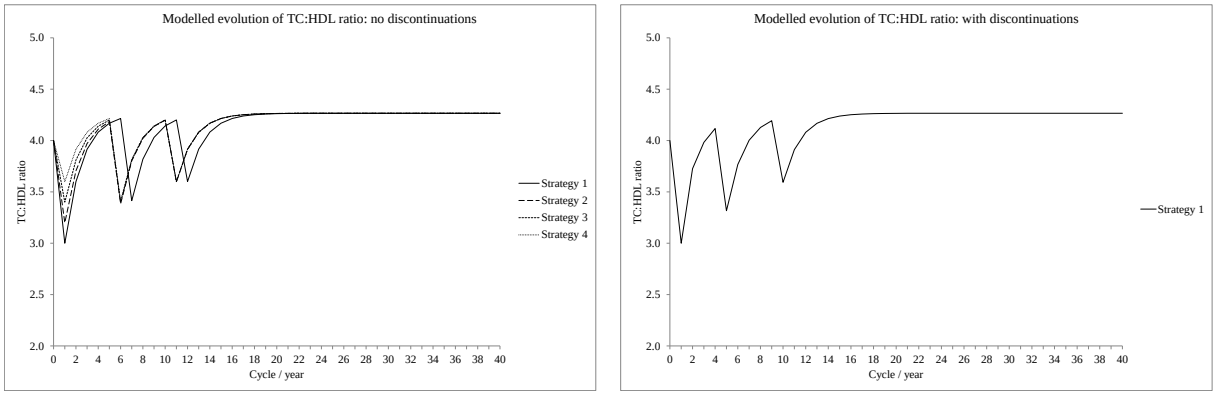

Figure 16 Example of the modelled evolution of the TC:HDL ratio

The modelled evolution of HBA1c, SBP and the TC:HDL ratio for a range of inputted patient characteristics was cross checked with that modelled by the UKPDS OM1 at central UKPDS68

parameter values. The modelled evolutions values were typically around 99.99% of the values simulated by the UKPDS OM1 model.

The evolution of the patient BMI is based upon a mean annual increase in weight of 0.1kg as has typically been used in previous NICE assessments of treatments for diabetes and is apparently originally sourced from the 2006 NICE CG on obesity. Over the course of NICE assessments and guidelines development for treatments for T2DM, quite a lot of discussion has focussed upon what is reasonable to assume about the duration of weight effects. There has been some argument that initial weight losses associated with treatment may tend to be transient, while initial weight gains associated with treatment may tend to be more permanent. In the light of this five scenarios are modelled:

- Treatment weight changes maintained with no rebound to natural history
- Treatment weight gains maintained, weight losses rebound to natural history after one year
- Treatment weight gains maintained, weight losses rebound to natural history at intensification
- Treatment weight changes rebound to natural history after one year
- Treatment weight changes rebound to natural history at intensification

The following figures (Figure **17** and Figure **18**) illustrates weight changes being maintained for a patient of 85kg at baseline. Initial hypothetical treatment effects are +5kg, -5kg, +10kg and -4kg for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of +3kg and +7kg. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is +4kg with the additional weight gains in the alternative sequence thereafter being assumed to be the same as in the original sequence.

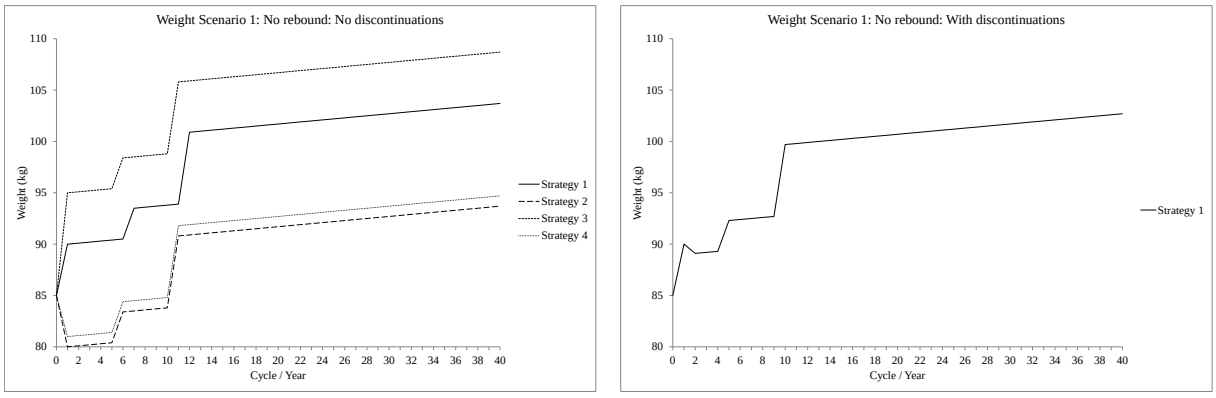

Figure 17 Example of the modelled evolution of patient weight: no rebound

The above is largely self-explanatory. Within the evolution of weight for the patient under strategy 1 who discontinues there is a drop in weight between year 1 and year 2. This arises due to the patient being assumed to come off their original treatment which would have increased their weight by 5kg

and to move onto the alternative treatment which only increases their weight by 4kg. Quite when the patient would discontinue and as a consequence quite what the balance would be in practise between the 5kg increase and the 4kg increase during the first line of treatment is a moot point.

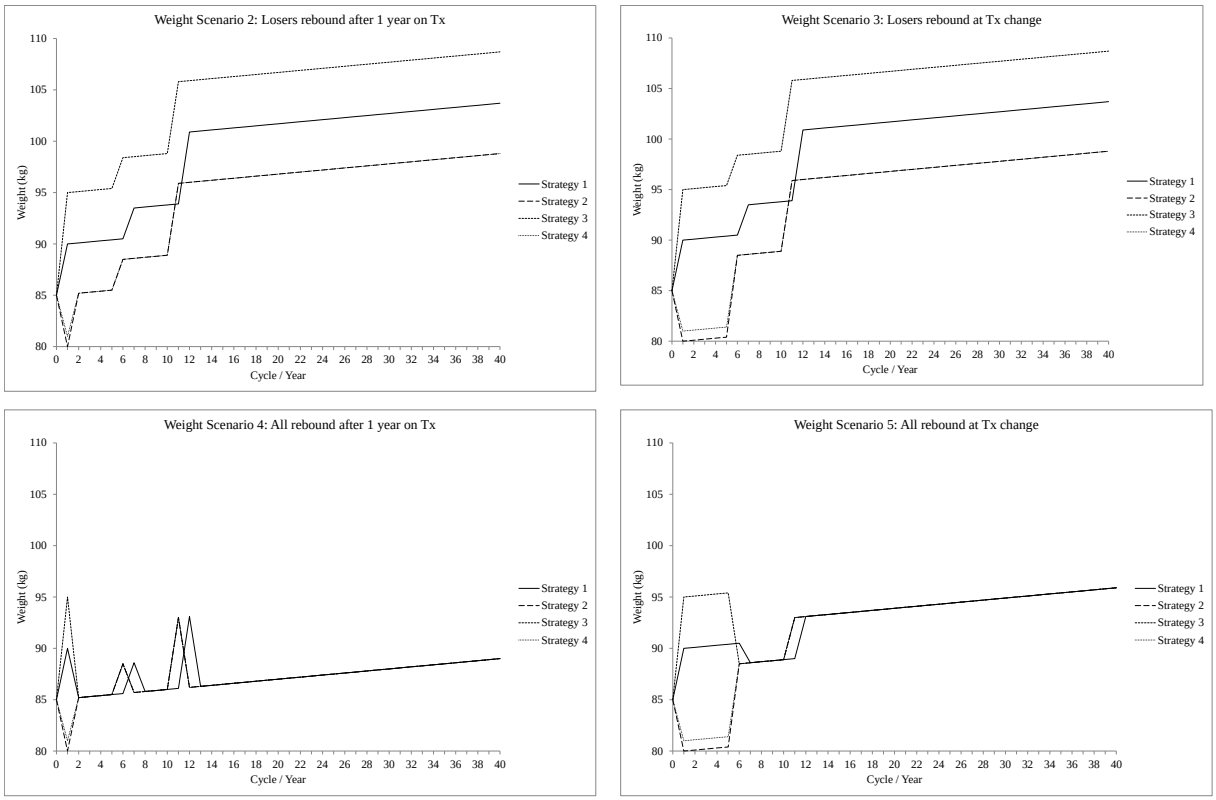

Figure 18 Example of the modelled evolution of patient weight: rebound scenarios

BMI scenarios 2 and 3 which have weight losses rebounding to natural history do not affect strategy 1 and strategy 2 as they only incur weight gains.

BMI scenario 2 sees weight losses rebound to natural history after one year. So at year 2 both strategy 2 and strategy 4 have rebounded to natural history and 85.2kg weight. Thereafter they follow the same weight profile since their treatment intensifications also occur at the same time: year 6 and year 11.

BMI scenario 3 sees weight losses rebound to natural history at treatment intensification. To model this, the rebound to natural history that would have applied in the previous year is first calculated, 85.5kg, to which the intensification treatment effect of +3.0kg is added to give a weight of 88.5kg at year 6. An alternative way of looking at this is to view the intensification treatment effect of +3.0 kg being composed of two parts: +0.1kg natural history and +2.9kg additional treatment effect.

BMI scenario 4 sees all weight changes rebound to natural history after one year. The figure is largely self-explanatory, with all initial treatment effects being removed at year 2. Thereafter, strategies 2, 3 and 4 intensify treatment at years 6 and 11, and see the weight gains associated with intensifications rebound to natural history at years 7 and 12. Strategy 1 intensifies later at years 7 and 12, hence the later rebounds to natural history.

BMI scenario 5 sees all weight changes rebound to natural history at treatment change. Strategies 2, 3 and 4 intensify treatment at years 6 and 11, so rebound to natural history the following year. But the weight gains associated with the intensifications are then added to where the patients rebound to. As a result, after the first intensification at year 6 the patient weight is 88.5kg for strategies 2, 3 and 4. For strategy 1 the intensification is one year later, with it joining the other strategies at a weight of 88.6kg in year 7. Much the same happens at the subsequent intensification.

Note that the BMI scenarios 4 and 5 may be felt to be literally unrealistic, with weight gains rebounding to natural history after one year or at the next treatment change. But they may be better thought of as causing weight to converge between strategies either after one year or at treatment change. In terms of the modelling of the impact of BMI upon quality of life this will not be exactly arithmetically correct due to the floor of 25kgm^{-2} on the BMI quality of life coefficient of -0.0061. Given the baseline BMI of 31.6kgm^{-2} (s.d. 6.0kgm^{-2}) around 13% of patients are modelled as having a BMI of less than 25kgm^{-2}. For some of these patients, the rebounds of scenarios 4 and 5 may not be exactly equivalent in their quality of life impacts to weight converging between the strategies by some other means, e.g. at the value of strategy with the higher BMI. But the AG is of the opinion that any differences are likely to be minor.

Note that there is a minor error within the implementation of weight in the AG modelling. The UKPDS 68 requires that the BMI at diagnosis is used and this has been implemented correctly. But the AG modelling assumes that the BMI at diagnosis also applies at baseline. It can be argued that the BMI at baseline should be the BMI at diagnosis plus the natural history increase that would be implied by the duration at baseline. But since the mean duration of diabetes at baseline is estimated to be 2.0 years and that this adjustment would only affect results for the subset of patients during the cycles they bordered the 25kgm^{-2} threshold, this error will have negligible effects upon net results.

Diabetic ketoacidosis

There has been some suggestion that the flozins may increase the risk of diabetic ketoacidosis (DKA). But rates are low in absolute terms, with the EMA reporting 101 cases over about 500,000 patient years of flozins use.

The Diabetics With Eating Disorders surveyed England's PCTs in 2010.[200] Among the 45 PCTs that responded the mean cost per DKA event was £1,438, or £1,552 in 2014 prices. But given an event rate of 1 per 5,000 patient years the average increase in costs associated with this is minimal: around 30p per year of treatment. The typical duration of DKA events is also quite short, certainly less than one week, though there may be recurrence. But even with quite a large quality of life decrement, given the absolute event rate and the short duration any overall average QALY impact will also be minimal.

There remains the possibility of an increased mortality with DKA among those with T2DM. This could have more of an impact upon the modelled average QALY in the flozin arms. But there is no simple means of incorporating this mortality into the OM1 modelling, this being a black box to the AG.

For the above reasons DKA has not been incorporated into the economic modelling.

Quality of life: Diabetes and the complications of diabetes

Given the use of the OM1 model, the AG draws the quality of life value for those without any complications and quality of life impacts for the complications of diabetes from the UKPDS62 as below (Table **56**). A value for renal failure is not given in the UKPDS62 and as a consequence the AG has used the OM1 default value of -0.263 as drawn from Kiberd and Jindal.[201]

Table 56 Quality of life values for OM1 complications

	Mean	S.E.	Distribution
No complications	0.785	0.005	Beta
MI	-0.055	0.006	LogNormal
IHD	-0.090	0.018	LogNormal
Stroke	-0.164	0.030	LogNormal
CHF	-0.108	0.031	LogNormal
Amp	-0.280	0.056	LogNormal
Blind	-0.074	0.033	LogNormal
Renal	-0.263	0.020	LogNormal

Quality of life: Weight

In common with most NICE assessments of treatment for T2DM and the draft NICE T2DM CG the AG applies the utility decrement of -0.0061 (s.e. 0.001) of Baghust and Beale.[191] Within Baghust and Beale, this decrement applies if the patient BMI is above 25kgm^{-2}.

The mean BMI within the UKPDS RCT was 27.7kgm^{-2} and it is from here that the mean baseline utility of 0.785 is drawn. As a consequence, since the modelling applies the -0.0061 quality of life decrement when the patient BMI rises above 25kgm^{-2}, it can be argued that the baseline utility of 0.785 should have 0.0061* 2.7 = 0.0165 added to it. This modification is adopted for the AG base case.

Quality of life: Treatment discontinuations

Based upon the draft NICE T2DM CG treatment discontinuations were assigned a QALY decrement associated with nausea as drawn from Matza et al.[202] 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.

Quality of life: Adverse events

The 2012 NICE clinical guideline on infection, CG139[203], undertook a systematic review of the literature for studies of the quality of life impacts of symptomatic UTIs. This identified 11 studies, but a number of these are of limited relevance to the current assessment due to; e.g. being among patients with spinal cord injuries. Of the 11 studies, 5 appear most relevant to the current assessment.

CG139 also undertook economic modelling of treatments for UTIs. But due to the available clinical effectiveness estimates being largely limited to those with spinal cord injury, the quality of life values applied are of limited relevance to the current assessment. This modelling also considered progression from symptomatic UTIs through to 1st line drug resistance and multi drug resistance with these causing increased costs and mortality.

The AG modelling for the current assessment only considers the quality of life and cost impacts of treating UTIs and GTIs, with the assumption that none will progress to a more serious condition. So there are caveats around these estimates and for a given set of inputs they could be seen as being biased and on the low side.

Barry et al[196] used the Index of Wellbeing (IWB) to estimate quality of life among young women with UTIs. The IWB is a generic QoL instrument. The mapping function from the IWB to quality of life values was apparently based upon 62 American nurses and non-medical graduate students ranking health states on a sixteen point scale. Barry et al report that the IWB includes hospitalisation, self-care and ambulatory status and permits the inclusion of the following symptoms: pain, bleeding, itching discharge from sexual organs, painful burning or frequent urination, burning or itching rash on large areas of the body, taking medication, fever or chills with aching all over and pain in the chest,

stomach, sides, back or hips. But Barry et al do not describe quite how the quality of life values for the health states for their model have been derived. It appears to be based upon an index patient with a set of symptoms; i.e. expert opinion linked to the IWB. They estimated disutilities of 0.3732 for pyelonephritis, and 0.2894 for vaginitis and persistent dysuria. Their duration was estimated to be 10 days, 5 days and 5 days respectively.

Gold et al[204] catalogued 130 health states using the Health and Activity Limitation Index (HALex) with the score being based upon the answers to two questions of the US National Health Interview Survey. A multi-attribute utility model resulted in quality of life estimates of 1.00 for perfect health, and 0.73 for bladder infection and 0.66 for kidney infection. The derivation of these weights is not particularly clear within the paper.

Ackerman et al[205] used the standard gamble to estimate quality of life values among 13 men with moderate to severe benign prostatic hyperplasia. A variety of health states were described, with the quality of life impacts of severe UTIs being estimated among these. The six risk averse men reported an average value of 0.972 for a severe UTI, while the seven non-risk averse men reported an average value of 0.893. Over the 13 respondents this suggests an average disutility per severe UTI of 0.071.

Ellis and Verma[206] measured the impact of UTIs among 118 otherwise healthy Canadian women through a case controlled analysis using the SF-36 with a recall period of 1 day. The mapping from the SF-36 to the EQ-5D quality of life values based upon the algorithm of Ara and Brazier[207] appears to have been undertaken by the NICE CG, since Ellis and Verma only report the mean values for the eight main elements of the SF-36. This resulted in those with no UTI having a mean quality of life of 0.922 compared to 0.724 for those with a UTI.

Ernst et al[208] used the Quality of Wellbeing (QWB) to estimates the quality of life among 146 American women diagnosed with acute cystisis, and the effect of treatment upon quality of life. Those with T2DM were excluded from the study. The QWB was administered 3, 7, 14 and 28 days after the initial visit. The quality of life at baseline was 0.68 (s.d. 0.03) compared to 0.81 (s.d. 0.11) at the 28 day point. Quality of life among those cured compared to those not cured was statistically significantly different at the 5% level at day 3, 7 and 14 with respective QWB scores of 0.77 vs 0.72, 0.82 vs 0.71 and 0.83 vs 0.76. See Table **57**.

Table 57 Quality of life estimates for infections

Source	Barry et al[196]		Gold et al[204]	Ackerman et al[205]		Ellis & Verma[206]	Ernst et al[208]
Year	1997		1998	2000		2000	2005
Country	USA		USA	USA		Canada	USA
N	n.a.		n.a.	13 men		118 women	146 women
Method	IWB		HALex	SG		SF-36	QWB
Condition	Pyelonephritis	Vaginitis / Dysuria	Bladder	Kidney	UTIs	UTIs	Cystitis
Disutility	0.3732	0.2894	0.27	0.33	0.028-0.107	0.198	0.05-0.13

Of the above papers, Ackerman et al[205] could be argued as coming closest to the NICE reference case. But the usefulness of these estimates is compromised by the small sample size. As a consequence, the AG will use the results of the Janssen TTO study for the base case of quality of life impact of -0.19 for a UTI and -0.25 for a GTI. Nicolle et al[93] estimated median durations of UTIs of between 11.0 days and 12.5 days, and as a consequence the base case will assume 2 weeks average duration.

Quality of life: Hypoglycaemia

Following the lead of the current draft NICE CG for T2DM, the source for the base case for the quality of life decrements associated with hypoglycaemia events will be Currie et al.[195] This 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 non-severe and severe hypoglycaemic episodes with coefficients of 1.773 (s.e. 0.230) and 5.881 (s.e. 1.553) respectively. 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).

Given the 3 month recall period, the mapping between non-severe hypoglycaemia event rates and the patient's score on the Hypoglycaemic Fear Survey requires that rates be converted to 3 monthly rates before the 1.773 HFS coefficient can be applied to arrive at the correct QALY decrement.

The authors of the draft NICE CG for T2DM also point out that the table 4 coefficient of Currie et al for non-severe hypoglycaemia events is based upon the natural logarithm of the event rate rather than the event rate. As such it is non-linear. To account for this the AG has followed the method of the authors of the draft NICE CG for T2DM and applied a Poisson distribution to give the spread of possible patient event rates prior to applying the coefficients of Currie et al.[195]

The 5.881 HFS coefficient of table 4 of Currie et al[195] for severe hypoglycaemic events was derived on a dichotomous basis, equal to 1 if there were any events reported during the previous 3 months and equal to 0 if there were none reported. The draft NICE clinical guideline gives a quite complicated formula for accounting for this using a binomial distribution, but this apparently simplifies to the quarterly probability times the utility decrement (Personal communication, Gabriel Rogers, NICE, 17 Aug 2015).

The following (
Table **58**) present a range of estimates based upon this method.

Table 58 AG QALY decrements by hypoglycaemia event rates.

	Severe	Non-severe					
Annual	1.00	10	20	30	40	50	60
Quarterly	0.22	2.50	5.00	7.50	10.00	12.50	15.00
HFS	1.30	1.39	2.65	3.44	3.98	4.40	4.74
Annual QALY loss	-0.010	-0.011	-0.021	-0.032	-0.035	-0.038	-0.040

But the values of Currie et al[195] 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 entirely 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 events within a quarter.

The patient number and demographics reported by Currie et al[195] 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 AG cannot further interrogate the data underlying the estimates of Currie et al, and it is possible that they may be over-estimates. Note that in common with previous analyses, the method of the table above in effect assumes that a patient experiences at most one severe hypoglycaemic event per quarter. There may be an argument for dividing the QALY decrement associated with severe hypoglycaemic events by 1.47, the mean event rate reported in Currie et al.

Costs: Direct drug costs

Treatment costs are based upon the NHS drug tariff, and upon list prices where there are no entries in the NHS drug tariff. Daily doses are assumed to be 60mg for gliclazide modified release, 45mg for

pioglitazone, 6.0mg for repaglinide, 100mg for sitagliptin, 10mg for dapagliflozin, 25mg for empagliflozin and 300mg for canagliflozin. Insulins costs are based upon a requirement of 0.3IU/kg when starting NPH, with this rising to 0.55IU/kg when adding bolus which itself is required at 0.2IU/kg.

AG expert opinion also suggests that those receiving pioglitazone should have their BNP measured, perhaps initially six-monthly but annually thereafter. A marginal cost of £21has been taken from Craig et al[41] and inflated to 2014 prices using a 1.25 multiplier from the PSSRU HCSC index. This has also been assumed to require a dedicated GP appointment, costed at £46 using the 2014 PSSRU Unit Costs of Health and Social Care.

This results in the following treatment costs for the oral therapies (see Table **59**).

Table 59 AG sequences drug and administration costs

Strategy	Mono	Cost	1st intens.	Cost	2nd intens.	Cost	3rd intens.	Cost
S1	Empa.	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Empa.	£476.98	Empa.	£476.98	Empa.	£476.98
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S1 Total Cost		£476.98		£539.16		£730.63		£947.88
S2	Cana.	£476.93	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Cana.	£476.93	Cana.	£476.93	Cana.	£476.93
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S2 Total Cost		£476.93		£539.11		£730.58		£947.83
S3	Dapa.	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Dapa.	£476.98	Dapa.	£476.98	Dapa.	£476.98
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S3 Total Cost		£476.98		£539.16		£730.63		£947.88
S4	Sita.	£433.57	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Sita.	£433.57	Sita.	£433.57	Sita.	£433.57
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S4 Total Cost		£433.57		£495.75		£687.22		£904.47
S5	Pio.	£93.25	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S5 Total Cost		£93.25		£155.43		£346.90		£564.15
S6	Glicl. MR	£62.18	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S6 Total Cost		£62.18		£155.43		£346.90		£564.15
S7	Repag.	£71.91	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S7 Total Cost		£71.91		£155.43		£346.90		£564.15

The AG modelled sequences differ from those of the company submissions in that patients add NPH insulin rather than switch to it and as a consequence the cost differences between the sequences are maintained over the horizon of the modelling. In the light of this, a scenario analysis is undertaken which withdraws the initial monotherapies when patients switch to NPH insulin. Note that this only affects the direct drug costs and not the clinical effectiveness estimates.

Costs: Treatment intensifications and switches

Treatment intensifications due to breaching the 7.5% HbA1c threshold and treatment switches due to intolerance are assumed to involve one 12 minute GP appointment. This is costed using the 2014 PSSRU Unit Costs of Health and Social Care at £46.

Costs: Adverse events

The AG treatment assumptions are in broadly line with those of the Janssen submission as below, with this resource use being confirmed by AG expert opinion. Medication for UTIs is assumed to be seven days of trimethropim 200mg twice daily, for male GTIs fluconazole 200mg and for female GTIs 3 200mg clotrizamole pessaries (see Table **60**).

Table 60 AG resource use and costs of UTIs and GTIs

UTI	GP visits	Unit cost	Cost	Drug Tariff	Cost/day	Days	Cost	Total Cost
Male	2	£46	£92	£1.87	£0.62	7	£4.36	£96
Female	1	£46	£46	£1.87	£0.62	7	£4.36	£50
Total UTI cost								£73
GTI	GP visits	Unit cost	Cost	Drug Tariff	Cost/day	Days	Cost	Total Cost
Male	1	£46	£46	£6.23	£0.89	7	£6.23	£52
Female	1	£46	£46	£3.10	..	..	£3.10	£49
Total GTI cost								£51

These costs are largely based upon assumption and have consequently been treated deterministically within the probabilistic modelling.

Costs: Hypoglycaemic events

The AG have followed the current draft NICE CG when costing severe hypoglycaemic events.

Hammer et al[209] in an industry sponsored study surveyed 147 UK patients with T2DM using insulin with 19 reporting at least one severe hypoglycaemic episode in the previous year with 10 of these being treated by the NHS. Hammer et al acknowledge the non-random selection of their patient sample, but provide few details about it other than to note that it was predominantly through health

care professionals. Patients were surveyed using a structured questionnaire about the resource use associated with their events.

Patients were divided into three groups: those who had their severe hypoglycaemic event treated by family members; by medical practitioners in the community; and, in hospital. The mean direct costs by type in 2007 prices were £33 for those treated by family members, due to NHS follow up costs, £231 for those treated by the NHS in the community and £862 for those treated in hospital. Due to the non-random sample selection there is no definitive means to translate these into a weighted average cost. But the GDG of the draft NICE CG were reportedly happy to use the sample proportion treated by family members (9/19) coupled with an assumption that of the remainder 65% would be treated in hospital.

This results in a mean cost per severe hypoglycaemic event of £353 in 2007 prices which when uplifted by a 1.16 multiplier from the 2014 PSSRU Unit Costs of Health and Social Care results in an estimate of £411.

Costs: Diabetes and the complications of diabetes

The costs of diabetes and the complications of diabetes are taken from the UKPDS84 tables, and uprated for inflation using a multiplier of 1.03 from the PSSRU HCHS index (see Table **61**).

Table 61 Costs of diabetes and its complications

	Inpatient costs			Outpatient costs			Total
	Mean	S.E.	Dist	Mean	S.E.	Dist	Mean
No event	£472	£33	Gamma	£547	£23	Gamma	£1,019
Event year							
Fatal myocardial infarction	£1,564	£531	Gamma				£1,564
Fatal ischaemic heart disease	£3,873	£1,250	Gamma				£3,873
Fatal stroke	£4,066	£1,158	Gamma				£4,066
Myocardial infarction	£6,560	£1,062	Gamma	£990	£95	Gamma	£7,550
Ischaemic heart disease	£10,044	£1,484	Gamma	£888	£78	Gamma	£10,932
Stroke	£6,998	£1,685	Gamma	£1,122	£191	Gamma	£8,120
Heart failure	£3,281	£846	Gamma	£1,007	£167	Gamma	£4,288
Amputation	£9,816	£1,849	Gamma	£2,775	£713	Gamma	£12,592
Blindness in one eye	£1,393	£588	Gamma	£1,841	£571	Gamma	£3,234
Subsequent years							
Myocardial infarction	£1,187	£158	Gamma	£690	£49	Gamma	£1,877
Ischaemic heart disease	£1,249	£153	Gamma	£673	£42	Gamma	£1,922
Stroke	£1,157	£234	Gamma	£777	£89	Gamma	£1,934
Heart failure	£1,515	£347	Gamma	£1,001	£98	Gamma	£2,515
Amputation	£1,843	£494	Gamma	£1,657	£242	Gamma	£3,499
Blindness in one eye	£466	£99	Gamma	£759	£89	Gamma	£1,225

It should be noted that these costs are for a representative 60 year old male patient, and are for a patient with only one complication. Costs are to a degree a function of age. There are interactions between complications within the UKPDS82 which mean that those with more than one complication do not necessarily incur a simple sum of the individual complication costs. Only one set of the costs of complications can be fed into the OM1. As a consequence, it has not been possible to take these effects into account, but they are not particularly marked.

The UKPDS84 does not provide a costing for renal disease. In common with the draft NICE CG for diabetes, these have been drawn from Lamping et al[210] with the inpatient cost in 1996 prices of £20,802 (s.e. £613) being uprated for inflation using a multiplier of 1.75 from the PSSRU HCSC index.

Assessment group sensitivity analyses

All scenario analyses have been run deterministically with a cohort of 50,000 patients and 1,000 inner loops to reduce Monte-Carlo error. The sensitivity analyses around the -0.0061 quality of life decrement per BMI point above 25kgm^{-2} and the rebound of treatments' effect upon weight are presented for all analyses:

- BMI 1: natural history progression with no rebound
- BMI 2: natural history progression with weight losses rebounding after one year
- BMI 3: natural history progression with weight losses rebounding at treatment change
- BMI 4: natural history progression with weight rebounding after one year
- BMI 5: natural history progression with weight rebounding at treatment change

The AG has also undertaken the following sensitivity analyses.

- SA01: At the third intensification patients switch to insulin plus gliclazide, and cease their other treatments
- SA02: Applying the UTI and GTI rates to all cycles of the model
- SA03: Assuming that all patients when starting monotherapy have an HbA1c of 7.5%
- SA04: Adjusting the HbA1c treatment effect for patients' baseline HbA1c values as in the NICE CG
- SA05: Not applying the discontinuation rates
- SA06: Applying the NICE CG baseline TC:HDL values and the UKPDS68 TC:HDL progression
- SA07: Applying the UKPDS68 year 2 parameter for the evolution of HbA1c
- SA08: Intensifying when adding gliclazide having a -0.47% HbA1c effect
- SA09: Applying the Janssen linear evolutions of HbA1c for all treatments
- SA10: Assuming that those discontinuing from a treatment omit any subsequent intensification step that reapplies this treatment
- SA11: SA01 and SA08 combined

Assessment group base case results

The disaggregate costs of the base case are as below (Table **62**).

Table 62 AG base case: Disaggregate costs

Quantity	Empa. 25	Cana. 300	Dapa. 10	Sita. 100	Pio.	Glicl.	Repag.
OM1 Costs	£22,880	£22,925	£22,926	£23,039	£22,905	£22,876	£22,871
Tx Costs	£9,768	£9,624	£9,811	£9,199	£4,521	£4,323	£4,401
Tx change	£95	£92	£96	£96	£94	£91	£92
Hypos	£20	£20	£21	£21	£19	£20	£46
UTI	£8	£10	£8	£3	£3	£3	£3
GTI	£4	£5	£5	£1	£1	£1	£1
Total costs	£32,775	£32,676	£32,866	£32,358	£27,543	£27,314	£27,413

The UKPDS OM1 costs are slightly lower for empagliflozin than for canagliflozin despite its smaller effect upon HbA1c. This seems likely to have arisen due to the larger SBP effect of empagliflozin, but

the differences are slight. All the flozins are similar, with slightly lower costs than sitagliptin due in part to the latter having little impact upon SBP whereas the flozins reduce it.

Pioglitazone, gliclazide and repaglinide are estimated to have similar or slightly lower UMPDS OM1 costs than the flozins which is in line with the estimates of them having slightly larger effects upon HbA1c.

Treatment costs are the main source of the differences in costs, as would be anticipated. The flozins are of similar cost, but canagliflozin is a reasonable amount cheaper. This arises due to the greater HbA1c effect of canagliflozin meaning that patients will tend to intensify to the more expensive subsequent lines of treatment slightly later.

For the base case, with the exception of repaglinide and to a lesser extent gliclazide, patients remain on their initial monotherapy throughout, adding treatments to it when they intensify. As a consequence, the annual treatment costs difference between sitagliptin and the flozins is maintained over the time horizon of the model and the sitagliptin treatment costs are noticeably lower than those of the flozins. This outweighs the slightly higher UKPDS OM1 costs for sitagliptin, and its total costs are a reasonable amount less than those of the flozins.

Pioglitazone, gliclazide and repaglinide treatment costs are considerably lower than those of the flozins and sitagliptin. Treatment costs cause the total costs of pioglitazone, gliclazide and repaglinide to be considerably less than those of the flozins and sitagliptin.

The disaggregate quality of life impacts of the base case are as below. Within this the total QALYs estimated under the UKPDS OM1 model and those associated with treatment switching, hypoglycaemic events and UTIs and GTIs are summed to give a subtotal. This subtotal corresponds to the sensitivity analysis of assuming that a patent's BMI has no impact upon the patient's quality of life. The QALY impacts from assuming a -0.0061 quality of life decrement for each BMI point above 25kgm^{-2} are then presented for each of the five weight progression scenarios that are modelled (see Table **63**).

Table 63 AG base case: Disaggregate QALYs

Quantity	Empa. 25	Cana. 300	Dapa. 10	Sita. 100	Pio.	Glicl.	Repag.
OM1 QALYs	10.380	10.382	10.369	10.355	10.385	10.393	10.390
Tx Switch	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Hypos	-0.001	-0.000	-0.000	-0.000	-0.000	-0.000	-0.001
UTI and GTI	-0.001	-0.002	-0.002	-0.000	-0.000	-0.000	-0.000
SubTotal	10.378	10.380	10.367	10.355	10.384	10.392	10.389
BMI 1	-0.631	-0.600	-0.633	-0.697	-0.772	-0.759	-0.726
BMI 2	-0.694	-0.689	-0.696	-0.700	-0.772	-0.759	-0.726
BMI 3	-0.684	-0.673	-0.686	-0.699	-0.772	-0.759	-0.726
BMI 4	-0.612	-0.610	-0.612	-0.616	-0.622	-0.622	-0.619
BMI 5	-0.622	-0.613	-0.623	-0.636	-0.656	-0.653	-0.645

The QALY estimates are driven by the UKPDS OM1 outputs, and the BMI quality of life decrements if these are applied. The other elements have little impact, though it should be borne in mind that the base case only applies the UTI rates and GTI rates during the first year.

The QALY losses associated with the -0.0061 quality of life decrement for each BMI point above 25kgm^{-2} may appear large at around 6% of the total QALYs. But the baseline QoL of 0.801 in the absence of complications, the quality of life impacts of complications and the baseline mean BMI of 31.9kgm^{-2} should be borne in mind. The baseline mean BMI of 31.9kgm^{-2} when coupled with the -0.0061 quality of life decrement per BMI point above 25kgm^{-2} reduces the baseline QoL of 0.801 in the absence of complications by around 4.5% by itself.

A summary of the total costs and QALYs with treatments ranked from the least expensive to the most expensive is presented below (Table **64**).

Table 64 AG base case: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,314	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£27,413	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,543	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£32,358	10.355	9.657	9.655	9.655	9.739	9.719
Cana. 300	£32,676	10.380	9.780	9.691	9.707	9.770	9.767
Empa. 25	£32,775	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£32,866	10.367	9.734	9.671	9.681	9.756	9.745

These quantities can be subtracted from one another to present how much more costly and effective each treatment is compared with the least costly treatment as below (Table **65**).

Table 65 AG base case: Lifetime net costs and QALYs versus the least costly treatment

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..	..
Repag.	£100	-0.003	0.030	0.030	0.030	-0.001	0.005
Pio.	£230	-0.008	-0.021	-0.021	-0.021	-0.008	-0.011
Sita. 100	£5,045	-0.037	0.024	0.022	0.022	-0.031	-0.020
Cana. 300	£5,362	-0.012	0.147	0.057	0.074	0.000	0.028
Empa. 25	£5,461	-0.015	0.113	0.050	0.061	-0.005	0.017
Dapa. 10	£5,553	-0.025	0.101	0.038	0.048	-0.015	0.006

There is a large step in total costs when moving from pioglitazone to sitagliptin driven by treatment costs. There is a reasonable step in total costs when moving from sitagliptin to canagliflozin.

Pioglitazone is estimated to be both more costly and less effective than repaglinide under all the BMI scenarios. Similarly, empagliflozin and dapagliflozin are estimated to be more costly and less effective than canagliflozin under all BMI scenarios, though the differences are not particularly large. This dominance is reflected in the estimates of cost effectiveness as tabulated below (Table **66**). Note that the following ICERs are not relative to the least costly treatment, but are relative to the next least costly treatment which is not dominated. In other words for BMI 1 the cost effectiveness of repaglinide compared to gliclazide is £3,331 per QALY and the cost effectiveness of canagliflozin relative to repaglinide is £44,994 per QALY.

Table 66 AG base case: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,331	£3,331	£3,331	Dom	£18,507
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£44,994	£192k	£119k	Dom	£235k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

If the effects of BMI upon quality of life are ignored or assumed not to apply gliclazide is estimated to be both the cheapest and the most effective treatment. It is cheaper than sitagliptin and the flozins by quite a large amount, though the differences in the total lifetime QALYs are less marked.

For the scenarios of BMI progressing with natural history and the -0.0061 BMI quality of life impact applying, if there is no rebound of treatment weight effects or only weight losses rebound the weight gain associated with gliclazide reduces its relative effectiveness. The smaller weight gain associated with repaglinide means that it is estimated to have a cost effectiveness of £3,331 per QALY compared to repaglinide under these scenarios.

The scenarios of both weight gains and weight losses rebounding may be felt to be unrealistic. But these are better seen as scenarios that explore when weight might tend to converge between the alternative treatments. If this happens after only one year the differences in weight between gliclazide and repaglinide are not maintained long enough for the BMI QALY effects to outweigh the QALYs estimated under the UKPDS OM1 and repaglinide remains dominated. Maintaining the difference for a longer period up until treatment change is sufficient for repaglinide to confer more QALYs and yields a cost effectiveness estimate of £18,507 per QALY.

Pioglitazone is estimated to yield slightly fewer QALYs under the UKPDS OM1 than gliclazide, and its larger weight gain than gliclazide further hampers it. It remains dominated by gliclazide under all scenarios. But this should not obscure the fact that the UKPDS OM1 estimates pioglitazone to be more effective than sitagliptin and marginally more effective than the flozins. Pioglitazone is also considerably cheaper than sitagliptin and the flozins. Without the quality of life impacts of weight changes pioglitazone is formally estimated to dominate sitagliptin and the flozins. Even with the quality of life impacts of weight changes the cost effectiveness estimates for sitagliptin and the flozins

compared to pioglitazone are poor and well above conventional thresholds. Only canagliflozin and empagliflozin show any reasonable cost effectiveness estimates compared to pioglitazone, and these only occur if treatment weight changes and the resulting differences in weight between treatments are assumed to be maintained over the patient lifetime. The BMI 1 scenario results in cost effectiveness estimates for canagliflozin and empagliflozin compared to pioglitazone of £30,537 per QALY and £38,889 per QALY respectively.

The UKPDS OM1 estimates sitagliptin to be slightly less effective than gliclazide. Being weight neutral its weight profile is superior to gliclazide, but this is insufficient to render it cost effective at conventional thresholds under any of the BMI scenarios when compared to gliclazide. Sitagliptin is dominated by gliclazide if there are no direct quality of life impacts from weight, and for the BMI scenario 4 and 5. For the BMI scenarios 1, 2 and 3 the cost effectiveness estimates for sitagliptin compared to gliclazide are £207k, £231k and £227k per QALY.

The UKPDS OM1 estimates canagliflozin to be slightly less effective than both gliclazide and repaglinide. Its superior weight profile means that applying the -0.0061 quality of life impact per BMI point canagliflozin is estimated to provide more benefits than both gliclazide and repaglinide, except for the scenario of all weight changes rebounding after one year. The cost effectiveness of canagliflozin compared to repaglinide is £44,994 per QALY if weight changes are maintained indefinitely. But for the other scenarios the cost effectiveness estimates are well into six figures.

If the flozins main comparator is sitagliptin, this eliminates the much less costly alternatives. The net quantities relative to sitagliptin are as follows (Table **67**).

Table 67 AG base case: Flozin cost effectiveness estimates relative to sitagliptin

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Sita. 100	..	..	..	..	..	..	..
Cana. 300	£318	0.025	0.123	0.036	0.052	0.031	0.048
Empa. 25	£416	0.023	0.089	0.028	0.038	0.026	0.037
Dapa. 10	£508	0.013	0.077	0.017	0.026	0.017	0.026

The cost effectiveness estimates for the flozins compared to sitagliptin is outlined below (Table **68**).

Table 68 AG base case: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
Empa. 25	£18,341	£4,676	£14,716	£10,841	£15,734	£11,300
Dapa. 10	£40,383	£6,632	£30,710	£19,787	£30,487	£19,679

Even without their superior weight profiles, canagliflozin and empagliflozin are estimated to have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY respectively. Factoring in the weight profiles and assuming that the -0.0061 quality of life decrement applies improves these cost effectiveness estimates. The picture for dapagliflozin is more mixed, in part due to the estimate of its impact upon HbA1c being similar to that of sitagliptin.

Assessment group sensitivity analyses results

SA01: Patients switch to insulin plus gliclazide and drop other therapies

Applying the same cost for the insulin containing regimes across the treatment arms results in the flozins changing their ordering when ranked by increasing total cost. Canagliflozin 300mg is now slightly more expensive than the other flozins. This is probably due to the larger HbA1c effect of canagliflozin meaning that patients on average switch to insulin slightly later compared to the other flozins (see Table **69**).

Table 69 AG SA01: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,628	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£26,719	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£26,835	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£28,875	10.355	9.657	9.655	9.655	9.739	9.719
Empa. 25	£28,990	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£29,010	10.367	9.734	9.671	9.681	9.756	9.745
Cana. 300	£29,040	10.380	9.780	9.691	9.707	9.770	9.767

Total costs have fallen. As would be expected they have fallen furthest for the flozins and by almost as much for sitagliptin when compared to the base case (see Table **70**). Since only the treatment costs are changing there is not difference in QALYs.

Table 70 AG SA01: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£685	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	-£694	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	-£709	0.000	0.000	0.000	0.000	0.000	0.000
Sita. 100	-£3,483	0.000	0.000	0.000	0.000	0.000	0.000
Empa. 25	-£3,785	0.000	0.000	0.000	0.000	0.000	0.000
Dapa. 10	-£3,856	0.000	0.000	0.000	0.000	0.000	0.000
Cana. 300	-£3,635	0.000	0.000	0.000	0.000	0.000	0.000

Due to the reordering of the treatments by total costs, empagliflozin is no longer dominated (see Table **71**).

Table 71 AG SA01: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,026	£3,026	£3,026	Dom	£16,814
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Empa. 25	Dom	£27,230	£112,991	£74,209	Dom	£201k
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£1,504	£6,882	£3,722	Dom	£4,559
Dom = Dominated: i.e. more costly and less effective than another treatment						

The cost effectiveness of repaglinide compared to gliclazide improves slightly for the BMI 1, 2 and 3 scenarios to £3,026 per QALY and for the BMI 5 scenario to £16,814 per QALY.

The flozins remain dominated if there are no direct quality of life impacts from weight changes. For the BMI scenarios 1, 2 and 3 the cost effectiveness of empagliflozin compared to repaglinide is £27,230 per QALY, £113k per QALY and £74,209 per QALY, while for the BMI scenario 5 it is £201k per QALY. But these cost effectiveness estimates for empagliflozin are extendedly dominated by canagliflozin, which has cost effectiveness estimates compared to repaglinide of £19,850 per QALY, £84,634 per QALY and £52,571 per QALY for the BMI scenarios 1, 2 and 3, and £104k per QALY for the BMI scenario 5.

For the cost effectiveness of the flozins compared to sitagliptin the estimates improve quite considerably due to the greater cost reductions for the flozins (see Table **72**).

Table 72 AG SA01: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£6,567	£1,347	£4,637	£3,179	£5,335	£3,447
Empa. 25	£5,054	£1,288	£4,055	£2,987	£4,335	£3,114
Dapa. 10	£10,739	£1,764	£8,166	£5,262	£8,107	£5,233

SA02: UTI and GTI rates applied to all model cycles

If the UTI and GTI rates are applied to all model cycles this has a slightly larger impact upon the flozins than the other treatments. Compared to the values of the base case the following changes occur (see Table **73**).

Table 73 AG SA02: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£65	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Repag.	£65	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Pio.	£66	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Sita. 100	£68	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Cana. 300	£93	-0.010	-0.010	-0.010	-0.010	-0.010	-0.010
Empa. 25	£84	-0.009	-0.009	-0.009	-0.009	-0.009	-0.009
Dapa. 10	£86	-0.009	-0.009	-0.009	-0.009	-0.009	-0.009

The pattern of dominated strategies is as for the base case. Given the similarity of changes for both gliclazide and repaglinide the costs effectiveness estimates for repaglinide compared to gliclazide are little different from those of the base case.

Due to the flozins being slightly worse affected by this, the cost effectiveness estimates for canagliflozin compared to repaglinide for BMI scenarios 1, 2, 3 and 5 worsen slightly to £46,721 per QALY, £223k per QALY, £131k per QALY and £283k per QALY. There is also some worsening in the cost effectiveness estimates for the flozins compared to sitagliptin (see Table **74**).

Table 74 AG SA02: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£15,805	£2,875	£10,656	£7,065	£12,465	£7,709
Empa. 25	£21,167	£4,987	£16,622	£11,973	£17,878	£12,513

Dapa. 10	£52,010	£7,093	£37,364	£22,660	£37,046	£22,523

SA03: A common baseline HbA1c of 7.5%

The common baseline HbA1c of 7.5% does not changes the ordering of treatments by their total costs, with the aggregate outcomes being as below (Table **75**).

Table 75 AG SA03: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,593	10.432	9.687	9.687	9.687	9.810	9.776
Repag.	£26,710	10.429	9.717	9.717	9.717	9.810	9.784
Pio.	£26,814	10.425	9.665	9.665	9.665	9.802	9.763
Sita. 100	£31,501	10.404	9.716	9.714	9.714	9.787	9.767
Cana. 300	£31,925	10.421	9.831	9.742	9.766	9.810	9.815
Empa. 25	£32,003	10.420	9.800	9.737	9.752	9.808	9.803
Dapa. 10	£32,044	10.414	9.789	9.728	9.742	9.801	9.794

Total costs have fallen and the total QALYs have increased compared to the base case as outlined below (below (

Table **76**).

Table 76 AG SA03: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£721	0.040	0.054	0.054	0.054	0.039	0.037
Repag.	-£703	0.041	0.054	0.054	0.054	0.040	0.040
Pio.	-£730	0.041	0.053	0.053	0.053	0.040	0.035
Sita. 100	-£858	0.049	0.059	0.059	0.059	0.048	0.048
Cana. 300	-£751	0.041	0.050	0.052	0.059	0.040	0.048
Empa. 25	-£772	0.043	0.053	0.054	0.058	0.042	0.047
Dapa. 10	-£822	0.046	0.055	0.057	0.061	0.045	0.049

While the effects are reasonably similar across all the treatments, they appear to be larger for sitagliptin and in some instances for the flozins too. While the differences in total QALYs are sometimes slight for sitagliptin compared to the cheaper alternatives, there is always a cheaper alternative that offers slightly more QALYs. The cost differences remain large and as a consequence sitagliptin remains dominated.

For BMI scenarios 1, 2 and 3 the cost effectiveness of repaglinide compared to gliclazide rises slightly to £3,911 per QALY. For BMI scenarios 1, 2, 3 and 5 the cost effectiveness of canagliflozin worsen slightly to £45,968, £207k, £107k and £173k respectively.

For the cost effectiveness of the flozins compared to sitagliptin the estimates worsen due to the relative improvement of sitagliptin (see Table **77**).

Table 77 AG SA03: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£24,939	£3,717	£14,961	£8,237	£18,309	£8,880
Empa. 25	£30,150	£6,042	£21,643	£13,310	£24,300	£13,972
Dapa. 10	£54,863	£7,442	£38,256	£19,902	£38,725	£20,011

SA04: Initial HbA1c treatment effect a function of baseline HbA1c

If the monotherapies' treatment effects upon HbA1c are made a function of patients' baseline HbA1c, as derived from the NICE CG modelling which implies a larger effect for those with a higher baseline value, the following applies (see Table **78**).

Table 78 AG SA04: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,410	10.393	9.629	9.629	9.629	9.771	9.738
Repag.	£27,518	10.389	9.658	9.658	9.658	9.770	9.741
Pio.	£27,650	10.384	9.608	9.608	9.608	9.762	9.729
Sita. 100	£32,588	10.358	9.654	9.651	9.652	9.742	9.718
Cana. 300	£32,782	10.381	9.777	9.687	9.700	9.771	9.760
Empa. 25	£32,953	10.380	9.744	9.680	9.687	9.768	9.751
Dapa. 10	£33,100	10.371	9.732	9.669	9.674	9.759	9.740

And the following changes from the baseline values (see Table **79**).

Table 79 AG SA04: Total costs and QALYs compared to the base case

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£97	0.001	-0.004	-0.004	-0.004	0.001	-0.001
Repag.	£105	0.000	-0.005	-0.005	-0.005	0.000	-0.003
Pio.	£106	0.000	-0.004	-0.004	-0.004	0.000	0.001
Sita. 100	£230	0.003	-0.003	-0.004	-0.004	0.002	-0.001
Cana. 300	£106	0.001	-0.003	-0.003	-0.008	0.001	-0.006
Empa. 25	£179	0.003	-0.003	-0.003	-0.007	0.002	-0.005
Dapa. 10	£234	0.004	-0.002	-0.003	-0.007	0.003	-0.004

This does not change the treatments that are modelled as being dominated. The cost effectiveness estimates for repaglinide compared to gliclazide are little changed at £3,747 per QALY for the BMI scenarios 1, 2 and 3 and but the cost effectiveness estimate for the BMI scenario 5 worsens to £34,225 per QALY due to the similarity in effectiveness between the two treatments.

For the BMI scenarios 1, 2, 3 and 5 the cost effectiveness estimate for canagliflozin compared to repaglinide are broadly similar to those of the base case at £44,115 per QALY, £179k per QALY, £127k per QALY, and £272k per QALY.

The cost effectiveness estimates for the flozins compared to sitagliptin are typically slightly better than those of the base case (see Table **80**).

Table 80 AG SA04: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£8,314	£1,570	£5,367	£4,037	£6,636	£4,570
Empa. 25	£16,222	£4,063	£12,671	£10,411	£13,894	£11,064
Dapa. 10	£37,733	£6,582	£29,767	£23,093	£29,242	£22,808

SA05: No discontinuation rates

Not applying the treatment discontinuation rates results in the following (see Table **81** and Table 82).

Table 81 AG SA05: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,320	10.393	9.634	9.634	9.634	9.771	9.739
Repag.	£27,421	10.389	9.665	9.665	9.665	9.770	9.745
Pio.	£27,571	10.383	9.610	9.610	9.610	9.761	9.727
Sita. 100	£32,456	10.354	9.658	9.655	9.656	9.739	9.718
Cana. 300	£32,735	10.379	9.781	9.690	9.707	9.769	9.766
Empa. 25	£32,826	10.377	9.747	9.683	9.694	9.765	9.755
Dapa. 10	£32,944	10.367	9.735	9.671	9.681	9.755	9.744

Table 82 AG SA05: Total costs and QALYs compared to the base case

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£6	0.000	0.001	0.001	0.001	0.000	0.000
Repag.	£7	0.000	0.002	0.002	0.002	0.000	0.001
Pio.	£28	-0.001	-0.002	-0.002	-0.002	-0.001	-0.001
Sita. 100	£98	-0.001	0.000	0.000	0.000	-0.001	0.000
Cana. 300	£59	-0.001	0.001	0.000	0.000	-0.001	0.000
Empa. 25	£52	0.000	0.001	0.000	0.000	0.000	0.000
Dapa. 10	£78	-0.001	0.001	0.000	0.000	-0.001	0.000

Repaglinide increases in cost slightly but the small increases in the total QALYs are proportionally slightly greater and there is a minor improvement in the cost effectiveness estimates for repaglinide compared to gliclazide compared to those of the base case for the BMI scenarios 1, 2, 3 and 5.

The costs for sitagliptin and the flozins increase slightly with minimal impact upon the total QALYs associated with them. Compared to the cost effectiveness estimate of the base case the cost effectiveness estimates for canagliflozin compared to repaglinide for the BMI scenarios 1, 2, 3 and 5 worsen slightly, but the effect is small.

SA06: NICE CG baseline TC:HDL values and UKPDS68 progression

If the NICE CG baseline TC:HDL values are applied and the TC:HDL ratio is evolved as per the UKPDS68 equation 13 the patient outcomes worsen and costs rise as below (see Table **83** and Table **84**).

Table 83 AG SA06: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,783	10.006	9.273	9.273	9.273	9.404	9.373
Repag.	£27,884	10.003	9.302	9.302	9.302	9.404	9.379
Pio.	£27,996	9.997	9.251	9.251	9.251	9.394	9.361
Sita. 100	£32,676	9.963	9.289	9.287	9.287	9.367	9.348
Cana. 300	£32,968	9.990	9.411	9.325	9.341	9.400	9.398
Empa. 25	£33,057	9.989	9.379	9.318	9.329	9.397	9.387
Dapa. 10	£33,154	9.977	9.366	9.305	9.315	9.385	9.375

Table 84 AG SA06: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£469	-0.386	-0.361	-0.361	-0.361	-0.367	-0.366
Repag.	£470	-0.386	-0.361	-0.361	-0.361	-0.366	-0.365
Pio.	£452	-0.388	-0.362	-0.362	-0.362	-0.368	-0.367
Sita. 100	£318	-0.392	-0.368	-0.368	-0.368	-0.372	-0.371
Cana. 300	£292	-0.390	-0.369	-0.366	-0.366	-0.370	-0.369
Empa. 25	£283	-0.389	-0.367	-0.365	-0.365	-0.369	-0.368
Dapa. 10	£288	-0.390	-0.369	-0.366	-0.366	-0.370	-0.370

The costs effectiveness estimates for repaglinide compared to gliclazide are little different from those of the base case.

The cost effectiveness estimates for canagliflozin compared to repaglinide for the BMI scenarios 1, 2, 3 and 5 of £46,562 per QALY, £129k per QALY, £223k per QALY and £272k per QALY are broadly similar to those of the base case.

The cost effectiveness estimates of the flozins compared to sitagliptin show some improvements compared to the base case estimates (see Table **85**).

Table 85 AG SA06: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£10,601	£2,403	£7,748	£5,420	£8,807	£5,845
Empa. 25	£14,657	£4,237	£12,152	£9,208	£12,873	£9,552
Dapa. 10	£33,394	£6,284	£26,373	£17,585	£26,173	£17,486

SA07: Applying the UKPDS68 year 2 parameter for the evolution of HbA1c

Applying the UKPDS68 year 2 parameter of equation 11 for the evolution of HbA1c has little impact upon results compared to the base case in absolute terms (see Table **86**).

Table 86 AG SA07: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£7	0.001	0.001	0.001	0.001	0.001	0.001
Repag.	£3	0.001	0.001	0.001	0.001	0.001	0.001
Pio.	-£4	0.000	0.000	0.000	0.000	0.000	0.000
Sita. 100	-£5	0.001	0.001	0.001	0.001	0.001	0.001
Cana. 300	-£16	0.000	0.000	0.000	0.000	0.000	0.000
Empa. 25	-£12	0.000	0.000	0.000	0.001	0.000	0.000
Dapa. 10	-£8	0.001	0.001	0.001	0.001	0.001	0.001

The costs effectiveness estimates for the treatments that are not dominated are little different from those of the base case. The cost effectiveness estimates compared to sitagliptin are similar to those of the base case (see Table **87**).

Table 87 AG SA07: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,919	£2,527	£8,936	£6,036	£10,356	£6,563
Empa. 25	£18,616	£4,635	£14,818	£10,825	£15,879	£11,294
Dapa. 10	£41,268	£6,630	£31,255	£19,911	£31,026	£19,801

SA08: Intensifying by adding gliclazide has a -0.47% HbA1c reduction

If the intensification of adding gliclazide to a monotherapy only results in a -0.47% reduction in HbA1c this has very little impact upon those who had gliclazide and repaglinide monotherapy due to this only affecting the small percentage that discontinue due to adverse events. But the impact upon the other treatments is quite marked. For these the change affects the vast majority of patients. They have an overall smaller clinical effect applied which is in itself harmful, and will also tend to progress through to insulin more quickly than compared to the base case (see Table **88**).

Table 88 AG SA08: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,320	10.393	9.634	9.634	9.634	9.771	9.739
Repag.	£27,421	10.389	9.665	9.665	9.665	9.770	9.745
Pio.	£27,571	10.383	9.610	9.610	9.610	9.761	9.727
Sita. 100	£32,456	10.354	9.658	9.655	9.656	9.739	9.718
Cana. 300	£32,735	10.379	9.781	9.690	9.707	9.769	9.766
Empa. 25	£32,826	10.377	9.747	9.683	9.694	9.765	9.755
Dapa. 10	£32,944	10.367	9.735	9.671	9.681	9.755	9.744

This results in the following differences in costs and QALYs compared to the base case (see Table 89).

Table 89 AG SA08: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£5	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	£13	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	£273	-0.016	-0.020	-0.020	-0.020	-0.016	-0.016
Sita. 100	£299	-0.019	-0.023	-0.023	-0.023	-0.018	-0.018
Cana. 300	£266	-0.018	-0.023	-0.023	-0.023	-0.018	-0.018
Empa. 25	£281	-0.018	-0.022	-0.022	-0.022	-0.018	-0.017
Dapa. 10	£286	-0.020	-0.024	-0.024	-0.024	-0.020	-0.019

And the following cost effectiveness estimates (see Table **90**).

Table 90 AG SA08: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,604	£3,604	£3,604	Dom	£19,784
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£58,292	£1.1mn	£254k	Dom	£1.1mn
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

If 2nd line gliclazide is less effective, and crucially is less effective than the 2nd line pioglitazone in the gliclazide and repaglinide arms, this considerably worsens the cost effectiveness estimates for the flozins compared to gliclazide and repaglinide. It also worsens their cost effectiveness estimates compared to pioglitazone.

For the comparisons with sitagliptin the costs effectiveness estimates for the flozins is as below (Table **91**).

Table 91 AG SA08: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£11,125	£2,311	£7,903	£5,435	£9,065	£5,909
Empa. 25	£17,003	£4,442	£13,784	£10,214	£14,676	£10,638
Dapa. 10	£43,173	£6,551	£32,025	£20,133	£31,759	£19,999

The flozins continue to show reasonable cost effectiveness estimates compared to sitagliptin, though again the picture is more mixed for dapagliflozin.

SA09: Applying the Janssen linear evolutions of HbA1c

Applying the Janssen linear evolutions for treatments causes pioglitazone to become the cheapest as below (see Table **92**).

Table 92 AG SA09: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	£25,818	10.486	9.740	9.740	9.740	9.861	9.811
Glicl.	£25,986	10.476	9.734	9.734	9.734	9.852	9.807
Repag.	£26,139	10.470	9.761	9.761	9.761	9.849	9.812
Sita. 100	£31,303	10.426	9.741	9.738	9.739	9.808	9.782
Cana. 300	£31,385	10.465	9.882	9.793	9.821	9.853	9.857
Empa. 25	£31,643	10.453	9.836	9.773	9.790	9.840	9.831
Dapa. 10	£31,836	10.438	9.817	9.754	9.769	9.825	9.813

Compared to the base case costs have fallen considerably in for all treatments, and total QALYs have risen (see Table **93**).

Table 93 AG SA09: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	-£1,725	0.101	0.128	0.128	0.128	0.099	0.082
Glicl.	-£1,328	0.084	0.101	0.101	0.101	0.082	0.069
Repag.	-£1,275	0.081	0.098	0.098	0.098	0.079	0.067
Sita. 100	-£1,055	0.071	0.083	0.083	0.083	0.069	0.063
Cana. 300	-£1,291	0.085	0.102	0.102	0.114	0.083	0.091
Empa. 25	-£1,131	0.076	0.090	0.090	0.096	0.074	0.075
Dapa. 10	-£1,030	0.071	0.083	0.083	0.088	0.069	0.068

Gliclazide is now dominated by pioglitazone, though the pattern of dominance of the base case has not otherwise changed.

Table 94 AG SA09: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	..	..	..	..	..	..
Glicl.	Dom	Dom	Dom	Dom	Dom	Dom
Repag.	Dom	£15,633	£15,633	£15,633	Dom	£343k
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£43,246	£163k	£86,862	Dom	£115k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

The cost effectiveness estimates for repaglinide compared to pioglitazone are somewhat worse than the corollaries for repaglinide compared to gliclazide of the base case. The cost effectiveness estimates for canagliflozin compared to repaglinide are surprisingly similar, though that for BMI scenario 5 and to a lesser extent scenario 3 have improved (see Table **94**).

Despite the quite radical change in the evolution of HbA1c the cost effectiveness estimates for the flozins compared to sitagliptin are not radically different from those of the base case, but have improved somewhat for canagliflozin and empagliflozin (see Table **95**). The picture for dapagliflozin remains mixed.

Table 95 AG SA09: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£11,125	£2,311	£7,903	£5,435	£9,065	£5,909
Empa. 25	£17,003	£4,442	£13,784	£10,214	£14,676	£10,638
Dapa. 10	£43,173	£6,551	£32,025	£20,133	£31,759	£19,999

SA10: Those discontinuing a treatment omit the intensification step that applies this treatment

This sensitivity analysis has little impact upon results and does not affect the ordering of treatments by their total costs. The pattern of dominated treatments is also not affected.

The cost effectiveness of repaglinide compared to gliclazide is estimated to improve for the BMI scenarios 1, 2 and 3 to £2,744 per QALY and for BMI scenario 5 to £14,190 per QALY.

The cost effectiveness estimates of canagliflozin compared to repaglinide are little affected, being £45,679 per QALY, £206k per QALY, £124k per QALY and £257 per QALY for the BMI scenarios 1, 2, 3 and 5 respectively.

The cost effectiveness estimates for the flozins compared to sitagliptin are essentially those of the base case.

SA11: SA01 and SA08 combined

If intensifying from monotherapy by adding gliclazide only results in a -0.47% reduction in patients HbA1c and when switching to insulin patients receive only insulin and gliclazide the combined effects of this are as below. As for SA01, canagliflozin is now estimated to be the most expensive treatment (see Table **96**).

Table 96 AG SA11: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,631	10.392	9.633	9.633	9.633	9.770	9.739
Repag.	£26,730	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,054	10.368	9.592	9.592	9.592	9.746	9.713
Sita. 100	£28,922	10.336	9.634	9.632	9.632	9.721	9.701
Empa. 25	£28,988	10.359	9.724	9.661	9.671	9.748	9.738
Dapa. 10	£29,018	10.347	9.710	9.647	9.657	9.736	9.726
Cana. 300	£29,022	10.361	9.758	9.668	9.685	9.752	9.749

The pattern of changes in cost is much as per SA01, while the pattern of changes in QALYs is as per SA08 (see Table 97).

Table 97 AG SA11: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£682	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	-£684	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	-£489	-0.016	-0.020	-0.020	-0.020	-0.016	-0.016
Sita. 100	-£3,437	-0.019	-0.023	-0.023	-0.023	-0.018	-0.018
Empa. 25	-£3,787	-0.018	-0.022	-0.022	-0.022	-0.018	-0.017
Dapa. 10	-£3,848	-0.020	-0.024	-0.024	-0.024	-0.020	-0.019
Cana. 300	-£3,654	-0.018	-0.023	-0.023	-0.023	-0.018	-0.018

Due to the reordering of the treatments by total costs, empagliflozin is no longer dominated.

Table 98 AG SA11: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,278	£3,278	£3,278	Dom	£17,994
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Empa. 25	Dom	£36,837	Dom	£268k	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£1,030	£460k	£2,581	Dom	£470k
Dom = Dominated: i.e. more costly and less effective than another treatment						

Note that the erratic pattern for canagliflozin as the BMI scenarios are worked across is due to it being compared to empagliflozin for the BMI scenarios 1, 3 and 5 but to repaglinide for the BMI scenarios 2 and 4 (see Table 98).

The flozins remain dominated if there are no direct quality of life impacts from weight changes. For the BMI scenarios 1 and 3 the cost effectiveness of empagliflozin compared to repaglinide is £36,837 per QALY and £268k per QALY. But these cost effectiveness estimates for empagliflozin are extendedly dominated by canagliflozin, which has cost effectiveness estimates compared to repaglinide of £24,226 per QALY and £105k per QALY for the BMI scenarios 1 and 3.

For the cost effectiveness of the flozins compared to sitagliptin the estimates improve quite considerably due to the greater cost reductions for the flozins and sitagliptin seeing similar falls in total QALYs as the flozins (see Table **99**).

Table 99 AG SA11: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£3,927	£816	£2,789	£1,918	£3,199	£2,085
Empa. 25	£2,818	£736	£2,285	£1,693	£2,432	£1,763
Dapa. 10	£8,399	£1,274	£6,230	£3,917	£6,178	£3,891

Summary of the assessment group modelling

The AG modelling base case estimates that the lifetime QALYs arising from diabetes, its complications and adverse events are highest for gliclazide at 10.392 QALYs, with repaglinide having a similar estimate of 10.389 QALYs. Pioglitazone accrues slightly fewer at 10.384 QALYs. The flozins lie a little below this with canagliflozin being estimated to yield 10.380 QALYs, empagliflozin 10.378 QALYs and dapagliflozin 10.367 QALYS. Sitagliptin fares worse at 10.355 QALYs. Gliclazide is estimated to be superior to the flozins by 0.012 QALYs compared to canagliflozin, 0.015 QALYs compared to empagliflozin and 0.025 QALYs compared to dapagliflozin. Adverse events contribute relatively little to these estimates, and even less to the estimates of the differences between treatments. To place these amounts in context, at the baseline quality of life of 0.801 they would be equivalent to survival gains of around 6 days compared to canagliflozin, 7 days compared to empagliflozin and 11 days compared to dapagliflozin.

But these amounts ignore the direct quality of life effects of weight changes. The flozins have a superior weight profile, with canagliflozin providing the largest weight losses. If the monotherapy weight changes are retained over the patient lifetime canagliflozin is estimated to yield an additional 0.147 QALYs compared to gliclazide: equivalent to 67 days additional survival at the baseline quality of life of 0.801. These gains are reduced if it is assumed that weight losses rebound after one year to only 0.057 QALYs, and if it is assumed that weight losses rebound at treatment change to 0.074 QALYs.

The flozins and to a slightly lesser extent sitagliptin are estimated to be considerably more expensive than gliclazide, repaglinide and pioglitazone, the increases in lifetime costs ranging between £5,000 and £5,500.

In the light of the above, if there are no direct quality of life effects from weight changes, the flozins are estimated to be dominated. But if there are direct quality of life impacts from weight changes and the monotherapy weight changes persist throughout the patient life time the flozins are no longer dominated. Repaglinide remains more expensive than gliclazide but now yields slightly more QALYs and has a cost effectiveness estimate compared to gliclazide of £3,331 per QALY. Canagliflozin has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. While canagliflozin formally dominates the other flozins, the cost effectiveness estimates for empagliflozin and for dapagliflozin compared to gliclazide are £48,169 per QALY and £55,000 per QALY respectively.

It may be unrealistic to expect the monotherapies' weight changes and the differences they imply between treatments to persist indefinitely. If weight losses rebound after one year the cost effectiveness of canagliflozin compared to repaglinide worsens considerably to £192k per QALY. If they persist until treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £119k per QALY.

The companies argue that the main comparator for the flozins is sitagliptin. The flozins are estimated to provide slightly greater total QALYs from the modelling of diabetes, its complications and the adverse events associated with treatments. The flozins are also associated with somewhat larger weight losses than sitagliptin, which is broadly weight neutral. Total costs are higher than sitagliptin by £318 for canagliflozin, £ 416 for empagliflozin and £508 for dapagliflozin. Even without the direct quality of life effects of weight changes, canagliflozin has a reasonable cost effectiveness compared to sitagliptin of £12,623 per QALY as does empagliflozin at £18,341 per QALY. Dapagliflozin fares worse with a cost effectiveness estimate of £40,383 per QALY.

With the direct quality of life effects of weight changes and weight changes being assumed to persist over the patient lifetime the cost effectiveness of the flozins compared to sitagliptin improves considerably. Canagliflozin has an estimate of £2,590 per QALY, empagliflozin has an estimate of £4,676 per QALY and dapagliflozin has an estimate of £6,632 per QALY. If weight changes are assumed to rebound either after one year or at treatment change, the cost effectiveness estimates for the flozins generally remain within conventional thresholds. The exception to this is dapagliflozin for which if weight rebounds after one year the cost effectiveness estimates go slightly above the £30,000 threshold.

A key difference between the AG modelling and that of the companies is that the AG has assumed that patients remain on their monotherapy and add treatments to it. When patients intensify to insulin, they do so by adding it to their existing regime e.g. they intensify from canagliflozin plus gliclazide to canagliflozin plus gliclazide plus insulin. Retaining the original monotherapy increases the total costs,

and in particular increases the total cost for the flozins and to a slightly lesser extent sitagliptin. If it is assumed that the monotherapies are discontinued when the patients intensify to insulin the net costs fall to be within the range £2,362 to £2,412 for the flozins and to £2,247 for sitagliptin.

The flozins remain dominated if the direct quality of life impact of weight changes are not included, but applying them and assuming weight changes persist indefinitely improves the costs effectiveness estimates for the flozins compared to repaglinide to £19,850 per QALY for canagliflozin, £27,230 per QALY for empagliflozin and £32,288 per QALY for dapagliflozin. Weight losses rebounding after one year cause these estimates to worsen to £84,634 per QALY, £112k per QALY and £274k per QALY respectively, while weight losses rebounding at change of treatment cause these estimates to worsen to £52,571 per QALY, £74,209 per QALY and £128k per QALY respectively.

This sensitivity analysis also sees the flozins being estimated to be cost effective relative to sitagliptin under all the weight change scenarios including that of no direct quality of life impact from weight changes.

The base case applied the baseline HbA1c values for those starting a monotherapy of the NICE CG which had a mean of 8.4% (s.d. 1.8%). This differs from some of the companies' modelling, which assumed a common baseline HbA1c of 7.5%. As would be expected this both improved patient outcomes and lowered total costs. It did not alter the patterns of dominance, and while the cost effectiveness estimates for the flozins compared to repaglinide worsened the effect was not major.

Of more interest was that the cost effectiveness estimates of the flozins compared to sitagliptin worsened. With no direct quality of life impacts from weight these worsened to £24,939 per QALY for canagliflozin, £30,150 per QALY for empagliflozin and £54,863 per QALY for dapagliflozin. With the monotherapy BMI effects persisting for the patient lifetime these cost effectiveness estimates improve to £3,717 per QALY, £6,042 per QALY and £7,442 per QALY respectively. Weight loss rebound after one year reduces the improvements to £14,961 per QALY, £21,643 per QALY and £38,256 per QALY, while weight loss rebound at treatment change reduces the improvements to £8,237 per QALY, £13,310 per QALY, and £19,902 per QALY respectively.

Making the HbA1c treatment effect a function of patients' baseline HbA1c had little practical impact upon the cost effectiveness estimates for the flozins compared to gliclazide, repaglinide and pioglitazone. But it improved the cost effectiveness estimates for canagliflozin compared to sitagliptin by around one third. The impact for empagliflozin is less, and there was little impact for dapagliflozin. This is as would be expected given the greater HbA1c effect for canagliflozin compared to sitagliptin,

the slightly greater effect for empagliflozin and broad equivalence between dapagliflozin and sitagliptin.

Janssen applied linear evolutions of HbA1c with the annual rate of change being treatment specific. Applying the same annual rates of change within the AG modelling reduced total costs and increased total QALYs quite considerably. It also caused pioglitazone to be estimated as the cheapest treatment, with it dominating gliclazide. Pioglitazone also dominated repaglinide if there were no direct quality of life impacts from weight changes. Including these with no rebound for weight gains caused the cost effectiveness of repaglinide compared to pioglitazone to improve to £15,633 per QALY. The pattern of dominance was not otherwise altered.

The linear HbA1c evolutions still saw the flozins dominated unless there were direct quality of life impacts from weight changes. Given these, the cost effectiveness estimates for canagliflozin compared to repaglinide were surprisingly similar to those of the base case, though the higher cost effectiveness estimates varied more due to the divisions by small net QALY gains.

Assuming that adding gliclazide at the 1st intensification causes only a -0.47% reduction in HbA1c compared to the -1.01% reduction of the base case has little to no impact for gliclazide and repaglinide as patients will not use this intensification. But it increases costs and reduces QALYs in the other arms, so worsening the cost effectiveness estimates for the flozins. The cost effectiveness estimates for the flozins compared to sitagliptin are not particularly affected, though those for dapagliflozin do worsen slightly.

Assuming that the UTI and GTI rates apply throughout the modelling rather than just for the first cycle has little practical impact upon results.

Summary: A comparison of the modelling exercises' assumptions and inputs

NICE checklist

The modelling exercises and their data sources can be assessed against the NICE reference case checklist (see Table **100**).

Table 100 NICE reference case checklist: Companies and AG

	Janssen	AZ	BI	AG
Comparator(s) :	The individual flozins were assessed alongside Sita. 100mg, Pio and SU.	The flozins were grouped into a class effect, as are the gliptins, with Pio and SU also being considered.	The main analysis compared Empa. 10mg, Empa. 25mg, Sita. 100mg, Pio, SU and repaglinide.	Cana. 100mg, Dapa. 10mg, Empa. 10mg, Empa. 25mg, Sita. 100mg, Pio and SU.
Patient group	Adult patients with T2DM unable to take metformin starting monotherapy			
Perspective: Costs	NHS & PSS			
Perspective: Benefits	Patient			
Analysis	Cost utility			
Time horizon	40 years			
Clinical evidence	Own NMA	Own NMA	Own NMA	Own NMA
Outcome measure	QALYs			
Health states generic QoL: Other than UTIs & GTIs UTIs and GTIs	 Yes, EQ-5D No	 Yes, EQ-5D IWB	 Yes, EQ-5D IWB	 Yes, EQ-5D No
Benefit valuation: Other than UTIs & GTIs UTIs and GTIs	 TTO Janssen TTO	 TTO Ranking scale	 TTO Ranking scale	 TTO Janssen TTO
HRQL pref. data.: Other than UTIs & GTIs UTIs and GTIs	 UK Tariff 100 UK Public	 UK Tariff 62 US Med/Pub	 UK Tariff 62 US Med/Pub	 UK Tariff 100 UK Public
Discount rates	3.5% for both costs and benefits			
Equity	Equal QALY regardless of patient characteristics			
Probabilistic modelling	Yes	Yes	No (Model B)	Yes
Sensitivity analyses	Yes	Yes	No	Yes

Modelling assumptions

In terms of the main assumptions and data sources the companies and the AG have used the following (see Table **101**).

Table 101 Main assumptions: Companies and AG

	Janssen	Astrazeneca	BI	AG
HbA1c	Linear	UKPDS68	UKPDS68	UKPDS68
SBP	Linear	UKPDS68	UKPDS68	UKPDS68
TC:HDL	Linear	UKPDS68	UKPDS68	UKPDS68
Weight	Linear	Linear	Linear	Linear
Complications modelling	Variety	UKPDS82	UKPDS68	UKPDS68
QoL main source	CODE-2	UKPDS62	Alva 2014	UKPDS62
Costs main source	UKPDS84	UKPDS65/84	UKPDS84	UKPDS84

The above is a simplification. For instance, the Janssen submission has a large number of health states associated with eGFR levels which also have ongoing costs associated with them. These are not sourced from the UKPDS84. The ECHO-T2DM model used by Janssen has been submitted to the Mt. Hood challenges. But the Janssen implementation of the ECHO-T2DM and base case assumptions is likely to have differed quite considerably from that submitted to the Mt. Hood challenges.

But the above does help highlight the main differences between the submissions and the AG modelling. Janssen is the outlier in terms of its approach, both in terms of the modelling of its complications and its assumptions about the linearity of the evolution of HbA1c and SBP. Astrazeneca, and Boehringer Ingelheim use the UKPDS68 to model the evolution of HbA1c, SBP and the TC:HDL ratio. The AG does as well with the exception of the TC:HDL ratio which is assumed to be constant for the base case, but is evolved using the UKPDS68 in a sensitivity analysis. Janssen argues that the evolutions of the UKPDS include the effects of treatment intensifications so cannot be used when the modelling is separately accounting for the treatment intensifications. There is some force to this argument. But it then has to be asked whether the alternative of linear evolutions is preferable. The treatment specific linear evolutions of HbA1c within the Janssen submission are not obviously related to the treatments under consideration. There are also concerns with linear evolutions maintaining absolute differences indefinitely when the UKPDS clearly suggests convergence.

As already discussed, the UKPDS OM2 which is based upon the UKPDS82 was not available to the AG. As a consequence, in line with the modelling of Boehringer Ingelheim the older OM1 was used to model the complications of diabetes, this being based upon the UKPDS68. The Astrazeneca modelling was based upon the UKPDS68 for the evolution of the risk factors and the UKPDS82 for the calculation of event probabilities, as implemented within the CDM. As far as the AG is aware this version of the CDM has not been previous used, has not been submitted to the Mt. Hood challenge and has not been independently interrogated or validated.

A concern with the Janssen and the Astrazeneca models is that there has been little presented on model convergence. The AG has relied upon the work of the draft NICE CG for diabetes, which resulted in deterministic model runs having 50,000 patients simulated with 1,000 inner loops for each patient to reduce the Monte-Carlo error. The draft NICE CG for diabetes could be read as suggesting that only 100 inner loops are necessary for convergence, but even this seems to be somewhat more model runs that any of the company submissions. As a consequence, the AG is uncertain whether the company models have reliably converged. Boehringer Ingelheim did present some work on convergence and concluded that results of the OM1 stabilised after 1,000 inner loops for each patient had been run, choosing to run the model with 10,000 inner loops though only for 9,211 patients so around 92mn model runs: approximately double the 50mn of the AG.

Monotherapies modelled and sequences compared

The companies and the AG considered the following monotherapies (see Table **102**).

Table 102 Base case comparators considered: Companies and AG

	Janssen	AZ	BI		AG
Analysis	Base	Base	24 week	52 week	Base
		Flozin			
	Cana. 100mg		Cana. 100mg		
	Cana. 300mg		Cana. 300mg		Cana 300mg
			Dapa. 5mg		
	Dapa. 10mg		Dapa. 10mg		Dapa. 10mg
	Empa. 10mg		Empa. 10mg	Empa. 10mg	
	Empa. 25mg		Empa. 25mg	Empa. 25mg	Empa. 25mg
		Gliptin			
	Sita. 100mg			Sita. 100mg	Sita. 100mg
	Pioglitazone	Pioglitazone		Pioglitazone	Pioglitazone
	Sulfonylurea	Sulfonylurea		Sulfonylurea	Gliclazide
				Repaglinide	Repaglinide

Note that Janssen considered repaglinide in a scenario analysis.

Astrazeneca pooled the flozins into a single treatment group, with pooled treatment effect estimates and weighted average direct drug costs. The gliptins were similarly pooled.

The following treatment intensifications were assumed for the base cases, with treatment intensifications occurring when a patient's HbA1c was modelled as breaching the 7.5% intensification threshold (see Table **103**).

Table 103 Base case intensifications: Companies and AG

	Janssen	AZ	BI	AG
1st intensification	+ Glicl.	Switch to NPH	+SU; or +Sita.	-Repag. +Pio; and/or +Glicl.
2nd intensification	Switch to NPH	Intensify NPH	Switch to NPH	+ NPH
3rd intensification	+ Aspart	None	None	-Glicl., +Bolus

Within the Boehringer Ingelheim submission all but gliclazide had a 1st intensification of adding gliclazide to the existing monotherapy. Those on gliclazide monotherapy had a 1st intensification of adding sitagliptin.

Similarly, for the 1st intensification within the AG modelling all but gliclazide added gliclazide to the existing monotherapy. Those on gliclazide monotherapy has a 1st intensification of adding pioglitazone. The repaglinide monotherapy arm stands out, having repaglinide withdrawn and both pioglitazone and gliclazide added. For the 2nd intensification all strategies intensify by adding NPH insulin. The 3rd intensification adds bolus insulin and withdraws gliclazide.

The AG modelled sequences differ from those of the company submissions in that patients add NPH insulin rather than switch to it. The retention of the monotherapies in the AG triple therapy combinations with gliclazide and NPH means that the differences in costs between the monotherapies are retained throughout the AG base case modelling. In the light of this, a scenario analysis was undertaken which withdraws the initial monotherapies when patients now in effect switch to NPH insulin though this only affected the direct drug costs and not the clinical effectiveness estimates.

Patient characteristics and complications prevalences at baseline

The patient baseline characteristics were as below (Table **104**).

Table 104 Main baseline risk factors: Companies and AG

	Janssen	AZ	BI	AG
Source	Cana. trials	NMA	CPRD	THIN/EHS
Age	56.2	55.0	63.1	59.8
Duration diabetes	0.0	3.6	2.9	2.0
Male	53%	55%	57%	57%
BMI	29.7	28.9	31.1	31.9
Male	..		31.0	..
Female	..		32.0	..
HbA1c	8.02%	7.50%	8.49%	8.40%
SBP	127.7	128.3	134.7	137.5
TC	5.17	5.07	..	4.96
HDL	1.25	1.20	1.20	1.18
LDL	3.06	3.32	4.02	..
Current smoker	9.0%	36.90%	16.7%	18.1%
Past smoker	..	..	36.5%	34.0%

Note that the baseline HbA1c of 7.5% of Astrazeneca is based upon the treatment intensification threshold rather than the Astrazeneca NMA, which had a mean of 8.2%. The Astrazeneca proportion who smoke has been taken from the electronic model, where it is ambiguous whether this is the proportion at diagnosis, the proportion at baseline, or both.

The mean baseline age differs quite a lot across the companies' and AG's estimates, with the AG's estimate lying somewhere in the middle. Baseline age is likely to affect results as this determines the amount of time left for the longer term impacts of clinical effects to be realised. Perhaps more pertinently, it will also affect the amount of time the direct quality of life impacts of weight changes apply if weight changes are modelled as being maintained into the long term.

The proportion modelled as smoking is unclear within the Janssen submission but it seems likely to have been somewhat lower than the other exercises. Within the Astrazeneca submission it is somewhat higher, though there is some ambiguity about this. The AG assumption, given the electronic copy of the CDM that was submitted, is that the 36.9% is the proportion at both diagnosis and at baseline as only one value for smoking could be found.

The prevalences of the complications of diabetes at baseline were as below (Table **105**).

Table 105 Prevalence of main complications at baseline: Companies and AG

	Janssen	AZ	BI	AG
Atrial fibrillation	..	0.00%	6.63%	0.81%
PVD	0.00%	0.00%	3.18%	0.51%
MI	0.80%	0.00%	2.21%	0.80%
CHF	0.00%	0.00%	1.92%	0.50%
Stroke	0.10%	0.00%	1.62%	0.50%
IHD	1.20%	0.00%	6.13%	2.70%
Amputation	0.10%	0.00%	0.29%	0.10%
Blindness	0.00%	0.00%	0.23%	0.40%
Renal failure	0.00%	0.00%	0.05%	0.20%

Given the recentness of the diagnosis of diabetes, the companies and the AG all suggest low prevalences of complications at baseline. But Astrazeneca assumes these to be zero. Since the CDM models the instances of initial events, and some secondary events, this will slightly bias the analysis of Astrazeneca towards the more effective treatment.

Again, the above does some disservice to the Janssen submission which modelled a range of other microvascular conditions.

Clinical effectiveness estimates

The main clinical effect estimates are as follows (see Table **106**). The Janssen NMA is for BMI rather than for weight in kg. To aid comparison with the other estimates the Janssen estimates have been converted to kg at assuming a patient weight of 85kg and a patient BMI of 30kgm^{-2}. The Janssen BMI estimates are presented in brackets.

Table 106 Central clinical effectiveness estimates: Companies and AG: HbA1c %

	Janssen	AZ	BI		AG
Treatment	Base	Base	24 week	52 week	Base
Flozins pooled		-0.74			
Cana. 100mg	-0.97		[redacted]		
Cana. 300mg	-1.20		[redacted]		-1.153
Dapa. 5mg			[redacted]		
Dapa. 10mg	-0.64		[redacted]		-0.704
Empa. 10mg	-0.73		[redacted]	[redacted]	
Empa. 25mg	-0.85		[redacted]	[redacted]	-0.870
Gliptins pooled		-0.64		[redacted]	
Sita. 100mg	-0.72			[redacted]	-0.723
Pioglitazone	-0.78	-0.90		[redacted]	-1.200
Sulfonylurea	-0.59	-0.95		[redacted]	-1.301
Repaglinide	-1.28			[redacted]	-1.200*
* Assumed as no estimate within NMA					

The estimates for the HbA1c changes are broadly in line for the flozins and sitagliptin. Among the flozins all sources that provide individual estimates suggest that canagliflozin 300mg provides that largest reduction, though the practical clinical differences between these estimates is a moot point. The AG estimates for pioglitazone and sulfonylurea are larger than those of the companies to the extent that these are estimated to be more effective than canagliflozin 300mg (see Table **107**).

Table 107 Central clinical effectiveness estimates: Companies and AG: SBP mmHg

	Janssen	AZ	BI		AG
Treatment	Base	Base	24 week	52 week	Base
Flozins pooled		-5.87			
Cana. 100mg	-3.71		[redacted]		
Cana. 300mg	-5.41		[redacted]		-1.338
Dapa. 5mg			[redacted]		
Dapa. 10mg	-3.21		[redacted]		-2.931
Empa. 10mg	-2.60		[redacted]	[redacted]	
Empa. 25mg	-3.40		[redacted]	[redacted]	-3.743
Gliptins pooled		-1.53		[redacted]	
Sita. 100mg	+0.80			[redacted]	+0.394
Pioglitazone	+0.88	-1.31		[redacted]	-1.400*
Sulfonylurea	+0.19	-0.65		[redacted]*	-0.600*

Repaglinide	+0.19*			[redacted] *	-1.000*
* Assumed as no estimate within NMA					

There is a greater variety between the sources when SBP is considered. The AG estimate for canagliflozin 300mg is slightly below that of the other sources, the latter suggesting that canagliflozin 300mg again has the largest effect (see Table **108**).

Table 108 Central clinical effectiveness estimates: Companies and AG: Weight kg

	Janssen	AZ	BI		AG
Treatment	Base (BMI)	Base	24 week	52 week	Base
Flozins pooled		-2.81			
Cana. 100mg	-2.40 (-0.85)		[redacted]		
Cana. 300mg	-3.42 (-1.21)		[redacted]		-3.577
Dapa. 5mg			[redacted]		
Dapa. 10mg	-1.61 (-0.57)		[redacted]		-2.457
Empa. 10mg	-1.72 (-0.61)		[redacted]	[redacted]	
Empa. 25mg	-1.84 (-0.65)		[redacted]	[redacted]	-2.471
Gliptins pooled		-0.13		[redacted]	
Sita. 100mg	+0.82 (+0.29)			[redacted]	-0.003
Pioglitazone	+2.35 (+0.83)	+2.61		[redacted]	+2.962
Sulfonylurea	+0.62 (+0.22)	+0.07		[redacted]	+1.397
Repaglinide	+0.62 (+0.22)			[redacted]	+0.100*
* Assumed as no estimate within NMA					

While not perfectly aligned, the estimates of weight changes are similar across the sources. The AG suggests slightly larger reductions in weight than the companies' estimates for dapagliflozin 10mg and empagliflozin 25mg, with the AG also suggesting that sitagliptin is broadly weight neutral. The Boehringer Ingelheim estimate for pioglitazone, sulfonylurea and repaglinide lie a reasonable amount above those of the other sources.

Quality of life values

Turning to the main quality of life values these are as follows, though again the presentation is slightly biased against the Janssen submission due to the number of health states within the ECHO-T2DM model and these not being particularly aligned with those of the other modelling (see Table **109**).

Table 109 Main health state QoL values: Companies and AG

	Janssen	Astrazeneca	BI	AG
No complications	0.843	0.882	0.720	0.801
MI year	-0.028	-0.055	-0.065	-0.055
MI history	-0.028	-0.055	0.008	-0.055
IHD	-0.028	-0.090	-0.028	-0.090
Stroke	-0.115	-0.164	-0.165	-0.164
CHF	-0.028	-0.108	-0.101	-0.108
Amputation	-0.272	-0.280	-0.172	-0.280
Blindness	-0.057	-0.074	0.033	-0.074
ESRD	-0.175	-0.263	-0.263	-0.263
per BMI > 25	-0.0061	-0.0061	-0.0061	-0.0061
Severe hypo	-0.0470	-0.0470	-0.0470	-0.0470
Non-severe hypo	-0.0142	-0.0142	-0.0142	-0.0142
UTI (QALY)	-0.0043	-0.0028	-0.0028	-0.0073
GTI (QALY)	-0.0046	-0.0028	..	-0.0096

Janssen is unusual in selecting the CODE-2 dataset as its main source of quality of life estimates. But this is a respected publication and since Janssen is using the ECHO-T2DM model, the health states of their model are not so obviously aligned with the health states of the UKPDS OM1 and OM2 for which UKPDS quality of life estimates are available for. Astrazeneca, Boehringer Ingelheim and the AG all use models based upon the UKPDS, and as a consequence quality of life estimates from the UKPDS are a natural choice.

For quality of life, Boehringer Ingelheim draws most of its values from the fixed effects estimates of Alva et al (2014), which is an analysis of the updated UKPDS dataset with Alva et al expressing a clear preference for the fixed effects estimates over their OLS estimates. This explicitly analyses the data longitudinally in order to estimate the quality of life pre and post and event and the impact of events upon an individual, rather than comparing patients cross-sectionally. This has obvious attractions, but there may be some difficulty when applying these estimates in that the coefficients for blindness and a history of MI are positive. Within Alva et al, these coefficients and that for IHD are not statistically significant so it could be argued that these could or should be set to zero. But if these are set to zero, it would obviously be preferable for the coefficients to have been further explored or excluded within the analysis of Alva et al, in order to explore the impact that this would have upon the estimates of the other coefficients. But given its choice of Alva et al as the source of its quality of life estimates, this option was not available to Boehringer Ingelheim.

The AG is not as familiar with the Alva et al estimates as with those from the UKPDS62. It seems likely that there is an age effect within the estimates of Alva et al as well, due to the mean age at completion of the 1st questionnaire being 62 compared to a mean age of 71 for the 7th, coupled with negative and statistically significant coefficients for the questionnaires. Whether it is reasonable to apply the mean value of the EQ-5D in the absence of complications of 0.72 or whether it would be better to estimate it from the fixed effect model is a moot point, but it can be noted that the constant for the fixed effects model was somewhat higher at 0.807. But the values of Alva et al are reasonable to apply.

All the analyses have used the CODE-2 quality of life decrement for BMI above 25kgm^{-2}. Astrazeneca may not have restricted this to when the patient BMI is above 25kgm^{-2}, but given baseline BMIs the impact of this will not have been large. All analyses also rely upon the estimates of Currie et al (2005) for the quality of life impacts of hypoglycaemic events, though again it appears that Astrazeneca may have applied the coefficient for non-severe hypoglycaemia to the event rate rather than to its logarithm.

And all analyses apply fairly similar absolute QALY decrements per UTI and per GTI: they are small. Those of the AG are slightly higher, this probably being due to the assumption of 2 weeks duration as drawn from Nicholle et al (2014) who estimated median durations of UTIs of between 11.0 days and 12.5 days.

Costs

Turning to the main costs these are as follows, though again the presentation is slightly biased against the Janssen submission. The Janssen submission has a number of health states associated with a patient's eGFR and the cost in the absence of complications will not have been zero. But it is difficult to identify quite what the cost in the absence of complications was. In the opinion of the AG, it is likely to have been quite small (see Table **110**).

Table 110 Monotherapy direct drug costs: Companies and AG

	Janssen	AZ	BI	AG
Empagliflozin 10mg	£477.30	£476.98	£477.98	£476.98
Empagliflozin 25mg	£477.30	£476.98	£477.98	£476.98
Dapagliflozin 5mg	..	..	£477.98	..
Dapagliflozin 10mg	£477.30	£476.92	£477.98	£476.98
Canagliflozin 100mg	£477.26	£476.93	£477.98	£476.93
Canagliflozin 300mg	£608.63		£608.21	£476.93
Flozin average	..	£481.79	..	..
SU (Gliclazide MR)	£25.81	£65.70	£68.36	£62.18
Pioglitazone	£20.48	£19.03	£24.25	£20.99
Repaglinide 6mg	£71.10	..	£93.40	£71.91
Sitagliptin 100mg	£433.86	£433.57	£433.86	£433.57
Glitpin average	..	£429.13	..	..

It seems likely that Janssen assumed the costs for gliclazide rather than the costs for gliclazide modified release. The company submissions also predated the recent change to the canagliflozin 300mg cost.

Note that the AG adds an additional £72.26 to the cost of pioglitazone for BNP monitoring: £26.26 for the test itself and £46.00 for a dedicated GP appointment (see Table **111** and Table **112**).

Table 111 Main health state costs: year of event: Companies and AG

	Janssen	Astrazeneca	BI	AG
No complications	£0	£0	£459	£1,019
Complications 1st year				
Fatal MI	£1,566	£2,605	£1,521	£1,564
Fatal IHD	£3,818	£0	£3,766	£3,873
Fatal stroke	£4,255	£5,188	£3,954	£4,066
Fatal CHF	£3,366	£0	£3,191	n.a.
Non-fatal MI	£6,665	£7,938	£6,379	£7,550
Non-fatal IHD	£10,116	£12,762	£9,767	£10,932
Non-fatal stroke	£7,247	£11,450	£6,805	£8,120
Non-fatal CHF	£3,337	£5,180	£3,191	£4,288
Amputation	£11,810	£13,499	£9,546	£12,592
Blindness	£2,260	£6,502	£1,355	£3,234
ESRD	£26,297	£18,776	£35,715	£36,801

Table 112 Main health state costs: history of event: Companies and AG

	Janssen	Astrazeneca	BI	AG
MI	£875	£2,177	£1,154	£1,877
IHD	£920	£1,395	£1,215	£1,922
Stroke	£934	£1,378	£1,125	£1,934
CHF	£1,527	£1,656	£1,473	£2,515
Amputation	£2,531	£4,618	£1,792	£3,499
Blindness	£215	£2,307	£453	£1,225
ESRD	£26,152	£18,776	£35,631	£36,801

For Janssen the first year costs of events appear to be broadly in line with those of the AG. But the costs for those with a history of events are somewhat lower. It appears that these costs may not have included the outpatient costs.

For Astrazeneca the costs of all events are somewhat higher than those of the AG. The AG cannot definitively identify the source of these discrepancies, and any error may well be on the side of the AG. But it seems possible that Astrazeneca may have indexed the UKPDS84 costs from 2007 rather than from 2012. Astrazeneca also assumed zero costs in the absence of complications which is not in line with the UKPDS84. This will have tended to exaggerate the differences between treatments' total costs.

Boehringer Ingelheim appears to have only applied the inpatient costs of the UKPDS84, and to have ignored the outpatient costs (see Table **113**).

Table 113 Main health state costs: adverse events: Companies and AG

	Janssen	Astrazeneca	BI	AG
Severe hypo	£380	£424	£380	£411
Non-severe hypo	£0	£0	£0	£0
UTI	£82	£46	£36	£73
GTI	£51	£46	n.a.	£51

In the above presentation the Janssen costs for UTIs are a simple mean of the Janssen costs of upper UTIs and lower UTIs, but the Janssen modelling explicitly accounts for this.

Summary and conclusions: A comparison of the modelling exercises' results

All the company submissions apply the old £608 annual cost for canagliflozin300mg, rather than the recently revised list price that equalises this with the £477 annual canagliflozin 100mg. As a

consequence, the summary of cost effectiveness results of the companies concentrates upon the canagliflozin 100mg results.

Due in part to the assumed slow rate of HbA1c drift for pioglitazone, Janssen estimates that it has the lowest total costs of £20,264 and yields and average 9.998 QALYs. Gliclazide is estimated to be somewhat more expensive than pioglitazone with total costs of £2,956 and to yield 9.949 QALYs so is dominated by pioglitazone. Sitagliptin is also more expensive with a total cost of £23,442 and yields a total of 9.981 per QALY so is dominated by pioglitazone, though has a cost effectiveness estimate compared to gliclazide of £6,969 per QALY.

Janssen estimates that canagliflozin 100mg has total costs of £23,525 and yields 10.039 QALYs which implies a cost effectiveness estimate of £79,537 per QALY compared to pioglitazone. The cost effectiveness estimate compared to gliclazide is £3,377 per QALY, this being largely due to the higher costs in the gliclazide arm compared to pioglitazone. Canagliflozin 100mg is estimated to dominate empagliflozin 10mg, empagliflozin 25mg and dapagliflozin 10mg.

The Janssen cost effectiveness estimates for the flozins compared to sitagliptin are £1,414 per QALY for canagliflozin 100mg, £1,977 per QALY for empagliflozin 25mg, £4,724 per QALY for empagliflozin 10mg and £6,040 per QALY for sitagliptin.

If that annual rate of increase in HbA1c is equalised between the treatments and repaglinide is included as a comparator it appears that this worsens the cost effectiveness estimate for canagliflozin compared to repaglinide to £189k per QALY. The cost effectiveness estimates for canagliflozin 100mg compared to gliclazide and sitagliptin worsen to £21,580 per QALY and £21,470 per QALY respectively. Applying the UKPDS68 evolution of HbA1c results in broad clinical equivalence between canagliflozin 100mg and gliclazide, but the costs of canagliflozin 100mg are £744 greater.

Astrazeneca pooled the flozins into a class effect. Given this pioglitazone was estimated to be the least costly with total costs of £26,067 and to yield 13.111 QALYs. The sulfonylureas were estimated to have a total cost of £26,582 so £515 higher than pioglitazone, and to yield 13.179 QALYs so have a cost effectiveness estimate of £7,574 per QALY compared to pioglitazone. The gliptins were estimated to have a total cost of £27,873 and to yield 13.188 QALYs or only 0.009 QALYs more than the sulfonylureas, hence have a cost effectiveness compared to the sulfonylureas of £143k per QALY. The flozins were only £106 more expensive than the glitpins and yielded an additional 0.018 QALYs so had a cost effectiveness compared to the gliptins of £5,904 per QALY. But the flozins cost effectiveness compared to the sulfonylureas was poor at £52,047 per QALY.

Astrazeneca sensitivity analyses showed results were sensitive to the HbA1c intensification threshold and to the assumptions around the evolution of weight.

Boehringer Ingelheim presented four modelling exercises, with all four having been previously summarised above. The following summary concentrated upon the lifetime OM1 modelling which compares empagliflozin 10mg and 25mg with pioglitazone, repaglinide, gliclazide and sitagliptin. This estimates that pioglitazone is the least expensive treatment with a total cost of [redacted] and yields [redacted] QALYs. Only repaglinide is close to being cost effective compared to pioglitazone, yielding an additional 0.025 QALYs at an additional cost of £635 hence a cost effectiveness estimate of £25,349 per QALY. Empagliflozin 25mg and empagliflozin 10mg are estimated to be £2,834 and £2,834 more expensive than pioglitazone to yield an additional 0.061 and 0.056 QALYs, so have cost effectiveness estimates of £46,480 per QALY and £50,892 per QALY compared to pioglitazone. The cost effectiveness estimates for empagliflozin 25mg and 10mg compared to sitagliptin were somewhat better. The net costs are estimated to be £330 and £333 with additional patient gains of [redacted] and [redacted], resulting in cost effectiveness estimates of around [redacted] per QALY and [redacted] per QALY respectively.

The AG modelling suggests that gliclazide is the least expensive with total costs of £27,314. Repaglinide and pioglitazone have similar total costs of £27,413 and £27,543 respectively. The increased costs for pioglitazone are due in part to the AG including a £72 allowance for annual BNP monitoring. Costs increase quite markedly with sitagliptin at a total cost of £32,358, and increase further with the flozins being clustered between £32,676 and £32,866. Sitagliptin is estimated to be £5,045 more expensive than gliclazide, and the flozins between £5,362 and £5,553 more expensive than gliclazide.

If there are no direct quality of life impacts from weight changes gliclazide is estimated to yield 10.392 QALYs. This is the highest total QALYs for this scenario and as a consequence gliclazide dominates all the other treatments.

Including direct quality of life impacts from weight changes and assuming that the weight changes associated with the monotherapies persist indefinitely results in repaglinide now being superior to gliclazide by 0.030 QALYs and so having a cost effectiveness estimate of £3,331 per QALY. Repaglinide formally dominates pioglitazone and sitagliptin, but canagliflozin yields an additional 0.177 QALYs at an additional cost of £5,262 so has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. If weight losses associated with treatment tend to rebound at either one year or at treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £192k per QALY and £119k per QALY respectively.

Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin. With no direct quality of life effects from weight changes it is estimated to be marginally more effective than empagliflozin by 0.002 QALYs and 0.013 QALYs more effective than dapagliflozin. Including the effects of weight upon quality of life increases these net gains to 0.034 QALYs and 0.046 QALYs if weight changes persist indefinitely. If they rebound after one year these gains fall to 0.007 QALYs and 0.019 QALYs, while if they rebound at treatment change they fall to 0.014 QALYs and 0.026 QALYs.

Both canagliflozin and empagliflozin have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY even if there are no quality of life impacts from weight changes. Including these effects improves their cost effectiveness estimates compared to sitagliptin.

Dapagliflozin fares slightly worse compared to sitagliptin. It costs an additional £508 but only yields an additional 0.013 QALYs if there are no direct quality of life impacts from weight changes, so has a cost effectiveness estimate of £40,383 per QALY compared to sitagliptin. This improves to £6,632 per QALY if weight changes have a quality of life impact and are assumed to persist indefinitely. If they only persist for one year the cost effectiveness estimate worsens to a little over £30,000 per QALY, but if they persist until treatment change the cost effectiveness estimate worsens but only to a little under £20,000 per QALY.

The AG results showed some sensitivity to whether patients add insulin to their existing treatments or switch to it, the application of a common 7.5% HbA1c baseline and applying a reduced -0.47% HbA1c effect for gliclazide as recently reviewed above.

Chapter 6 Discussion and Research Needs

Principal findings

The key findings are;

- Canagliflozin, dapagliflozin and empagliflozin are clinically effective in improving glycaemic control when used in monotherapy
- They also provide modest reductions in systolic blood pressure, and promote weight loss
- The main adverse effects are urinary tract and genital area infections
- There are concerns following reports of DKA and bone loss. DKA appears rare – about 1 per 3000 patient years. Fractures were not increased after 3 years of empagliflozin treatment in the empagliflozin outcomes trial.

Other options

The NICE scope did not include all possible comparators. Four not included were;

- Bariatric surgery which is covered by other guidance
- Early intensive treatment
- Very low calorie diets
- Intensive lifestyle interventions[211, 212]

Bariatric surgery

The NICE guidance on bariatric surgery[213] includes a section specific to type 2 diabetes, reproduced in Box 3 below

Box 3. NICE guidance on bariatric surgery for type 2 diabetes

1.11 Bariatric surgery for people with recent-onset type 2 diabetes

1.11.1 Offer an expedited assessment for bariatric surgery to people with a BMI of 35 or over who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

1.11.2 Consider an assessment for bariatric surgery for people with a BMI of 30–34.9 who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

1.11.3 Consider an assessment for bariatric surgery for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations (see recommendation 1.2.8) as

long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

Early intensive treatment

The use of intensive treatment at diagnosis was first reported by a Chinese study in 2004.[214] Two weeks of intensive insulin treatment (with CSII) improved beta cell function, after which 47% remained well controlled on diet alone for 12 months and 42% for two years. A later trial randomised 410 Chinese patients to intensive insulin, or oral agents (metformin or gliclazide or both). Once patients had been normoglycaemic for two weeks, the drugs were stopped. After insulin, 51% of the CSII group and 45% of the MDI group remained in good glycaemic control a year later, compared to 27% of those on oral agents, suggesting that how the normoglycaemia is achieved is important(Yang and Weng[215]).

A systematic review[216] published in 2013 by Kramer and colleagues found seven studies of short-term intensive insulin therapy at diagnosis of type 2 diabetes. Two were RCTs and five were case series from China. When considering data from China, we need to bear in mind that Chinese people with type 2 diabetes have a more insulin-deficient and less insulin-resistant pattern.

Two small studies in white populations were not included in the Kramer review. Ilkova and colleagues[217]from Turkey and Israel treated 13 patients with newly-diagnosed type 2 diabetes not responding to 3-6 weeks of diet and physical activity with CSII for 2 weeks. Most (9/13) responded and three had three to five years remission of diabetes. In 5 patients control deteriorated after 9 to 36 months but good control was restored after a second fortnight of CSII.

Ryan[218] in Canada treated 16 people newly diagnosed with type 2 diabetes with MDI for 2-3 weeks, and a year later 7 were on no glucose lowering agents.

Introducing metformin earlier after diagnosis has been advocated by Brown and colleagues.[219] They noted that in a cohort of 1,799 patients that had metformin as first ever glucose lowering drug, those who started it less than 3 months after diagnosis of diabetes had a lower failure rate (12.2% a year) than those who started metformin 12 or more months after diagnosis (about 20% a year).

Another form of early intensive treatment is triple therapy from diagnosis, Abdul-Ghani and colleagues[220] report the results of the EDICT (Efficacy and durability of initial combination therapy for type 2 diabetes) in which patients were treated from diagnosis with metformin, pioglitazone and exenatide, and compared to a control arm that had a more standard approach of starting with

metformin followed by addition of sulfonylurea then glargine as required. The hypothesis behind the trial combination was to have a combination of drugs to improve both insulin secretion and sensitivity. The triple therapy group had lower HbA1c (by 0.55%), far less hypoglycaemia, and 1.2kg weight loss compared to 4kg gain on the standard sequence.

Very low calorie diets

Tyalor and colleagues from Newcastle have challenged the consensus that diabetes is a progressive irreversible disease, by showing that very low calorie diets (600kcal.day) for 8 weeks) can reverse type 2 diabetes by restoring beta-cell function and hepatic insulin sensitivity. They did this first for relatively recent onset cases in the Counterpoint Study[221], but then showed that about half of people with long-standing diabetes could return to normal glucose levels and stop their glucose-lowering medications.[222] This was achieved by weight loss averaging 14-15 kgs. The 8-week time period was too short to show full effect on HbA1c but even by then it fell by 1.15 in the short duration group and by an average of 0.6% in the long-duration group. Stevens and Taylor report (2015) that email feedback from people who lost weight and kept it off, have continued to have normal glucose levels for up to 3 years, so far. So it appears that as long as weight loss is maintained, they remain non-diabetic.

Non-pharmacological interventions

A very large number of trials reporting effects of different drugs are mentioned in this report and the industry submissions. Research into the management of type 2 diabetes is very pharmaco-centric, partly because the manufacturers of the drug have to carry out such trials for licensing purposes. There is no such pressure on developers of lifestyle interventions, nor guaranteed funding. However, lifestyle interventions should also be considered. Type 2 diabetes is strongly associated with overweight and obesity, and physical inactivity, and lifestyle change can be effective.
The work of Aas and colleagues[211] has been reported in previous reviews for NICE. Aas et al carried out a trial in 38 diabetic subjects poorly controlled (HbA1c 8 to 10.5%; mean 9.0%) on oral drugs and being considered for insulin treatment. They were randomised to insulin treatment or to an intensive lifestyle intervention based on exercise and diet, or both. After 12 months, HbA1c improved by 1.2% in the lifestyle arm and by 1.5% in the insulin (NPH twice daily with short-acting at mealtimes if required) arm. Weight fell by 3 kg in the lifestyle arm but rose 4.9kg in the insulin arm. The lifestyle intervention comprised 14 sessions of dietary advice, two individual sessions and one hour of exercise of moderate intensity twice a week, including group aerobics, walking and swimming. Unfortunately a year after the intervention had finished, HbA1c and weight rose again in the lifestyle group.

The problem with lifestyle interventions is adherence. A previous health technology assessment on prevention of diabetes in people with impaired glucose tolerance noted the tendency for gains after lifestyle interventions to be lost once the intervention was stopped, with the exception of the Finnish Diabetes Prevention Study in which the intervention continued for four years.[223]

However ways of improving adherence have been researched. Perri and colleagues[224] randomised 379 adults to walking at different speeds, and found that increasing the frequency of exercise achieved better adherence than increasing the intensity. Their study was prompted by awareness of a public perception that health benefits would only be achieved by frequent high intensity exercise.

Hansen and colleagues[225] from the Belgium and the Netherlands also reported that prolonged low-to-moderate exercise was almost as effective as more intense exercise. Their participants had three sessions a week of supervised walking, cycling or cross-country ski-type exercise for six months. In the moderate intensity group, HbA1c fell from 7.4% at baseline to 7.2% at 6 months. There were modest improvements in weight (91.1kg) and total cholesterol. The higher intensity group did better, with HbA1c reduction of 0.5% and weight loss of 1.8kg. The authors note that participants are more likely to drop out of high intensity physical activity, partly because people with long-standing type diabetes often have comorbidities that restrict such exercise.

Walking supported by pedometer use has been reported to be effective in a 12-month trial from Leicester.[226] However arguments to the contrary have appeared in recent years, suggesting that short duration high intensity exercise may be effective with the brevity improving adherence.[227]

Snowling and Hopkins[228] carried out a meta-analysis of the effects of different forms of exercise (aerobic, resistance mixed) in type 2 diabetes. They reported an improvement in HbA1c of 0.8% which is as great as many drugs achieve.

A full review of the benefits of physical activity in type 2 diabetes is beyond the scope of this report. Reviews of exercise therapy in type 2 diabetes and the mechanisms are provided by Praet and van Loon[229] and Zanuso et al.[230]
The NICE Public Health Guidance on weight management[231] noted that even modest weight loss could be cost-effective if sufficient and maintained. An Australian review of six interventions to promote physical activity also concluded that most would be cost-effective.[232]

A review by Fujioka[233] also concluded that in type 2 diabetes, weight loss of 1-4kg improved metabolic control and cardiovascular risk, though greater weight loss achieved greater benefit. Wing and colleagues[234] reported from the Look AHEAD trial (Action for Health in Diabetes) that modest

weight loss (5-10% body weight, 7.25 kg) improved glycaemic control (HbA1c reduced by 0.5%), blood pressure (6 mmHg) and HDL cholesterol. but even minor weight loss (2-5%) showed some benefit (HbA1c reduced by about 0.25%, SBP by about 4mm Hg).

Coppell and colleagues from Otago[212] carried out a randomised trial of an intensive nutritional intervention (seven individual sessions with a dietitian, one group session and telephone calls) compared to standard care (general practitioner or hospital clinic). After six months, the intensive group recorded reductions in HbA1c (0.5%), weight (2.1kg), waist circumferences (3.5cm), SBP (4.1mm Hg) and total cholesterol (0.24mmol/l) while HDL-cholesterol was unchanged. The control group showed little change and none in HbA1c.

A full review of the benefits of weight loss in type 2 diabetes is outwith the scope of the this report, and others have reviewed the subject.[235] The cost-effectiveness of lifestyle interventions was reviewed by Jacobs-van der Bruggen et al[236] who concluded that short-term results showed that they were cost-effective. However they noted a lack of long-term maintenance of benefit.

In summary, there is a range of effective lifestyle interventions, but the main problems are adherence and long-term maintenance.

Research needs

The clinical effectiveness of the SGLT2 inhibitors for at least 2 years is not in doubt, and the main need now is for data on long-term effectiveness and safety. The empagliflozin cardiovascular outcomes trial[131] has reported, though some clarifications are required. The equivalent studies for canagliflozin (CANVAS[124] and dapagliflozin DECLARE[125] are underway. Continued monitoring for diabetic ketoacidosis (DKA) and fractures is required. FDA and EMA reports are expected in autumn of 2015.

The first trials of the SGLT2 in type 1 diabetes are emerging, and because of their insulin-independent mode of action, they would be expected to be useful there. However the DKA risk would be more of a concern than in type 2 diabetes.

Conclusions

The SGLT2 inhibitors are effective in improving glycaemic control, promoting weight loss and reducing blood pressure – the first oral drugs for diabetes to do so. Their safety record remains to be established, but the only common adverse effects are small increases in the frequency of urinary and genital tract infections, seldom serious.However they are much more expensive than older drugs such as gliclazide and pioglitazone.

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Appendix 1 Search strategy

Clinical effectiveness searches

1. *Searches for journal articles*

   Search strategy for Ovid Medline (1946- February 16, 2015) and Ovid Embase (1974-February 16th, 2015)

   1. (empagliflozin or canagliflozin or dapagliflozin or sodium glucose cotransporter 2 inhibitor* or sodium glucose co-transporter 2 inhibitor* or SGLT2 inhibitor* or SGLT-2 inhibitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
   2. randomized controlled trial.pt.
   3. random*.tw.
   4. 2 or 3
   5. 1 and 4

164 retrieved in Medline and 239 in Embase

There were no restrictions by language.

Weekly auto-alerts of both searches were then run from February 2015 until the end of August 2015 in Medline, Embase and PubMed to check for newly emerging studies.

A total of 403 records were downloaded into EndNote, and after removal of duplicates 246 unique records remained, of which 195 were excluded on the basis of title and abstract on the first screening. The full text of the 51 records remaining was obtained and a second screening was performed. Seven trials (8 full text articles) were included in clinical effectiveness.

Table x gives reasons for exclusion for full text studies.

2. *Search for meeting abstracts*

   2.1 Search strategy for Ovid Embase (1947 to 2015 Week 12)

   1. (empagliflozin or canagliflozin or dapagliflozin).m_titl.
   2. conference.pt.
   3. 1 and 2

   400 retrieved

   2.2 Search strategy for Web of Science Core Collection (from inception to February 2015)

   TITLE field: (empagliflozin or canagliflozin or dapagliflozin); Refined by: Document Types: (MEETING ABSTRACT)

239 retrieved

636 meeting abstracts were downloaded into Endnote, and after removing duplicates there were 372 unique records. These were screened on the basis of title (and abstract if available) and the completel abstracts of 46 were selected for further scrutiny, of which one was selected for inclusion.

Cost effectiveness searches

Ovid MEDLINE (1946 to July Week 1 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 13, 2015)

1. exp Economics/
2. exp "Costs and Cost Analysis"/
3. Health Status/
4. exp "Quality of Life"/
5. exp Quality-Adjusted Life Years/
6. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
7. (health state* or health status).tw.
8. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.
9. (markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.
10. (quality adj2 life).tw.
11. (decision adj2 model).tw.
12. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.
13. "resource use".tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (empagliflozin or canagliflozin or dapagliflozin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. (sodium glucose cotransporter 2 or sodium glucose co-transporter 2 or SGLT2* or SGLT-2*).m_titl.
17. 15 or 16
18. 14 and 17

29 retrieved

Ovid Embase 1974 to 2015 July 13

1. exp health economics/
2. exp health status/
3. exp "quality of life"/
4. exp quality adjusted life year/
5. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
6. (health state* or health status).tw.
7. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form or SF-12 or SF12 or SF-36 or SF36 or SF-6D or SF6D or HUI).tw.
8. (markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).tw.
9. (quality adj2 life).tw.
10. (decision adj2 model).tw.
11. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.
12. (resource* or quality of well-being or qwb).tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (empagliflozin or canagliflozin or dapagliflozin).mp.
15. (sodium glucose cotransporter 2 or sodium glucose co-transporter 2 or SGLT2* or SGLT-2*).m_titl.
16. 14 or 15
17. 13 and 16
18. (monotherap* or placebo).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. 17 and 18

136 retrieved

Cochrane Library – NHS Economic Evaluation Database in July 2015

(empagliflozin or canagliflozin or dapagliflozin) in Title, Abstract or Keywords

2 retrieved

The Endnote database had 167 references. Retained 43 for a second viewing; the full text of 6 were retrieved.

Searches for trials of gliclazide in monotherapy lasting 24-26 weeks, versus placebo

Search strategy in Ovid Medline (1946-April 7 2005)
1. gliclazide.mp. or exp Gliclazide/
2. randomized controlled trial.pt.
3. 1 and 2
142 retrieved

Search strategy in Ovid Embase
1. gliclazide.mp. or gliclazide/
2. (placebo or monotherapy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 and 2
4. random*.mp.
5. 3 and 4
6. randomized controlled trial/
7. 5 and 6
153 retrieved

295 in total in Endnote; 230 after removing duplicates; 138 selected in first screening, and 58 in the second screening of 11 full text requested

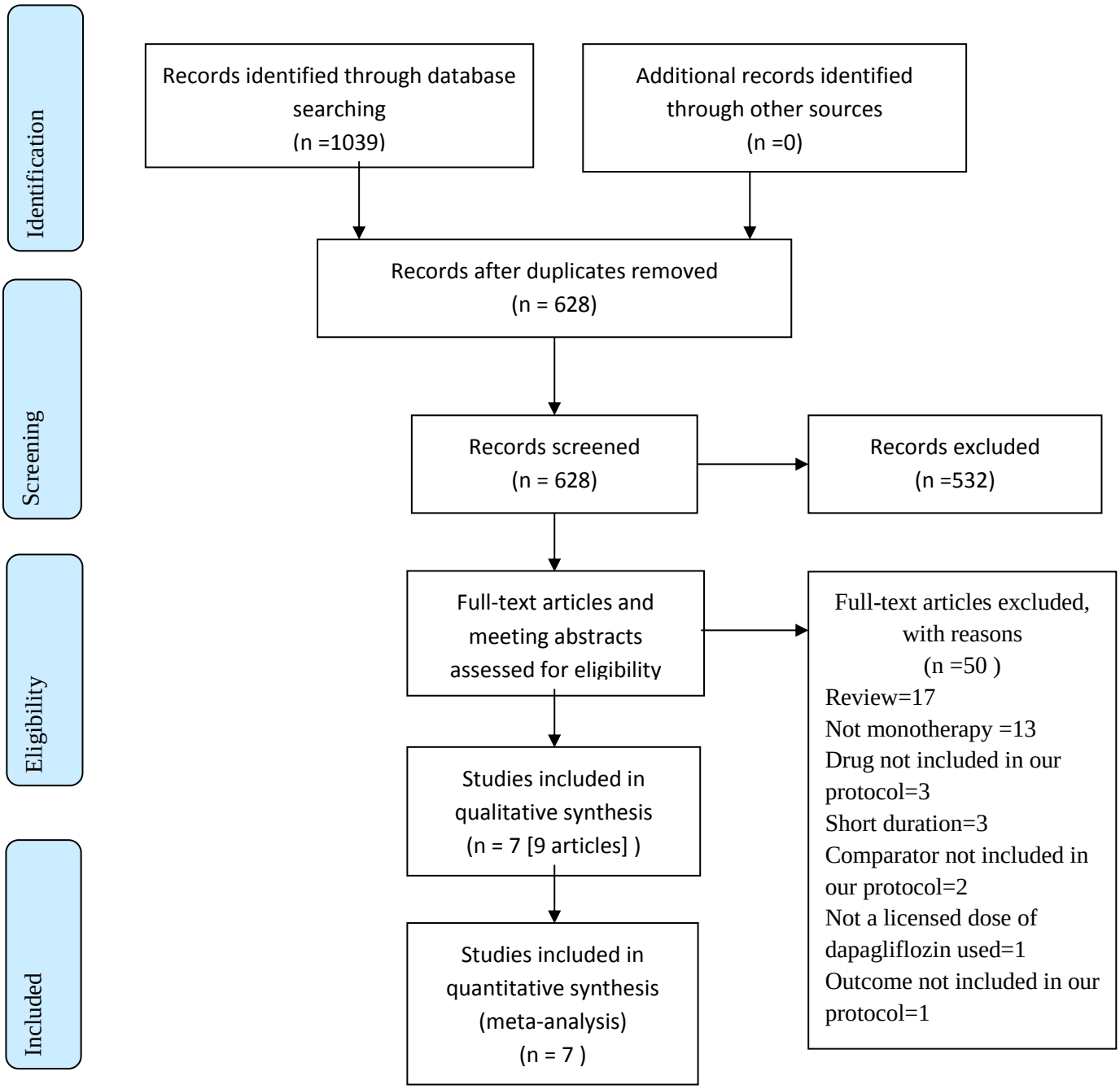
Searches for systematic reviews of sulphonylureas and gliclazide

Search strategy for Ovid Medline 1946 – April 7th – then updated September week 1, 2015
1. (sulfonylurea* or sulphonylurea* or gliclazide).tw.
2. meta-analysis.pt.
3. (systematic review or meta-analysis).tw.
4. 2 or 3
5. 1 and 4
143 retrieved

Ovid Embase 1974 – September 14, 2015
1. (sulfonylurea* or sulphonylurea* or gliclazide).tw.
2. (systematic review or meta-analysis).tw.
3. 1 and 2
263 retrieved

Total of 406 combined; after removal of duplicates it was 301. After a first screening 34 selected for a second screening and 15 full text were selected.

PRISMA Flow Diagram



Appendix 2 Reasons for Exclusions

Study ID	Reason for Exclusion
Bailey 2012[237]	Not a licensed dose of dapagliflozin used
Berhan 2013[238]	Review
Bluher 2014[239]	Review
Brand 2012[240]	Patients did not have diabetes
Escudero Vilaplana 2014[241]	Review
Ferrannini 2013[242]	Not monotherapy
Goring 2014[243]	Not monotherapy
Henry 2012[244]	Comparator not included in our protocol
Hussey 2013[245]	Short duration
Johnsson 2013a[96]	Review
Johnsson 2013b[246]	Review
Kadowaki 2014[247]	Short duration
Kaku 2014[248]	Comparator not included in our protocol
Lavalle-Gonzalez 2013[88]	Not monotherapy
Lutz 2014[249]	Review
Matthaei 2014[250]	Review
Nauck 2013[251]	Not monotherapy
Nauck 2011[114]	Not monotherapy
Orme 2014[252]	Not monotherapy
Pafili 2014[253]	Review
Phung 2014[254]	Review
Plosker 2012[255]	Review
Plosker 2014[256]	Review
Polidori 2014[257]	Outcome not included in our protocol
Raskin 2013[258]	Review
Rosenstock 2012a[259]	Not monotherapy
Rosenstock 2012b[260]	Not monotherapy
Rosenstock 2013[261]	Not monotherapy
Scheen 2015[262]	Review
Seino 2014a[263]	Drug not included in our protocol
Seino 2014b[264]	Drug not included in our protocol
Seino 2014c[265]	Drug not included in our protocol
Strojek 2011[266]	Not monotherapy
Strojek 2013[267]	Not monotherapy
Strojek 2014[268]	Not monotherapy
Tahrani 2013[126]	Review
Usiskin 2014[269]	Review
Wilding 2013[270]	Not monotherapy
Yang 2014[271]	Review
Zambrowicz 2013[272]	Short duration
Zhang 2014[273]	Review
Zinman 2014[132]	Protocol only

Appendix 3 Study characteristics

Study	Participants and baseline data	Intervention / Outcomes
CANAGLIFLOZIN		
CANTATA-M (Stenlöf 2013) **Setting:** multicentre (n=NR); 17 countries (United States, Austria, Colombia, Estonia, Guatemala, Iceland, India, Korea, Republic of, Lithuania, Malaysia, Mexico, Philippines, Poland, Puerto Rico, Romania, South Africa, Spain, Sweden) **Design:** phase 3 RCT, double blind, placebo controlled **Duration:** 26 weeks **Extension:** 26 week extension, replacing placebo with sitagliptin **Sponsor:** Janssen Research & Development, LLC	**N:** 584 (172/195 completers in the cana100 group, 175/197 in the cana300 group, 160/192 in the placebo group; 152/170 completed extension in cana100 group, 165/170 in cana300 group, 135/155 in placebo group); 91 in the high glycaemic substudy (40/47 completers in the cana100 group, 40/44 in the cana300 group) **Inclusion criteria:** age 18 to 80 years, type 2 diabetes inadequately controlled with diet and exercise or on anti-hyperglycaemic agents (AHA) who underwent washout of the agent; HbA1c for participants not on AHAs ≥7.0 to ≤10.0%; HbA1c for participants on AHA monotherapy or SU plus metformin ≥6.5 and ≤9.5% at screening and ≥7.0 and ≤10% and FPG <15 mmol/L at -2 weeks; substudy conducted for participants with HbA1c >10.0 and ≤12.0% at screening or -1 weeks and FPG ≤19.4 mmol/L at -1 weeks **Exclusion criteria:** repeated FPG repeatedly >15.0 mmol/L during pre-treatment (or >19.4 mmol/L for the high glycaemic substudy); history of type 1 diabetes, hereditary glucose-galactose malabsorption, primary renal glucosuria or cardiovascular disease; treatment with a PPARγ agonist, insulin, another SGLT2 inhibitor or any other AHA except as specified in the inclusion criteria within 12 weeks before screening; estimated glomerular filtration rate (eGFR) <50 ml/min/1.73m^2 at screening **Age (years):** *cana100:* 55.1 SD10.8; *cana300:* 55.3 SD10.2; *placebo:* 55.7 SD10.9; *cana100 high HbA1c:* 49.7 SD11.1; *cana300 high HbA1c:* 48.8 SD10.8 **Sex (%women):** *cana100:* 58.5%; *cana300:* 54.8%; *placebo:* 54.2%; *cana100 high HbA1c:* 51.1%; *cana300 high HbA1c:* 56% **Ethnicity:** *cana100:* 63.6% White, 9.2% Black, 13.8% Asian, 13.3% other; *cana300:* 69.5% White, 7.1% Black, 14.7% Asian, 8.6% other; *placebo:* 69.8% White, 4.7% Black, 15.1% Asian, 10.4% other; *cana100 high HbA1c:* 53.2% White, 6.4% Black, 23.4% Asian, 17.0% other; *cana300 high HbA1c:* 68.2% White, 2.3% Black, 15.9% Asian, 13.6% other **Diabetes duration (years):** *cana100:* 4.5 SD4.4; *cana300:* 4.3 SD4.7; *placebo:* 4.2 SD4.1; *cana100 high HbA1c:* 4.6 SD4.6; *cana300 high HbA1c:* 5.2 SD4.8 **HbA1c (%):** *cana100:* 8.1 SD1.0; *cana300:* 8.0 SD1.0; *placebo:* 8.0 SD1.0; *cana100 high HbA1c:* 10.6 SD0.9; *cana300 high HbA1c:* 10.6 SD0.6 **BMI (kg/m^2):** *cana100:* 31.3 SD6.6; *cana300:* 31.7 SD6.0; *placebo:* 31.8 SD6.2; *cana100 high HbA1c:* 30.4 SD7.1; *cana300 high HbA1c:* 30.5 SD5.5 **Baseline medication:** patients on AHA at screening: *cana100:* 48.2%; *cana300:*	**<u>Intervention</u>** **cana100 (n=195):** 100 mg/day canagliflozin **cana300 (n=197):** 300 mg/day canagliflozin **cana100 high HbA1c (n=47):** 100 mg/day canagliflozin in participants with HbA1c >10.0 and ≤12.0% **cana300 high HbA1c (n=44):** 300 mg/day canagliflozin in participants with HbA1c >10.0 and ≤12.0% **Control (n=192):** placebo **Run-in:** 8 weeks and diet and exercise and washout period for participants on AHA, followed by a 2 week single blind placebo run-in period; participants not on AHA directly entered the 2 week placebo run-in period; participants in the high glycaemic substudy entered a 1 week single blind placebo run-in period **Extension:** after 26 weeks, the placebo group received double blind sitagliptin (100 mg/day) **All groups:** rescue therapy with metformin was initiated if FPG was >15.0 mmol/L after day 1 to week 6, >13.3 mmol/L after week 6 to week 12 and >11.1 mmol/L after week 12 to week 26; HbA1c >8% after week 26 **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 26 **Secondary outcomes:** proportion achieving HbA1c <7.0%, FPG, 2h postprandial glucose, HOMA, systolic blood pressure, HDL-cholesterol, triglycerides, body weight **Other outcomes:** LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B, diastolic blood pressure, safety assessments (incl. laboratory, vital signs, hypoglycaemia) **Note:** the main outcomes for the extension period were only reported for the canagliflozin groups [not considered in the data extraction]; safety parameters for all groups

Study	Participants and baseline data	Intervention / Outcomes
	48.2%; *placebo:* 47.9%; *cana100 high HbA1c:* 23.4%; *cana300 high HbA1c:* 22.7%	
Inagaki 2014 **Setting:** multicentre (n=31); Japan **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 2 weeks post-intervention follow-up **Sponsor:** Mitsubishi Tanabe Pharma Corp	**N:** 183 in relevant comparison groups (84/90 completers in the cana100 group, 74/93 in the placebo group) **Inclusion criteria:** age ≥20 years, type 2 diabetes mellitus diagnosed ≥3 months before run-in, HbA1c 7.0 to 10%, on diet and exercise therapy for ≥55 days; patients on antihyperglycaemic treatment had to start a washout period of ≥55 days before starting run-in **Exclusion criteria:** non type 2 diabetes, current or history of severe diabetic complications, FPG >270 mg/dl, indication for insulin therapy, hereditary glucose-galactose malabsorption or renal glycosuria, inadequately controlled thyroid abnormality, anorexia or bulimia, current or history of urinary tract/genital infection <1 year before run-in, triglyceride ≥6.72 mmol/L, BP ≥160/≥100 mmHg during run-in or patients with known hypertension immediately requiring the addition/ modification of antihypertensive therapy, heart disease, serious liver disease, serious kidney disease, estimated glomerular filtration rate <50 ml/min/1.73 m^2; urinary albumin creatinine ratio ≥300 mg/g creatinine, history of malignancy, neuropsychiatric disorder likely to hinder study evaluations; history of drug-related shock or anaphylactic symptoms; unwilling to use contraception; pregnant or breast feeding women, prior use of canagliflozin **Age (years):** *cana100:* 58.4 SD10.4; *placebo:* 58.2 SD11.0 **Sex (%women):** *cana100:* 34.4%; *placebo:* 35.5% **Ethnicity:** 100% Japanese **Diabetes duration (years):** *cana100:* 4.72 SD4.59; *placebo:* 5.63 SD5.76 **HbA1c (%):** *cana100:* 7.98 SD0.73; *placebo:* 8.04 SD0.70 **BMI (kg/m^2):** *cana100:* 25.59 SD4.20; *placebo:* 25.85 SD4.39 **Comorbidities:** NR **Baseline medication:** *cana100:* 22.2% previously on OADs; *placebo:* 25.8% previously on OADs	**<u>Intervention</u>** **cana100 (n=90):** 100 mg/day canagliflozin, once daily before breakfast **Control (n=93):** placebo, once daily **Note:** the trial also included a 200 mg group, this was not considered here **Run-in:** 4 week single blind placebo lead-in **All groups:** patients were instructed to continue diet and exercise therapy as before **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight, proportion achieving HbA1c <7%, 2h postprandial glucose, waist circumference, lipids, blood pressure, HOMA, proinsulin, C-peptide **Other outcomes:** safety assessments (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
DAPAGLIFLOZIN		
Ferrannini 2010 / Bailey 2014 **Setting:** multicentre (n=85); USA, Canada, Mexico, Russia **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Extension:** 78 weeks (Bailey 2014), double blind **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 260 in relevant comparison groups (156/185 completers in the dapa10 groups, 63/75 in the placebo group; 42/56 completed extension in dapa10 AM group, 42/62 in placebo group) **Inclusion criteria:** age 18 to 77 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to treatment, BMI ≤45 kg/m^2, fasting C-peptide ≥1.0 ng/ml **Exclusion criteria:** type 1 diabetes, serum creatinine ≥133 µmol/L (men) or ≥124 µmol/L (women), urine albumin-to-creatinine ratio >200 mg/mmol, aspartate transaminase and/or alanine transaminase >3 times the upper limits of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes (incl. marked polyuria and polydipsia with >10% weight loss during last 3 months before enrolment); significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic diseases, cardiovascular event within 6 months of enrolment, severe uncontrolled BP (systolic ≥180 mmHg and/or diastolic ≥110 mmHg) **Age (years):** *dapa10 AM:* 50.6 SD10.0; *dapa10 PM:* 50.7 SD9.7; *dapa10 high HbA1c:* 47.9 SD12.1; *placebo:* 52.7 SD10.3 **Sex (%women):** *dapa10 AM:* 51.4%; *dapa10 PM:* 48.7%; *dapa10 high HbA1c:* 41.0%; *placebo:* 58.7% **Ethnicity:** *dapa10 AM:* 90% White, 2.9% Black, 4.3% Asian, 2.9% other; *placebo:* 94.7% White, 2.7% Black, 2.7% Asian **Diabetes duration (years, median, IQR):** *dapa10 AM:* 0.45 (0.1, 3.4); *dapa10 PM:* 0.40 (0.1, 2.45); *dapa10 high HbA1c:* 1.4 (0.2, 3.5); *placebo:* 0.5 (0.1, 3.4) **HbA1c (%):** *dapa10 AM:* 8.01 SD0.96; *dapa10 PM:* 7.99 SD1.05; *dapa10 high HbA1c:* 10.73 SD0.85; *placebo:* 7.84 SD0.87 **BMI (kg/m^2):** *dapa10 AM:* 33.6 SD5.4; *dapa10 PM:* 33.3 SD5.6; *dapa10 high HbA1c:* 31.1 SD5.9; *placebo:* 32.3 SD5.5 **Comorbidities:** *dapa10 AM:* 1.4% diabetic neuropathy, 1.4% microalbuminuria, 41.4% hypertension; *placebo:* 8% diabetic neuropathy, 1.3% diabetic neuropathy, 1.3% microalbuminuria, 52% hypertension **Baseline medication:** no OAD; *dapa10 AM:* 41.4% on anti-hypertensives; *placebo:* 41.3% on anti-hypertensives	**Intervention** **dapa10 AM (n=70):** 10 mg/day dapagliflozin, administered once daily in the morning in people with HbA1c 7 to 10% **dapa10 PM (n=76):** 10 mg/day dapagliflozin, administered once daily in the evening in people with HbA1c 7 to 10% **dapa10 high HbA1c (n=39):** 10 mg/day dapagliflozin, administered once daily in the morning in people with HbA1c 10.1 to 12% **Control (n=75):** placebo, once daily in people with HbA1c 7 to 10% **Note:** the trial also included 2.5 mg and 5 mg groups, these were not considered here **Run-in:** 2 week diet/exercise placebo lead-in (1 week for patients with HbA1c 10.1 to 12.0%) **Extension:** after 24 weeks, the placebo group received low dose metformin (500 mg/day) and the dapa groups received matching placebo; results only reported for main dapa AM groups versus placebo **All groups:** if fasting FPG was >270 mg/dl at week 4, >240 mg/dl at week 8, or >200 mg/dl at weeks 12 to 24, patients were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2000 mg); patients with HbA1c >8.0% for 12 weeks despite maximum tolerated metformin dose were discontinued; the strategy for rescue medication based on HbA1c was continued during the extension period. Patients received diet/exercise counselling according to American Diabetes Association recommendations throughout the study **Outcomes** **Primary outcome:** change from baseline in HbA1c at week 24 in the dapa10 AM group **Secondary outcomes:** FPG, body weight **Other outcomes:** safety assessments and adverse events (incl.

Study	Participants and baseline data	Intervention / Outcomes
		laboratory, vital signs, urinary tract and genital infections, hypoglycaemia)
Ji 2014 **Setting:** multicentre (n=40); China, Korea, Taiwan, India **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 28 days post intervention (not reported) **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 265 in relevant comparison groups (117/133 completers in the dapa10 group, 113/132 in the placebo group) **Inclusion criteria:** age ≥18 years, inadequately controlled type 2 diabetes mellitus (HbA1c ≥7.5 and ≤10.5% at enrolment and ≥7.0% and ≤10.5% during lead-in), drug naïve, BMI ≤45 kg/m^2, C-peptide ≥1.0 ng/ml **Exclusion criteria:** aspartate aminotransferase and/or alanine aminotransferase levels >3 times upper limit of normal, serum total bilirubin >34.2 µmol/L, serum creatinine ≥132.6 µmol/L for men or ≥123.8 µmol/L for women, haemoglobin ≤110 g/L for men and ≤100 g/L for women, creatine kinase ≥3 times the upper limit of normal, urine albumin to creatinine ratio >1800 mg/g, severe hypertriglyceridaemia (triglyceride >9.3 mmol/L), urinary excretion of N-acetyl-β-D-glucosaminidase >84 µmol/h per mmol creatinine, urinary excretion of α1 microglobulin >28 mg/g creatinine, parathyroid hormone value >1.5 times the upper limit of normal, calcium or serum phosphate values outside the normal reference range, abnormal free T4 values, positive hepatitis B surface antigen or positive anti-hepatitis C antibodies; currently unstable or serious vascular, renal, hepatic, haematologic, oncologic, endocrine, psychiatric, or rheumatic diseases **Age (years):** *dapa10:* 51.2 SD9.9; *placebo:* 49.9 SD10.9 **Sex (%women):** *dapa10:* 35.3%; *placebo:* 34.1% **Ethnicity:** *dapa10:* 88.7% Chinese, 6.8% Asian Indian, 3.8% Korean, 0.8% other Asian; *placebo:* 88.6% Chinese, 6.1% Asian Indian, 3.8% Korean, 0.8% Japanese, 0.8% other Asian **Diabetes duration (years):** *dapa10:* 1.67 SD2.8 (range 0 to 13); *placebo:* 1.3 SD2.0 (range 0 to 9.9) **HbA1c (%):** *dapa10:* 8.28 SD0.95; *placebo:* 8.35 SD0.95 **BMI (kg/m^2):** *dapa10:* 25.76 SD3.43; *placebo:* 25.93 SD3.64 **Comorbidities:** *dapa10:* 42.9% history of dyslipidaemia, 37.6% history of hypertension; *placebo:* 40.2% history of dyslipidaemia, 40.9% history of hypertension **Baseline medication:** no OAD; others not reported	**<u>Intervention</u>** **dapa10 (n=133):** 10 mg/day dapagliflozin, taken once daily before the first meal of the day **Control (n=132):** placebo, once daily **Note:** the trial also included a 5 mg group, this was not considered here **Run-in:** 6 week single blind placebo run-in with diet and exercise counselling consistent with China Diabetes Society recommendations **All groups:** open-label rescue therapy with metformin (500 mg daily, titrated to 2000 mg if necessary) could be given if glycaemic control was inadequate (during weeks 4 to 12, FPG >13.3mmol/L; during weeks 12 to 24, FPG level >11.1mmol/L); patients with FPG values consistently greater than protocol-specified values for 12 weeks despite a maximum tolerated dose of metformin were discontinued from the study **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, 2 h post-prandial glucose, proportion achieving HbA1c<7%, body weight **Other outcomes:** β-cell function and insulin resistance, waist circumference, lipids, proportion of patients with ≥3% or ≥5% reduction in total weight, fasting urinary glucose to creatinine ratio, safety and tolerability (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
Kaku 2014 **Setting:** multicentre (n=NR); Japan **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 3 week post-intervention follow-up **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 175 in relevant comparison groups (79/88 completers in the dapa10 group, 79/87 in the placebo group) **Inclusion criteria:** age ≥20 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to drug treatment or on antihyperglycaemic treatment (the latter underwent a washout period before study begin), HbA1c ≥6.5% and ≤10% for drug-naïve patients and ≤8% for patients on ongoing treatment **Exclusion criteria:** type 1 diabetes, FPG >13.3 mmol/L, creatinine kinase >3 times upper limit of normal, estimated glomerular filtration rate <45 ml/min or serum creatinine >133 µmol/L for men and >124 µmol/L for women; severe hepatic insufficiency and/or significant abnormal liver function (aspartate aminotransferase >3 times upper limit of normal and/or alanine aminotransferase >3 times upper limit of normal; New York Heart Association class IV congestive heart failure; unstable or acute congestive heart failure; treatment with thiazolidinediones <6 months before enrolment; pregnant or breastfeeding women **Age (years):** *dapa10:* 57.5 SD9.3; *placebo:* 60.4 SD9.7 **Sex (%women):** *dapa10:* 39.8%; *placebo:* 40.2% **Ethnicity:** 100% Japanese **Diabetes duration (years):** *dapa10:* 4.93 SD4.52; *placebo:* 5.29 SD6.17 **HbA1c (%):** *dapa10:* 7.46 SD0.61 (21.6% <7%); *placebo:* 7.50 SD0.63 (24.1% <7%) **BMI (kg/m^2):** *dapa10:* 26.06 SD4.52; *placebo:* 25.22 SD4.39 **Comorbidities:** *dapa10:* 50% history of cardiovascular disease, 40.9% hypertension only; *placebo:* 42.5% history of cardiovascular disease, 35.6% hypertension only, 2.3% congestive heart failure; most patients in both groups had mild to moderate renal impairment (69% stage 1 or mild chronic kidney disease, 28% stage 2 or moderate chronic kidney disease) **Baseline medication:** not reported	**Intervention** **dapa10 (n=88):** 10 mg/day dapagliflozin, administered once daily **Control (n=87):** placebo, once daily **Note:** the trial also included a 5 mg group, this was not considered here **Run-in:** 2 week screening period and 4 week single blind placebo lead-in **Follow-up:** post-intervention follow-up mainly used for safety monitoring – no further results reported **All groups:** no further information **Outcomes** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight **Other outcomes:** body weight in patients with BMI ≥25 kg/m^2, fasting insulin and C-peptide, systolic blood pressure, blood lipids, proportion achieving HbA1c <7%; safety assessments (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
EMPAGLIFLOZIN		
Lewin 2015 **Setting:** multicentre (n=197); 22 countries (no UK sites) **Design:** phase 3 RCT, double blind, parallel group **Duration:** 52 weeks**,** primary endpoint at 24 weeks **Follow-up:** follow-up visit 4 weeks after the last dose of study drug **Sponsor:** Boehringer Ingelheim; Eli Lilly	**N:** 404 in relevant comparison groups (398 with on treatment measurements) (114/133 completers in the empa25 group, 110/132 in the empa10 group, 116/133 in the lina5 group) **Inclusion criteria:** age ≥18 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, no therapy with OAD, GLP1-analogue or insulin for ≥12 weeks prior to randomisation, BMI ≤45 kg/m^2, HbA1c >7% and ≤10.5% **Exclusion criteria:** uncontrolled hyperglycaemia (FPG >13.3. mmol/L); estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2; acute coronary syndrome, stroke, or transient ischaemic attack within 3 months prior to consent; bariatric surgery in the past 2 years; treatment with anti-obesity drugs within 3 months prior to consent **Age (years):** *empa25:* 56.0 SD9.3; *empa10:* 53.9 SD10.5; *lina5:* 53.8 SD11.5 **Sex (%women):** *empa25:* 42.1%; *empa10:* 51.5%; *lina5:* 43.6% **Ethnicity:** *empa25:* 69.9% White, 14.3% Asian, 15.8% other; *empa10:* 75.0% White, 9.8% Asian, 15.2% other; *lina5:* 77.4% White, 12.8% Asian, 9.8% other; Asians were from Malaysia, the Philippines, Taiwan; no South Asian recruits; other mainly Hispanic **Diabetes duration (time since diagnosis):** *empa25:* 36.1% ≤1 yr, 36.1% >1 to 5 yrs, 18.8% >5 to 10 yrs, 9.0% >10 yrs; *empa10:* 32.6% ≤1 yr, 45.5% >1 to 5 yrs, 11.4% >5 to 10 yrs, 10.6% >10 yrs; *lina5:* 37.6% ≤1 yr, 42.9% >1 to 5 yrs, 16.5% >5 to 10 yrs, 3.0% >10 yrs **HbA1c (%):** *empa25:* 7.99 SD0.97 (27.1% ≥8.5%); *empa10:* 8.05 SD1.03 (28.8% ≥8.5%); *lina5:* 8.05 SD0.89 (25.6% ≥8.5%) **BMI (kg/m^2):** *empa25:* 31.2 SD5.7; *empa10:* 31.5 SD5.7; *lina5:* 31.9 SD5.9 **Comorbidities:** *empa25:* n=20 (15%) microalbuminuria, n=0 macroalbuminuria; *empa10:* n=21 (16%) microalbuminuria, n=3 (2%) macroalbuminuria; *lina5:* n=16 (12%) microalbuminuria, n=2 (1.5%) macroalbuminuria **Baseline medication:** no anti-hyperglycaemic medication	**<u>Intervention</u>** **empa25 (n=133):** 25 mg/day empagliflozin, taken once daily in the morning **empa10 (n=132):** 10 mg/day empagliflozin, taken once daily in the morning **lina5 (n=133):** 5 mg/day linagliptin, taken once daily in the morning **Note:** the trial also included fixed combination empagliflozin 25 mg / linagliptin 5 mg and empagliflozin 10 mg / linagliptin 5 mg groups, these were not considered here **Run-in:** 2 week placebo run-in **All groups:** rescue medication initiated if blood glucose >240 mg/dL after overnight fast between weeks 1 and 12, blood glucose >200 mg/dL after overnight fast between weeks 12 and 24, or blood glucose >180 mg/dL or HbA1c >8% after overnight fast between weeks 24 and 52 (initiation, choice, and dosage of rescue medication at the discretion of the investigator but use of DPP-4 inhibitors, GLP-1 analogues, SGLT2 inhibitors not permitted); in cases of hypoglycaemia, rescue medication was to be reduced in dose or discontinued; if hyper- or hypoglycaemia could not be controlled, participants was discontinued from the trial **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight, proportion achieving HbA1c <7% (of participants with HbA1c ≥7%) **Other outcomes:** systolic blood pressure, diastolic blood pressure, blood lipids, safety assessments (incl. laboratory, vital signs, hypoglycaemia)
Roden 2013/4 **Setting:** multicentre (n=124); nine countries	**N:** 986 (899 randomised, 87 in open-label empagliflozin) in relevant comparison groups (187/228 completed control, 206/224 completed empa10, 204/224 completed empa25, 206/223 completed sita100, 78/87 completed empa25open) **Inclusion criteria:** previously untreated type 2 diabetes (no oral or injected anti-	**<u>Intervention</u>** **Empa10 (n=224):** empagliflozin 10 mg/day in people with HbA1c 7 to 10% **Empa25 (n=224):** empagliflozin 25 mg/day in people with HbA1c

Study	Participants and baseline data	Intervention / Outcomes
(Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, USA) **Design:** phase 3 RCT, placebo-controlled, double blind , parallel group **Duration:** 24 weeks **Extension:** 76 week extension trial **Sponsor:** Boehringer Ingelheim and Eli Lilly	diabetes treatment for 12 weeks before randomisation or start of open-label treatment), age ≥ 18 years (≥20 years in Japan, 18 to 65 in India), BMI ≤45 kg/m^2, and insufficient glycaemic control despite diet/exercise regimen (HbA1c 7.0-10.0% (or 7.0 to 9.0% in Germany)) at screening for patients eligible for randomised treatment, or >10.0% for those eligible for the open-label treatment group (this arm not included in Germany or Ireland) **Exclusion criteria:** uncontrolled hyperglycaemia (plasma glucose >13.3mmol/L after overnight fast during placebo run-in phase and confirmed by 2nd measurement), eGFR (estimated using modification of diet in renal disease equation) <50 ml/min/1.73m^2 (or <60ml/min/1.73 m^2 in China), any contraindications to sitagliptin according to local label, treatment with anti-obesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in thyroid hormone dose within 6 weeks before informed consent, any uncontrolled endocrine disorder apart from type 2 diabetes **Age (years):** *empa10:* 56.2 SD11.6, *empa25:* 53.8 SD11.6, *sita100:* 55.1 SD9.9, *empa25open:* 50.2 SD11.3, *placebo:* 54.9 SD10.9 **Sex (%women):** *empa10: 37%*, *empa25:* 35%, *sita100:* 37%, *empa25open:* 26%, *placebo:* 46% **Ethnicity:** *empa10:* 64% Asian, 34% White, 1% Black/African American, <1% Hawaiian/Pacific Islander; *empa25:* 64% Asian, 33% White, 3% Black/African American; *sita100:* 64% Asian, 34% White, 1% Black/African American, <1% American-Indian/Alaska Native; *empa25open:* 61% Asian, 33% White, 2% Black/African American, 2% American-Indian/Alaska Native, 1% information not available, *placebo:* 64% Asian, 33% White, 3% Black/African American **Diabetes duration:** *empa10:* 39% ≤1 year, 41% 1 to 5 yrs, 13% 5 to 10 yrs, 7% >10 yrs; *empa25:* 41% ≤1 yr, 37% 1 to 5 yrs, 17% 5 to 10 yrs, 6% >10 years; *sita100:* 42% ≤1 yr, 39% 1 to 5 yrs, 14% 5 to 10 yrs, 5% >10 yrs; *empa25open:* 52% ≤1 yr, 25% 1 to 5 yrs, 14% 5 to 10 yrs, 8% >10 yrs; *placebo:* 32% ≤1 yr, 46% 1 to 5 yrs, 15% 5 to 10 yrs, 8% >10 yrs **HbA1c (%):** *empa10:* 7.87 SD0.88, *empa25:* 7.86 SD0.85, *sita100:* 7.85 SD0.79, *empa25open:* 11.50 SD1.39, *placebo:* 7.91 SD0.78 **BMI (kg/m^2):** *empa10:* 28.3 SD5.5, *empa25:* 28.2 SD5.5, *sita100:* 28.2 SD5.2, *empa25open:* 28.2 SD5.5, *placebo:* 28.7 SD6.2 **Baseline medication:** no oral/injectable anti-diabetic drug	7 to 10% **Sita100 (n=223):** sitagliptin 100 mg/day in people with HbA1c 7 to 10% **Empa25open (n=87):** empagliflozin 25 mg/day in people with HbA1c >10% **Control (n=228):** placebo once a day in people with HbA1c 7 to 10% **Run-in:** 2 week open-label placebo run-in **Extension:** 68.4% of the 899 patients continued in a double-blind extension (numbers in each group not given) for ≥52 weeks **All groups:** All received diet/exercise counselling according to local recommendations; rescue medication was started at FPG >13.3mmol/L between week 1 and 12 or FPG >11.1mmol/L between week 12 and 24 (drug of choice at the discretion of the investigator, but GLP1 agonists and DPP4 inhibitors were not permitted) **<u>Outcomes</u>** **Primary outcome:** change from baseline HbA1c at week 24 **Secondary outcomes:** weight, systolic and diastolic blood pressure **Other outcomes:** percentage achieving HbA1c <7.0% (of those with HbA1c >7.0% at baseline), FPG, percentage with >5.0% reduction in body weight, waist circumference, percentage of patients with previously uncontrolled hypertension who achieved controlled blood pressure (<130 mmHg systolic, <80 mmHg diastolic); use of rescue therapy, safety endpoints (vital signs, clinical laboratory parameters, adverse events e.g. hypoglycaemic episodes, urinary tract and genital infections

Abbreviations: AHA – anti-hyperglycaemic agent; BMI – body mass index; BP – blood pressure; FPG – fasting plasma glucose; HOMA – homeostatic model assessment (for insulin sensitivity); IQR – interquartile range; NR – not reported; OAD – oral antidiabetic drug; SU – sulphonylurea

Appendix 4 Quality assessment

Rate as: adequate, inadequate, unclear, not reported

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Canagliflozin										
CANTATA-M (Stenlöf 2013)	**unclear** method not reported; randomisation stratified by previous AHA use	**NR**	**adequate** double-blind	**NR**	**adequate** (main analysis) 11.8% discontinuation in cana100 group, 11.2% in cana300 group, 16.7% in placebo group	**adequate** intention-to-treat for all patients receiving at least one dose of study drug; last observation carried forward for missing data	**partial** some data only shown in graphs with no numeric values given	**adequate** for main study	**adequate** 90% power to detect a difference in HbA1c with 85 participants per group	5/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Inagaki 2014	**adequate** block randomisation (block size of 6 and 97 blocks); randomisation code list prepared by investigational product allocation manager and maintained until code was broken	**adequate** randomisation code not broken until data entry had been completed or unless needed in an emergency	**adequate** double-blind	**adequate** code not broken until data entry completed	**imbalance** 6.7% discontinuation in cana100 group, 20.4% in placebo group; reasons given	**adequate** efficacy analyses performed in the full analysis set of patients receiving at least one dose of study drug, except patients who did not have any efficacy data after administration of drug; last observation carried forward for missing data	**adequate** all outcomes reported as indicated in the methods section	**adequate** some difference between groups were noted regarding sex and glomerular filtration rate, but this seemed to apply mainly to the 200 mg canagliflozin group	**adequate** 95% power to detect a difference in HbA1c with 80 participants per group	8/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Dapagliflozin										
Ferrannini 2010 / Bailey 2014	**adequate** "computer-generated randomisation by an interactive voice response system, stratified by site in blocks of 7"	**adequate** "randomisation codes kept centrally at Bristol-Myers Squibb"	**adequate** "investigators, other clinical staff and participants blinded to treatment allocation during the 24 week initial and 78 week extension periods"	**adequate** see previous	**adequate** 15.7% discontinuation in dapa10 groups, 16% in placebo group; 60% completed extension in dapa10 AM group, 56% in placebo group; reasons given	**unclear** states that analyses were based on all participants taking at least one dose of medication, but main follow-up data appear to be based on fewer participants?	**adequate** all outcomes reported as indicated in the methods section	**adequate** between dapa10 AM/PM groups and placebo, the dapa10 high HbA1c group had a longer diabetes duration (other than a higher HbA1c)	**adequate** 90% power to detect a difference in HbA1c with 67 participants per group (primary endpoint)	8/9 adequate (main analysis)

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Ji 2014	**adequate** participants were "randomised sequentially by using an interactive voice response system in a blinded manner"	**adequate** see previous	**adequate** "patients, investigators and the sponsors were blinded to the treatment group"	**adequate** see previous	**adequate** 12.0% discontinuation in dapa10 group, 14.4% in placebo group; reasons given	**adequate** "patients randomised to treatment who received at least 1 dose of double-blind study medication and had both a baseline and post-baseline measurement were included in the efficacy analyses; patients who received at least 1 dose of double-blind study medication were included in the safety analyses"	**adequate** all outcomes reported as indicated in the methods section	**adequate** stated that demographic and baseline characteristics were similar between groups	**adequate** 97% power to detect a difference in HbA1c with 120 participants per group	9/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Kaku 2014	**NR**	**NR**	**adequate** "double-blind"	**NR**	**adequate** 10.2% discontinuation in dapa10 group, 9.2% in placebo group; reasons given	**adequate** "efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication"	**adequate** all outcomes reported as indicated in the methods section	**adequate** stated that demographic and baseline characteristics were similar between groups	**adequate** 90% power to detect a difference in HbA1c with 85 participants per group	6/9 adequate
Empagliflozin										
Lewin 2015	**adequate** third-party interactive voice and web response system; stratified by baseline HbA1c, eGFR and region	**NR**	**adequate** "double-blind"	**NR**	**adequate** 17% discontinuation in the empa25 group, 19.4% in the empa10 group, 15.6% in the lina5 group)	**adequate** efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication and had at least one on treatment HbA1c value; missing values imputed using last observation carried forward	**adequate** some data only shown one graph with no numeric values given	**adequate** stated that baseline characteristics were balanced between groups	**unclear** 89% power to detect a difference in HbA1c with 133 participants per group; slightly underpowered after drop-outs	6/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Roden 2013	**adequate** computer-generated random sequence in block sizes of four, stratified by region (Asia, Europe, North America), HbA1c at screening (< 8.5%, ≥ 8.5%) and eGFR (≥ 90, 60-89, 50-59)	**adequate** study sponsor allocated participants using an interactive voice and internet-based response system	**adequate** "patients, investigator and individuals involved in the analysis of trial data were masked to treatment assignment"	**adequate** see previous	**adequate** (all <20%) discontinuation rates: 18% control, 8% empa10, 9% empa25, 8% sita100, 10% empa25open; reasons given	**adequate** efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication; missing values imputed using last observation carried forward	**adequate** all outcomes reported as indicated in the methods section	**adequate** between empa10, empa25, sita100 and control groups; empa25open had greater proportion of participants at ≤1 year	**adequate** 95% power to detect a difference in HbA1c with 180 participants per group (primary endpoint)	9/9 adequate

Abbreviations: NR – not reported

Appendix 5 Cochrane risk of bias table: EMPAGLIFLOZIN-REG OUTCOME

Overall, the trial scores well, and it is likely that the unclear items are just failure to report the processes rather than causing a high risk of bias.

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk.	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Paper reports that a computerised randomisation system was used
Blinding of participants and personnel (performance bias)	Unclear	No information on appearance of placebo and empagliflozin tablets.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Unclear	Paper says "All CV outcome events and deaths are being prospectively adjudicated by the Clinical Events Committee (one for cardiac events and one for neurological events), as recommended in FDA guidelines" but gives no detail as to whether the assessors are blinded to allocation.
Blinding of outcome assessment (detection bias) (Mortality)	Unclear	As above. But death from any cause 8.3% in placebo group and 5.7% in empagliflozin group.
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	N/A	Outcomes long-term
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk.	Very good retention of participants with around 97% completing the study.
Selective reporting (reporting bias)	Low risk.	

Appendix 6 Trials excluded in NMA

Trial	Drug	Comparator	Notes
Abbatecola 2006[141]	repaglinide	glibenclamide	Baseline Hba1c 7.2%
Aronoff 2000[274]	Pioglitazone	Placebo	High drop-out rate and mean baseline HbA1c high
Barnett 2012[275]	linagliptin	Placebo then glimepiride	18 weeks versus placebo
Barzilai 2011[276]	Sitagliptin 50 or 100	placebo	High drop-out rate. Some not new to drug treatment. Mixed doses according to renal function
Chou 2012[277]	pioglitazone	placebo	Drop-out rate
Goldstein 2007[278]	Sitagliptin	placebo	High drop-out rate and entry HbA1c up to 11%
Jovanovic 2000[142]	repaglinide	Placebo	High drop out rate
Kamel 1997[279]	Glibenclamide, gliclazide,metformin, acarbose	placebo	Abstract only and only 43 patients across 5 arms.
Mohan 2009[280]	sitagliptin	placebo	Only 18 weeks
Moses 1999[281]	Repaglinide with/without metformin	metformin	All failed on metformin monotherapy and 25% Hba1c >9%. Duration
Moses 2001[282]	repaglinide	placebo	16 weeks
Raz 2006[283]	sitagliptin	placebo	Only 18 weeks
Saleem 2011[143], Shah 2011[144], Jibran 2006.[145]	Repaglinide	Glibenclamide	Wrong comparator and quality issues. The Jibran 2006and Saleem 2011 papers are very similar but have no authors in common. They are reported to be from different time periods but almost all figures are identical.
Scherbaum 2002[284]	pioglitazone	Placebo	Drop-out rate

Warwick Medical School

MCMDC Ltd. HEALTH & ECONOMICS

Addendum to Assessment Report on Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

Flozins for T2DM monotherapy: Probabilistic sensitivity analysis

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Flozins for T2DM monotherapy: Probabilistic sensitivity analysis

1. Introduction

The model was run probabilistically over 996 iterations for each of the BMI scenarios:

- No BMI direct effect upon quality of life
- BMI 1: natural history progression with no rebound
- BMI 2: natural history progression with weight losses rebounding after one year
- BMI 3: natural history progression with weight losses rebounding at treatment change
- BMI 4: natural history progression with weight rebounding after one year
- BMI 5: natural history progression with weight rebounding at treatment change

The central estimates for these are as below.

Table 1. Probabilistic central estimates of total costs and total QALYs

	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£28,222	10.649	9.850	9.850	9.850	9.996	9.963
Repag.	£28,338	10.645	9.880	9.873	9.875	9.995	9.968
Pio.	£28,456	10.640	9.827	9.827	9.827	9.987	9.952
Sita.	£33,472	10.612	9.878	9.874	9.874	9.966	9.944
Cana.	£33,813	10.635	10.005	9.909	9.927	9.995	9.991
Empa.	£33,922	10.634	9.972	9.903	9.915	9.992	9.982
Dapa.	£34,023	10.624	9.956	9.891	9.900	9.981	9.969

This suggests the following cost effectiveness estimates.

Table 2. Probabilistic central cost effectiveness estimates

	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,858	£4,949	£4,708	Dom.	£22,679
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita.	Dom.	Dom.	£34mn	Dom.	Dom.	Dom.
Cana.	Dom.	£43,952	£9,583	£105k	Dom.	£242k
Empa.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.

The patterns of dominance are the same across the deterministic results with the exception of the BMI scenario 2 where sitagliptin is no longer inferior to repaglinide but is now slightly superior to it. This

results in a cost effectiveness estimate for sitagliptin compared to repaglinide of £34mn per QALY. But given a cost effectiveness estimate for canagliflozin compared to repaglinide of £153k per QALY, sitagliptin is extendedly dominated.

Extended dominance.
Simple dominance is when another treatment offers more QALYs at a lower cost; e.g. in BMI scenario 2 repaglinide is both cheaper and more effective than pioglitazone.

Extended dominance occurs when it is possible to arrive at more QALYs at a lower cost by treating a proportion of patients with one treatment and the remainder with another treatment compared to the treatment under consideration. For instance, for the BMI scenario 2 treating 50% of patients with repaglinide and 50% of patients with canagliflozin would yield 9.891 QALYs at a cost of £31,075. This combination dominates sitagliptin.

Less formally but perhaps more intuitively, extended dominance can also be thought of along the following lines. If under BMI scenario 2 I am willing to pay £4,949 per QALY for repaglinide but to also then move to sitagliptin at a marginal cost of £34mn per QALY compared to repaglinide, I am certainly going to be willing to take the next step of paying £9,583 per QALY by moving up to canagliflozin. Sitagliptin cannot logically be the most cost effective treatment regardless of my willingness to pay.

The cost effectiveness estimates for repaglinide compared to gliclazide of £3,858 per QALY, £4,949 per QALY and £4,708 per QALY for BMI scenarios 1, 2 and 3 and £22,679 per QALY for the BMI scenario 5 are reasonably similar to the £3,331 per QALY for BMI scenarios 1, 2 and 3 and £18,507 per QALY for BMI scenario 5 of the deterministic analysis. In the opinion of the AG, the differences between the probabilistic analyses and the deterministic analyses are unlikely to be the result differences in the simulated complications of diabetes, hypoglycaemic events and adverse events. The most likely explanation is that the sampling of weight changes results in around 40% of the PSA iterations for repaglinide having a weight loss, but 0% of the PSA iterations for gliclazide. Apart from the scenario of weight changes having no impact upon quality of life, these repaglinide weight losses rebound under the various BMI scenarios. For the 40% of iterations with a repaglinide weight loss the cost effectiveness estimate for repaglinide compared to gliclazide worsens. As a consequence, the central estimate for the cost effectiveness estimate for repaglinide compared to gliclazide worsens.

The cost effectiveness estimates for canagliflozin compared to repaglinide are similar to those of the deterministic model, though for the BMI 2 scenario it has improved from the £192k per QALY of the

deterministic modelling to £153k per QALY. The issue around 40% of repaglinide iterations being associated with weight losses appears to have less of an impact due to the larger absolute QALY differences between canagliflozin and repaglinide compared to the differences between repaglinide and gliclazide.

The probabilistic cost effectiveness estimates of the individual flozins compared to sitagliptin are as below.

Table 3. Probabilistic ICERs for the flozins compared to sitagliptin

	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Sita.	..	..	..	..	..	..
Cana.	£14,714	£2,704	£9,583	£6,532	£11,685	£7,305
Empa.	£20,040	£4,795	£15,051	£11,168	£17,021	£12,048
Dapa.	£47,766	£7,110	£32,372	£21,194	£35,379	£22,208

The probabilistic central estimates for the cost effectiveness of the flozins compared to sitagliptin are much as per the deterministic estimates. While those for dapagliflozin have worsened slightly, they are qualitatively the same.

In the figures that follow the ordering of the legends helps to identify the curves. The topmost curve in the legend is the curve of the treatment which is the most likely to be cost effective at a willingness to pay of £0 per QALY; i.e. at the vertical axis. Since the willingness to pay is £0 per QALY only costs are of interest, so this point depict which treatment has the highest likelihood of being cost saving. The curve below this in the legend is the curve for the treatment which as the willingness to pay is increased next becomes the most likely to be cost effective. And so on down the legend until the frontier is specified. The curves within the legend that lie below the entry for the frontier in the legend are those that do not achieve the frontier at any willingness to pay in the range £0 to £50k per QALY. Where a curve is mentioned in the legend but is not visible in the figure it coincides with the horizontal axis: i.e. is estimated to have no probability of being cost effective over the willingness to pay range of £0 to £50k per QALY.

Also note that the frontier has been arbitrarily lifted by 0.5% in all figures so that it does not overlay the treatment curve to which it corresponds in order to ease identification of the relevant treatment curve.

2. Scenario analysis

2.1 BMI scenario of no direct effects from weight upon quality of life.

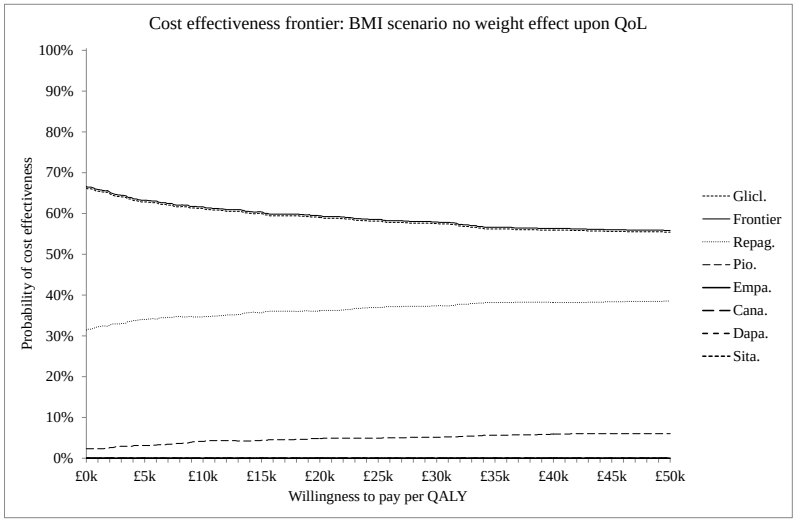

Figure 1. BMI no QoL effect: CEAF across all comparators

Table 4. BMI no QoL effect: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	4%	61%	35%
£20k	0%	0%	0%	0%	5%	59%	36%
£30k	0%	0%	0%	0%	5%	58%	37%
£40k	0%	0%	0%	0%	6%	56%	38%
£50k	0%	0%	0%	0%	6%	55%	39%

The probabilistic analysis suggests that the flozins and sitagliptin have no real probability of being cost effective. The main uncertainty is around whether glicalazide or repaglinide is the most cost effective, with it becoming more finely balanced between the two as the willingness to pay approaches £50k per QALY.

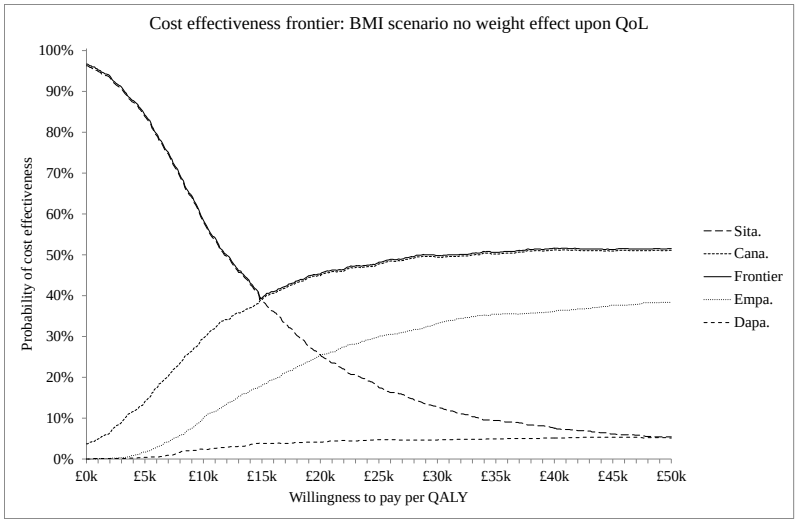

Figure 2. BMI no QoL effect: CEAF for flozins and sitagliptin

Table 5. BMI no QoL effect: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	10%	30%	2%	58%
£20k	26%	45%	4%	26%
£30k	33%	49%	5%	13%
£40k	36%	51%	5%	8%
£50k	38%	51%	5%	5%

At low values of willingness to pay the additional cost of the flozins is not warranted. Sitagliptin is estimated to be the most likely to be cost effective up to a willingness to pay of around £15k. Thereafter canagliflozin becomes the most likely to be cost effective, though the probability of empagliflozin being the most cost effective is not that far behind. Dapagliflozin fares worse, with there being little likelihood of it being the most cost effective at any willingness to pay value.

2.2 BMI scenario of weight changes retained indefinitely.

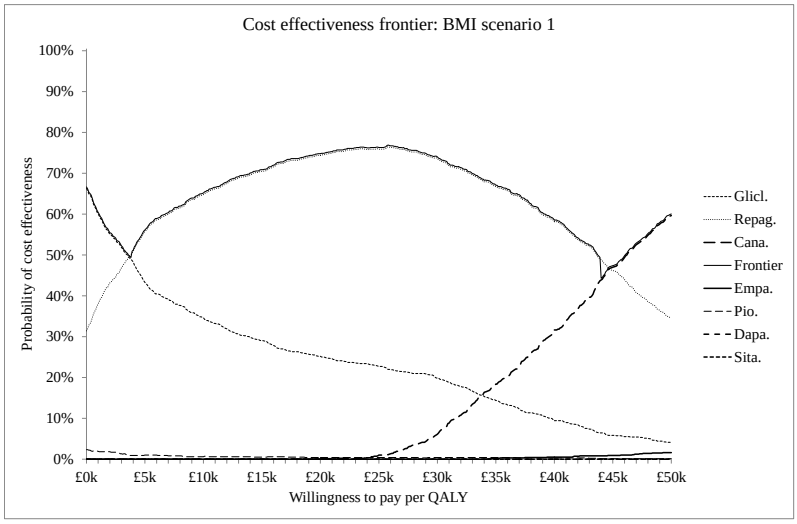

Figure 3. BMI scenario 1: CEAF across all comparators

Table 6. BMI scenario 1: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	35%	65%
£20k	0%	0%	0%	0%	0%	25%	74%
£30k	0%	6%	0%	0%	0%	20%	74%
£40k	1%	32%	0%	0%	0%	9%	58%
£50k	2%	60%	0%	0%	0%	4%	35%

With weight changes being retained indefinitely gliclazide is soon overtaken by repaglinide due to the greater weight gain with gliclazide. But canagliflozin is associated with the largest weight losses of the treatments. As the willingness to pay rises to around £45k per QALY canagliflozin has the highest likelihood of being cost effective. This £45k per QALY is broadly in line with the cost effectiveness estimate for canagliflozin of both the deterministic and the probabilistic modelling.

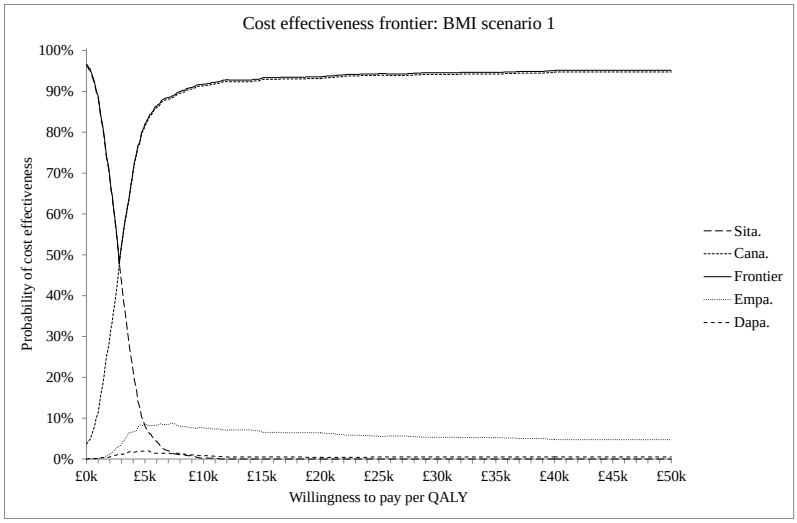

Figure 4. BMI scenario 1: CEAF for flozins and sitagliptin

Table 7. BMI scenario 1: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	8%	91%	1%	0%
£20k	6%	93%	0%	0%
£30k	5%	94%	1%	0%
£40k	5%	95%	1%	0%
£50k	5%	95%	1%	0%

Given the greater weight changes associated with canagliflozin, if weight changes are retained indefinitely canagliflozin is estimated to have the greatest likelihood of being cost effective at all but low willingness to pay values and there is little uncertainty around this.

2.3 BMI scenario of weight losses rebounding after one year.

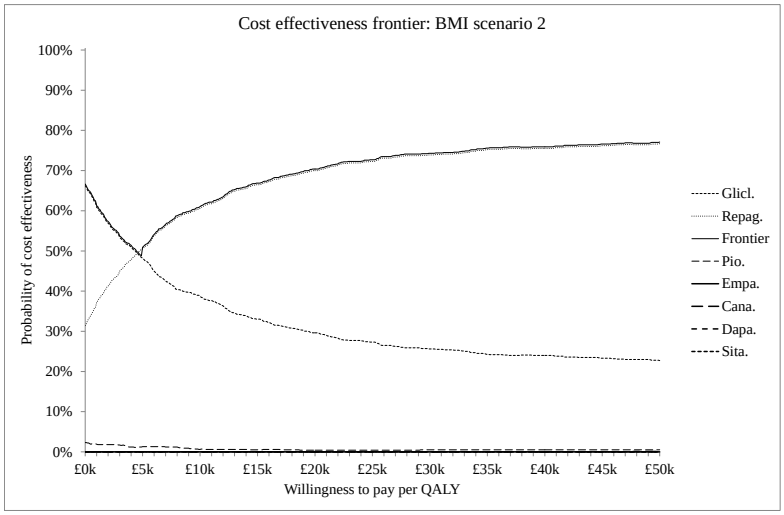

Figure 5. BMI scenario 2: CEAF across all comparators

Table 8. BMI scenario 2: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	39%	61%
£20k	0%	0%	0%	0%	0%	30%	70%
£30k	0%	0%	0%	0%	1%	26%	74%
£40k	0%	0%	0%	0%	1%	24%	76%
£50k	0%	0%	0%	0%	1%	23%	77%

If weight changes are only retained for one year compared to them being retained indefinitely there is little impact upon where gliclazide and repaglinide cross over. The main impact is that canagliflozin no longer shows a probability of being cost effect as the willingness to pay increases further towards £50k per QALY.

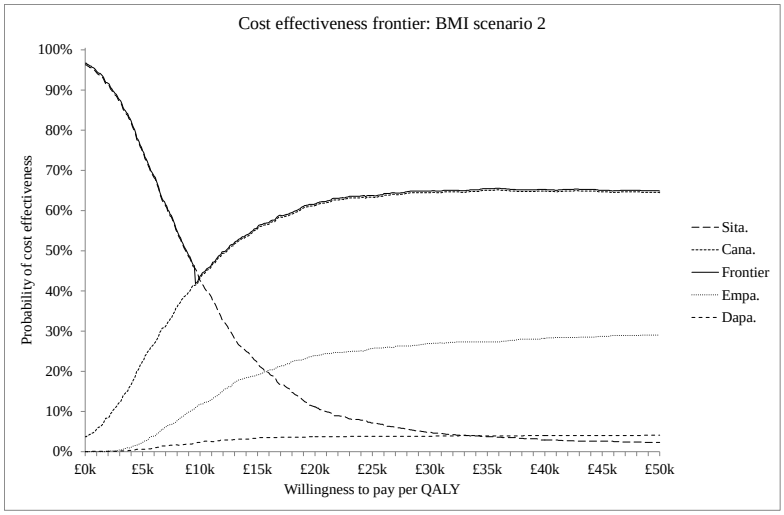

Figure 6. BMI scenario 2: CEAF for flozins and sitagliptin

Table 9. BMI scenario 2: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	12%	43%	2%	43%
£20k	24%	61%	4%	11%
£30k	27%	64%	4%	5%
£40k	28%	65%	4%	3%
£50k	29%	64%	4%	2%

Compared to the scenario of weight changes being retained indefinitely, the shorter retention of the larger weight gain from canagliflozin compared to empagliflozin means that there is greater uncertainty as to which is the most cost effective treatment. At a willingness to pay of £30k per QALY, the probability of canagliflozin being the most cost effective treatment is now only double that of empagliflozin.

2.4 BMI scenario of weight losses rebounding at treatment change.

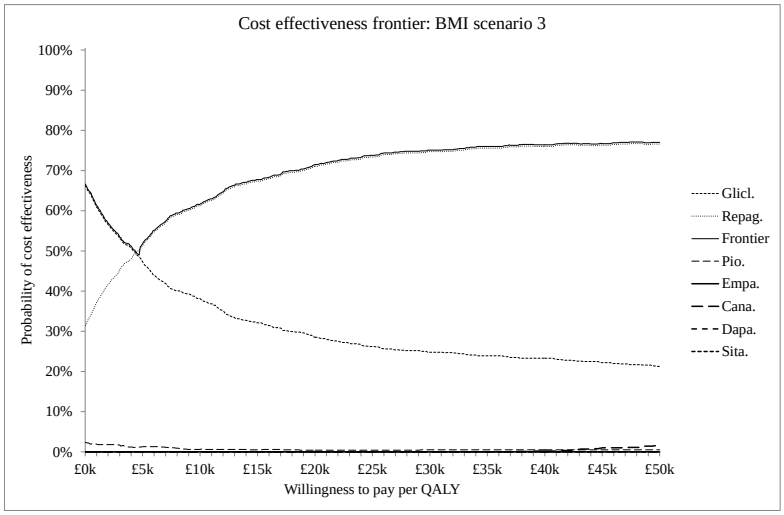

Figure 7. BMI scenario 3: CEAF across all comparators

Table 10. BMI scenario 3: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	38%	61%
£20k	0%	0%	0%	0%	0%	29%	71%
£30k	0%	0%	0%	0%	1%	25%	75%
£40k	0%	0%	0%	0%	1%	23%	76%
£50k	0%	2%	0%	0%	1%	21%	77%

The scenario of weight losses rebounding at treatment change is a half-way house. But this half-way house is still insufficient for canagliflozin to be modelled as having any real probability of being the most cost effective treatment. This requires weight changes to be modelled as being retained indefinitely.

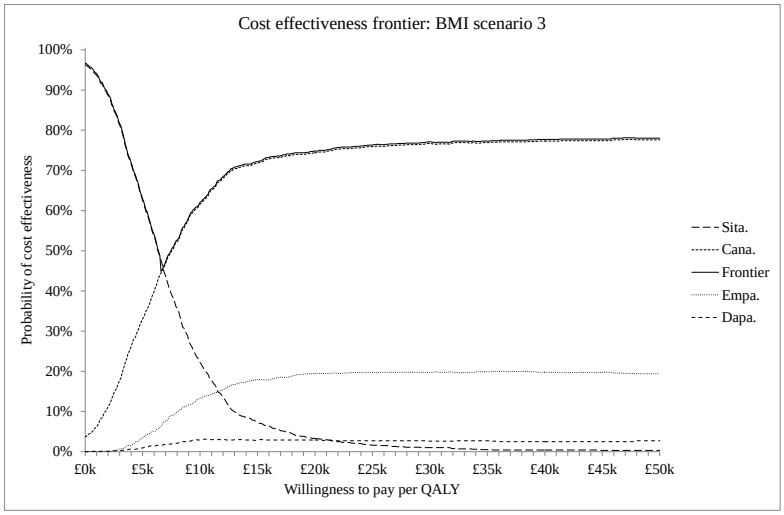

Figure 8. BMI scenario 3: CEAF for flozins and sitagliptin

Table 11. BMI scenario 3: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	13%	62%	3%	22%
£20k	19%	74%	3%	3%
£30k	20%	77%	3%	1%
£40k	20%	77%	3%	0%
£50k	19%	78%	3%	0%

The longer retention of weight changes compared to BMI scenario 2 means that the greater weight loss with canagliflozin compared to empagliflozin increases the likelihood of canagliflozin being the most cost effective and reduces that of empagliflozin.

2.5 BMI scenario of weight changes rebounding after one year.

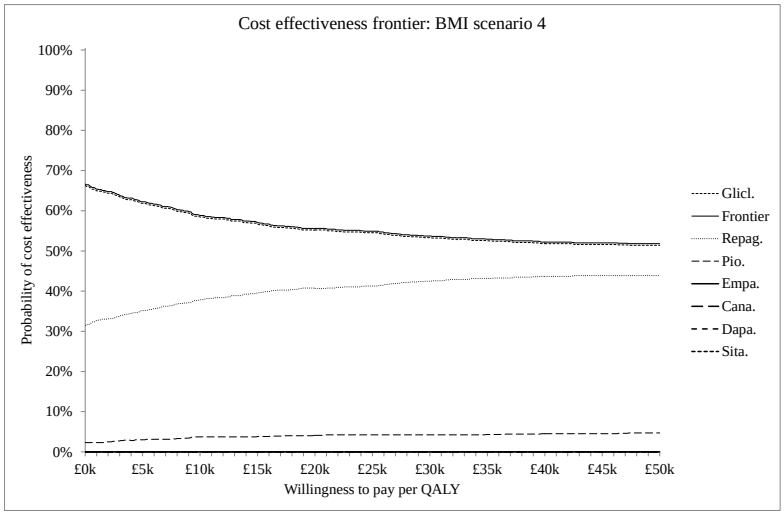

Figure 9. BMI scenario 4: CEAF across all comparators

Table 12. BMI scenario 4: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	4%	58%	38%
£20k	0%	0%	0%	0%	4%	55%	41%
£30k	0%	0%	0%	0%	4%	53%	42%
£40k	0%	0%	0%	0%	5%	52%	44%
£50k	0%	0%	0%	0%	5%	51%	44%

As would be expected given the short duration of weight changes, the CEAF is little difference from that of the scenario where BMI has no impact upon quality of life, though by a willingness to pay of £50k per QALY the curves for gliclazide and repaglinide show a slightly greater convergence.

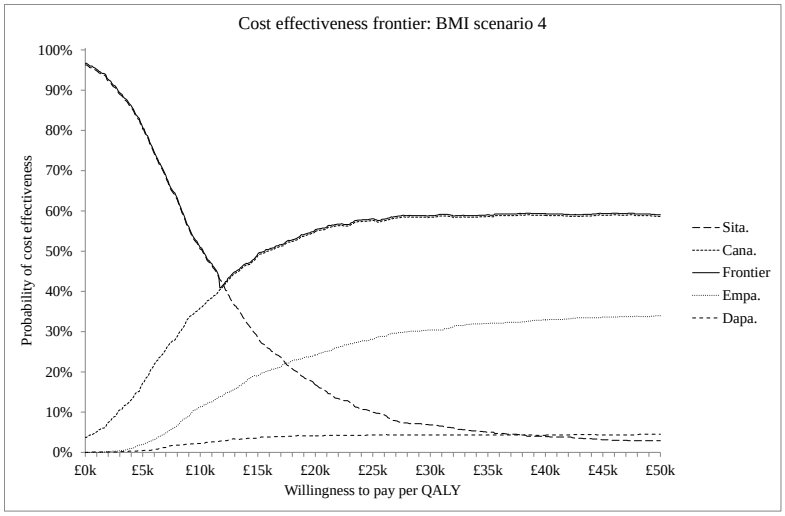

Figure 10. BMI scenario 4: CEAF for flozins and sitagliptin

Table 13. BMI scenario 4: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	11%	36%	2%	51%
£20k	24%	55%	4%	17%
£30k	30%	58%	4%	7%
£40k	33%	59%	4%	4%
£50k	34%	59%	5%	3%

Comparing weight changes being retained for one year to weight changes having no direct quality of life impact, the difference between the probability of canagliflozin being the most cost compared to that of empagliflozin is slightly greater. This increases as the willingness to pay increases.

2.6 BMI scenario of weight changes rebounding at treatment change.

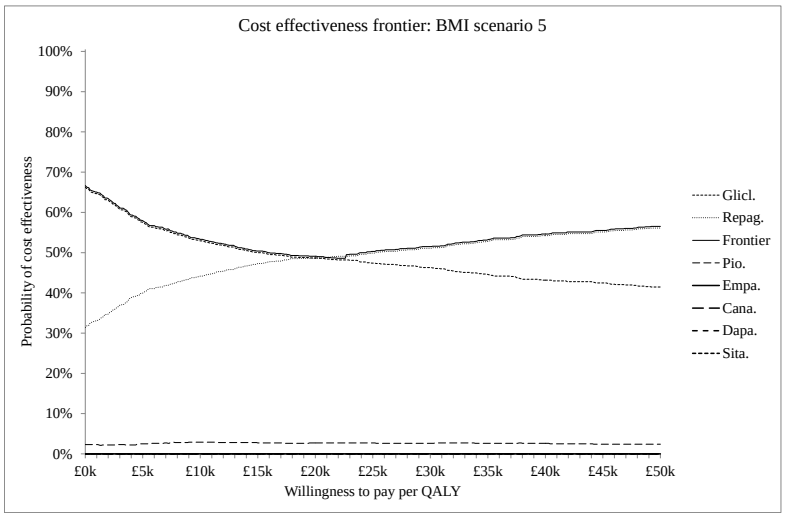

Figure 11. BMI scenario 5: CEAF across all comparators

Table 14. BMI scenario 5: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	3%	53%	44%
£20k	0%	0%	0%	0%	3%	49%	49%
£30k	0%	0%	0%	0%	3%	46%	51%
£40k	0%	0%	0%	0%	3%	43%	54%
£50k	0%	0%	0%	0%	2%	41%	56%

If weight changes are retained until treatment change the probabilities of being the most cost effective for gliclazide and for repaglinide are roughly equal at a willingness to pay of £20k per QALY, and have diverged only slightly at a willingness to pay of £30k per QALY.

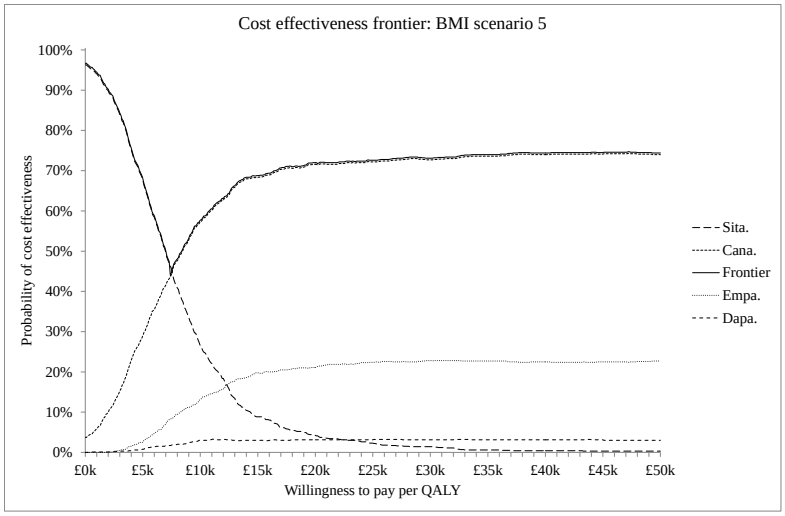

Figure 12. BMI scenario 5: CEAF for flozins and sitagliptin

Table 15. BMI scenario 5: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	13%	57%	3%	27%
£20k	21%	72%	3%	4%
£30k	23%	73%	3%	1%
£40k	22%	74%	3%	0%
£50k	23%	74%	3%	0%

Sitagliptin and canagliflozin have the highest estimates for their probabilities of being cost effective, with canagliflozin having the highest estimate at conventional NICE willingness to pay thresholds. Empagliflozin has some probability of being cost effective but it is only around a third that of canagliflozin.

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes.

Erratum to assessment report. 13th October 2015.

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Erratum to assessment report.

Background

The model used to generate the probabilistic results contains information which could if circulated be regarded being under the copyright of the UKPDS OM1 modellers. This model had to be developed by the AG in order to undertake the probabilistic modelling.

As a consequence, the AG implemented an excel worksheet which outputs the model inputs in a format suitable for inputting to the UKPDS OM1 excel version 1.302 implementation. This was developed to enable consultees to the assessment to cross check the AG deterministic modelling results. Consultees can generate the set of UKPDS OM1 inputs using the AG model, run the UKPDS OM1 model to estimates the UKPDS OM1 costs, QALYs and survival curves, paste these values back into the AG model and have it automatically collate these with the data on treatment switches, hypoglycaemic events and adverse events to yield estimates for the total costs and QALYs.

During the course of cross checking the model outputs and the correspondence between the results of the different modelling exercises the AG realised that it had set the baseline IHD prevalence to zero. Identifying this error was complicated by the UKPDS OM1 excel implementation seemingly ignoring the HF at baseline indicator. It appears that the UKPDS OM1 excel implementation applies the IHD at baseline indicator to determine the modelled prevalence of HF. To see this more clearly, it appears that the following applies within the OM1 excel version 1.302.

Table 1: Hypothetical four patients within the OM1

	Prevalence of complications at baseline			
	Inputted values		Values applied in OM1	
	IHD	HF	IHD	HF
Patient 1	No	No	No	No
Patient 2	No	Yes	No	No
Patient 3	Yes	No	Yes	Yes
Patient 4	Yes	Yes	Yes	Yes

This can be checked by setting the UKPDS OM1 *Run_Model* worksheet to have the following input values.

Table 2: Illustrative inputs for the OM1

Initial utility :	1.000
Cost with no complications :	£10

	At time of event			In subsequent years	
	Fatal	Non-fatal	Utility decr.	Cost	Utility decr.
IHD :		£100	-0.500	£100	-0.500
MI :	£1,000	£1,000	-0.500	£1,000	-0.500
Heart failure :	£10,000	£10,000	-0.500	£10,000	-0.500
Stroke :	£100,000	£100,000	-0.500	£100,000	-0.500
Amputation :	£1,000,000	£1,000,000	-0.500	£1,000,000	-0.500
Blindness :		£10,000,000	-0.500	£10,000,000	-0.500
Renal failure :	£100,000,000	£100,000,000	-0.500	£100,000,000	-0.500

Running the OM1 excel version 1.302 with these inputs results in the following estimates for the patients' costs of complications and costs in the first year.

Table 3: OM1 excel version 1.302 1st year cost and QALY results

	Cost	QALY
Patient 1	£10	1.000
Patient 2	£10	1.000
Patient 3	£10,100	1.000
Patient 4	£10,100	1.000

Patient 1 is correctly simulated as incurring £10 in the first year. But Patient 2 does not have the £10,000 cost of HF applied, but instead only has the £10 cost for no complications applied. Patient 3 does have the £100 cost of IHD applied, but also has the £10,000 cost of HF applied. Patient 4 is correctly simulated as having both the £100 cost of IHD and the £10,000 cost of HF.

The above also throws up another issue. The AG had assumed that the value inputted as the initial utility was the utility with no complications. But it appears that the UKPDS OM1 excel version 1.302 is quite literal in taking this to be the initial utility. It appears that for patients with a complication which is prevalent at baseline the UKPDS OM1 does not apply the utility decrement associated with that complication. The utility decrements associated with complications appear to only be applied to complications which are modelled as occurring after baseline. While the model is literally correct in its implementation, to the AG it seems undesirable not to apply the "*in subsequent years*" utility decrements to complications which were present at baseline.

So there are three problems:

- The UKPDS OM1 excel version 1.302 appears not to apply the utility decrements for complications that are prevalent at baseline.
- The UKPDS OM1 excel version 1.302 appears not to permit baseline IHD and HF prevalences to be specified correctly.
- The AG set the baseline IHD prevalence to 0%.

The first problem could be addressed by simulating patients in subgroups according to their complications at baseline: none, only IHD, IHD and HF, etc. and applying initial utility values specific to these patient subgroups. But since there are seven complications which can be present at baseline, there would be a large number of possible combinations which would be extremely laborious to explore individually and the AG does not propose to go down this route. The simpler alternative is to run a sensitivity analysis of having no complications at baseline to see if this has any practical impact upon results.

The third problem can be addressed by the AG revising its IHD prevalence to be 2.7% and seeing if this has any practical impact upon results.

But the second problem means that the AG model for circulation to consultees can only be used to cross check the AG modelling of no complications at baseline. In order to expand this and to come as close to the AG modelling of the base case that can be replicated by consultees, the AG has also undertaken a sensitivity analysis that retain the baseline complications with the exception of IHD and HF; i.e. it sets these latter to zero for all patients.

AG report base case modelling results

For ease of references table 64 and table 66 of the AG report that present the AG base case analysis are reproduced below.

Table 4: AG report Table 64 AG base case: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,314	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£27,413	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,543	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£32,358	10.355	9.657	9.655	9.655	9.739	9.719
Cana. 300	£32,676	10.380	9.780	9.691	9.707	9.770	9.767
Empa. 25	£32,775	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£32,866	10.367	9.734	9.671	9.681	9.756	9.745

Table 5: AG report Table 66 AG base case: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,331	£3,331	£3,331	Dom	£18,507
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£44,994	£192k	£119k	Dom	£235k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

Table 6: AG report Table 68 AG base case: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
Empa. 25	£18,341	£4,676	£14,716	£10,841	£15,734	£11,300
Dapa. 10	£40,383	£6,632	£30,710	£19,787	£30,487	£19,679

Setting the baseline prevalence of all complications to 0.0%

Assuming that there is a zero prevalence of complications at baseline results in the following.

Table 7: No complications at baseline: Lifetime total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,311	10.418	9.657	9.657	9.657	9.795	9.763
Repag.	£26,417	10.414	9.687	9.687	9.687	9.794	9.768
Pio.	£26,537	10.409	9.635	9.635	9.635	9.785	9.752
Sita. 100	£31,374	10.380	9.682	9.679	9.679	9.763	9.743
Cana. 300	£31,672	10.404	9.803	9.714	9.730	9.793	9.790
Empa. 25	£31,778	10.402	9.769	9.706	9.717	9.789	9.779
Dapa. 10	£31,876	10.393	9.758	9.695	9.705	9.780	9.768

As would be expected, the total costs fall somewhat if patients are assumed to have no complications at baseline. Total QALYs are also affected but this is not due to the removal of any quality of life decrements for the complications which are prevalent at baseline. Rather it appears to be due to fewer complications at baseline having a survival effect.

Table 8: No complications at baseline: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,538	£3,538	£3,538	Dom.	£19,882
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,153	£197k	£121k	Dom.	£243k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

But all treatment arms appear to have been affected to largely the same extent and the cost effectiveness estimates are essentially the same as those of the AG report base case.

Table 9: No complications at baseline: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,405	£2,444	£8,621	£5,847	£9,979	£6,356
Empa. 25	£18,940	£4,595	£14,945	£10,871	£16,046	£11,354
Dapa. 10	£41,187	£6,574	£31,172	£19,873	£30,944	£19,764

The cost effectiveness estimates for the flozins compared to sitagliptin are similarly little changed from those of the AG report base case.

Setting the baseline IHD prevalence to 2.7%

Applying the 2.7% baseline IHD prevalence results in the following.

Table 10: 2.7% IHD baseline prevalence: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,600	10.376	9.618	9.618	9.618	9.755	9.723
Repag.	£27,704	10.374	9.649	9.649	9.649	9.755	9.730
Pio.	£27,827	10.367	9.596	9.596	9.596	9.746	9.712
Sita. 100	£32,631	10.337	9.641	9.638	9.639	9.723	9.702
Cana. 300	£32,933	10.362	9.763	9.674	9.691	9.753	9.750
Empa. 25	£33,031	10.360	9.730	9.667	9.678	9.749	9.739
Dapa. 10	£33,136	10.350	9.718	9.656	9.665	9.740	9.729

Table 11: 2.7% IHD baseline prevalence: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,388	£3,388	£3,388	£434k	£16,413
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,641	£207k	£124k	Dom.	£259k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

The pattern of dominance is unchanged compared to the base case of the AG report with the exception of the BMI 4 scenario where repaglinide has changed from being modelled as being marginally inferior to being marginally superior compared to gliclazide.

The cost effectiveness estimates for canagliflozin compared to repaglinide are essentially the same as those of the AG report base case, though those in six figures show greater absolute changes due to the very small divisor.

Table 12: 2.7% IHD baseline prevalence: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,034	£2,467	£8,494	£5,820	£9,777	£6,312
Empa. 25	£17,278	£4,471	£13,917	£10,294	£14,864	£10,724
Dapa. 10	£37,871	£6,542	£29,341	£19,172	£29,116	£19,062

The cost effectiveness estimates for the flozins compared to sitagliptin are similarly close to those of the AG report base case, though those for the scenario of weight having no direct quality of life impact show some improvement for empagliflozin and dapagliflozin. There has been a marginal improvement in those for dapagliflozin such that the cost effectiveness ratios that were previously estimated as being slightly above £30k per QALY are now slightly below £30k per QALY.

Setting the baseline prevalences of IHD and HF to 0.0%

Given the above results, setting the baseline prevalences of IHD and HF to zero has only a limited impact upon the cost effectiveness estimates, as outlined below.

Table 13: 0% IHD & HF baseline prevalence: Lifetime total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,208	10.399	9.640	9.640	9.640	9.777	9.745
Repag.	£27,320	10.396	9.670	9.670	9.670	9.777	9.751
Pio.	£27,437	10.392	9.619	9.619	9.619	9.769	9.735
Sita. 100	£32,261	10.362	9.664	9.661	9.662	9.746	9.725
Cana. 300	£32,571	10.387	9.787	9.697	9.714	9.777	9.773
Empa. 25	£32,668	10.385	9.753	9.690	9.701	9.773	9.762
Dapa. 10	£32,766	10.375	9.741	9.678	9.688	9.763	9.752

Table 14: 0% IHD & HF baseline prevalence: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,668	£3,668	£3,668	Dom.	£18,901
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,126	£196k	£120k	Dom.	£241k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

Table 15: 0% IHD & HF baseline prevalence: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,326	£2,532	£8,718	£5,975	£10,033	£6,481
Empa. 25	£17,603	£4,558	£14,218	£10,510	£15,185	£10,950
Dapa. 10	£38,046	£6,540	£29,526	£19,243	£29,307	£19,137

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

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes [ID756]

AstraZeneca Response

Date of response: 9th November 2015

AstraZeneca UK Ltd

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Abbreviations table

BMI	Body Mass Index
CDM	CARDIFF Diabetes Model
CG	Clinical Guideline
CHF	Congestive Heart Failure
CrI	Credible Interval
DPP4	Dipeptidyl peptidase-4
eGFR	estimated Glomerular Filtration Rate
GLP1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin (A1c)
ICER	Incremental Cost-Effectiveness Ratio
MTA	Multiple Technology Appraisal
NMA	Network Meta-Analysis
NPH	Neutral Protamine Hagedorn
OM1	UKPDS Outcomes Model v1
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
SBP	Systolic Blood Pressure
SGLT2	Sodium-glucose co-transporter-2
SU	Sulfonylurea
TZD	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study

AstraZeneca thank NICE for the opportunity to respond to the assessment report.

The assessment group (AG) has understood the majority of challenges associated with the data in monotherapy; however the report's Plain English summary does not adequately communicate these challenges, and as such is misleading. The below response therefore focuses around outlining the following key points:

1 **It is not possible to meaningfully compare between the SGLT2 inhibitors (flozins) due to differences in trial design in monotherapy: canagliflozin, dapagliflozin, and empagliflozin should therefore be considered as a class**

- There are limited data available for within class comparisons of the SGLT2s in monotherapy. There are no head to head studies; and significant differences in patient characteristics exist between studies
- Tentatively drawn conslusions around the relative efficacy of dapagliflozin versus the other flozins are likely driven by study designs rather than treatment effects:

    1. One dapagliflozin trial (Kaku *et al.,* 2014) differs markedly from other SGLT2 trials; importantly lower mean baseline HbA1c and eGFR levels give clinical rationale to an expected lower change in HbA1c (which was observed) [1]
        - Sensitivity analyses removing Kaku *et al.,* from the AstraZeneca NMA, impacted the dapagliflozin change in HbA1c versus placebo from -0.62 (-0.89, -0.35), to -0.75 (-1.08, -0.43), demonstrating the uncertainties in using such a small evidence base
    2. Correspondingly, study characteristics vary between all SGLT2 studies, with substantial heterogeneity between trials (I-squared = 88.9%)
    3. A particularly high 'placebo effect' is observed in the dapaglifozin trials, impacting the relative effect sizes. The absolute effect of SGLT2s (excluding Kaku *et. al.)* in lowering HbA1C was found to be similar for all three flozins

- The report itself is generally balanced; however these challenges have not been clarified when summarising the effectiveness of individual SGLT2s: the following text in the Plain Summary is therefore misleading: "*The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins"*
- **AstraZeneca request that this text is redacted, and that it is clarified in both summaries that any comparisons between ICERs for the SGLT2s are compounded by differences between trials impacting the efficacy outcomes**

2 **SGLT2s are cost effective versus DPP4s in monotherapy**

- There is consistency between the AG model and all companies in demonstrating the cost-effectiveness of SGLT2s versus sitagliptin/DPP4s
    - Results compared to gliclazide or pioglitazone are more varied depending on the company assumptions; cost-effectiveness of the SGLT2s vs. these comparators is therefore uncertain

- The AG correctly model a range of weight scenarios given its impact on the model; however scenarios not considered realistic by AstraZeneca and clinical experts include assumptions that weight has no impact on QOL, and that weight loss rebounds after one year based on available evidence contrary to this

- **Excluding these less plausible scenarios, all SGLT2s are cost effective vs. sitagliptin**

3 SGLT2s should be recommended where monotherapy treatment with metformin, SUs, and pioglitazone is inappropriate

- The AG note a remaining unmet need for patients who cannot tolerate metformin, and are at risk of hypoglycaemia or additional weight gain (associated with Sus and pioglitazone)
- As concluded in the report, SGLT2s are effective at reducing hyperglycaemia with an added benefit of some reduction in blood pressure and weight
- Finally, the flozins offer a cost-effective treatment option compared to DPP4s
- **Therefore, on balance of the available evidence, SGLT2s as a class should be recommended as an option for patients who are unsuitable for monotherapy with metformin, SUs, or pioglitazone**

1 It is not possible to meaningfully compare between the SGLT2s: canagliflozin, empagliflozin, and dapagliflozin should be regarded as a class

The AG note limitations in interpretation of the NMA results (pg 101). As also described in the AstraZeneca submission, substantial cross-study heterogeneity prevents a meaningful flozin versus flozin assessment. Given the limited comparable evidence, assessing the class of drugs would be more appropriate.

Firstly, the Kaku *et al.,* a monotherapy study exploring 5mg and 10mg doses of dapagliflozin, **differs markedly in two aspects from all other SGLT2 studies, and may warrent exclusion from the NMA [2]. The following baseline characteristics may have been key drivers in the difference in efficacy reported, to the detriment of expected efficacy for dapagliflozin monotherapy.**

1. As noted on page 100, Kaku *et al.,* is distinct from the majority of trials with a mean baseline HbA1c of 7.5% versus around 8% (7.9%-8.3%) for other trials (table 2, pg 45)[1]
    - Importantly, although the published mean (7.5%) met the inclusion criteria for the NMA[1] (pg 79), the study mean baseline HbA1c reported in the Clinical Study Report was 7.49%, and median baseline HbA1c was [redacted] in the dapagliflozin arm and [redacted] in the placebo arm [2]
    - The low average HbA1c may be partly due to a cap of <8% on the maximal HbA1c allowed in the non-drug naive subjects at screening
- Since a lower baseline HbA1c leaves less room for improvement, the magnitude of effect is expected to be smaller. Indeed McGovern *et al.,* 2014 found that baseline HbA1c is a predictor of improvement in HbA1c (i.e. a higher baseline HbA1c equates to a likelihood of dapagliflozin reducing HbA1c; p <0.001) [3].

[1] The AstraZeneca systematic review or NMA did not have an exclusion criteria for baseline HbA1c: this study was therefore also included

- In agreement, a clinical expert noted that based on the mode of action (as a reabsorption inhibitor), SGLT2s are more effective when a patient's blood glucose levels are higher (Clinical expert opinion, 2015).

2. In the Kaku *et al.,* study, the mean eGFR was 67.1 mL/min1.73m^2: distinctly lower than all other trials. Pooled canagliflozin studies had a mean eGFR of 86 mL/min1.73m^2 (report page 124), empagliflozin trials ranged from 87.4 to 90.1 mL/min1.73m^2, and in the remaining dapagliflozin studies, baseline eGFR was 87 and 90mL/min1.73m^2 [4-7]
   - As SGLT2 inhibitor efficacy is directly related to eGFR, a difference in effect may be expected from this large difference between trials, to the detriment of dapagliflozin in the Kaku *et al.,* study
     - Indeed, consistent with the mechanism of action, reduced renal function has been shown to decrease the urinary glucose excretion by SGLT2 inhibitors thereby reducing their glycaemic efficacy [8]. Across the SGLT2 class, reduction in HbA1c is less in those with renal impairment (eGFR <60mL/min1.73m^2) than in studies with better renal function [9-11].

3. Additional differences between SGLT2 trials may include the wash-out period of non-drug naïve patients, or the definition of drug naïve patients. Importantly, the majority of patients in Kaku *et al.,* were treatment naïve (251 patients versus 35 non-drug naïve), so may have been more receptive to placebo 'treatment'. Given the definition and percentage of naive patients in other publications is unclear, it is difficult to assess the potential impact

In summary, given the differences in the Kaku *et al.,* study from the other monotherapy studies, efficacy results which include this study may reflect differences in study baseline characteristics rather than differences in the drugs being evaluated. Sensitivity analyses of the NMA results with Kaku *et al.,* removed are presented in Table 2 below.

In addition to concerns with the Kaku *et al.,* trial, the remaining SGLT2 trials also differ in baseline characteristics and in study design, all of which may have had an impact on the relative effectiveness of treatment versus placebo:

- The difference in BMI is acknowledged by the AG on page 100, with the Asian studies for both canagliflozin and dapagliflozin having a lower baseline BMI than the other SGLT2 trials conducted in Western populations
- The duration of diabetes varies greatly between trials; with Ferrannini *et al.,* having a median duration of ~0.45 years, while all canagliflozin trials have a duration of diabetes >4 years. The empagliflozin trials are less clear on the mean/median duration of diabetes (table 2, pg 45)
- As noted by the AG, dapagliflozin is the only SGLT2 in which the placebo arm HbA1c improved over the trials (pg 101). In both Ferannini *et al.,* and Kaku *et al.,* weight also substantially improved in the placebo arm (table 3, pg 50)
  - Notably the absolute effect of dapagliflozin in Ferrannini *et al.,* and Ji *et al.,* were similar or greater than the HbA1c reduction for patients on canagliflozin 100 mg and either empagliflozin dose (-0.79% to -1.11% for dapagliflozin versus -0.74% to -0.77% for canagliflozin and -0.66% to -1.01% for empagliflozin [the absolute effect in Kaku *et al.,* was -0.45%)]
  - The cause of the positive impact of placebo on HbA1c in the dapagliflozin trials is unknown; however it indicates an additional unidentified cause of heterogeneity between the SGLT2 trials (it was hypothesised in the AstraZeneca submission that this may have been due to differences in intensity of diet and exercise counselling between trials)

1.1 Additional analyses further demonstrate the challenges in the available evidence base in monotherapy

AstraZeneca originally submitted an NMA pooling the SGLT2s given the limited comparable evidence available. Below are supplementary analyses demonstrating i) the heterogeneity between trials ii) the impact of removing Kaku *et al.,* from the NMA on relative effect sizes for HbA1c.

i. Pairwise comparisons provide a means to assess the consistency of effect estimates among individual trials comparing the same two agents. For all treatment classes, moderate to substantial heterogeneity was evident. The class of treatment had I-squared values of:
   - TZDs: 89.6%
   - SGLT-2s: 88.9%
   - SUs: 75.6%
   - DPP4s: 47.2%

Where 30%-60% indicates moderate heterogeneity, and 50%-90% indicates substantial heterogeneity[2]. Specifically, comparison between the three dapagliflozin studies [1, 4, 5] produced an I-squared value of 82.4% (p=0.003), again indicating substantial heterogeneity[2]

ii. The relative effect sizes of mean change in HbA1c are presented in Table 1, split by SGLT2, and the analyses with Kaku *et al.,* removed are in Table 2 (caterpillar plots in Appendix 1). The random effects model was selected over the fixed effect model as this was the best fit for the base case.
   - By removing Kaku *et al.,* from the AstraZeneca NMA, the relative effect for dapagliflozin versus placebo improves from -0.62 (95%CrI: -0.89, -0.35) to -0.75 (95%CrI: -1.08, -0.43)
   - Moreover the statistically significant value for canagliflozin 300 mg versus dapagliflozin is no longer statistically significant when the outlier study, Kaku *et al.,* is removed

Table 1. Relative effect sizes from the random effects model: mean change in HbA1c

Regimen	Change in HbA1c from Baseline (%)	
	All vs. Placebo Mean (95% CrI)	Dapagliflozin vs. All Mean (95% CrI)
Placebo	*Reference Treatment*	-0.62 (-0.89, -0.35)*
DPP-4 inhibitors	-0.68 (-0.81, -0.55)*	0.06 (-0.24, 0.36)
TZDs	-0.94 (-1.14, -0.74)*	0.32 (-0.02, 0.65)
Sulfonylureas	-0.98 (-1.26, -0.72)*	0.37 (-0.01, 0.76)
Canagliflozin 100mg	-0.97 (-1.29, -0.65)*	0.35 (-0.07, 0.77)
Canagliflozin 300mg	-1.20 (-1.62, -0.78)*	0.58 (0.09, 1.08)*
Empagliflozin 10mg	-0.71 (-1.09, -0.32)*	0.09 (-0.39, 0.56)
Empagliflozin 25mg	-0.83 (-1.22, -0.45)*	0.21 (-0.25, 0.68)
Dapagliflozin	-0.62 (-0.89, -0.35)*	*Reference Treatment*

*indicates statistical significance. **CrI**=credible interval

[2] Interpretation of results based on the Cochrane Handbook

Table 2 Relative effect sizes from the random effects model: mean change in HbA1c with Kaku *et al*., removed

Regimen	Change in HbA1c from Baseline (%)	
	All vs. Placebo Mean (95% CrI)	Dapagliflozin vs. all Mean (95% CrI)
Placebo	*Reference Treatment*	-0.75 (-1.08, -0.43)*
DPP-4 inhibitors	-0.68 (-0.80, -0.56)*	-0.07 (-0.42, 0.27)
TZDs	-0.93 (-1.13, -0.74)*	0.18 (-0.18, 0.57)
Sulfonylureas	-0.98 (-1.25, -0.72)*	0.22 (-0.18, 0.66)
Canagliflozin 100mg	-0.97 (-1.28, -0.66)*	0.22 (-0.23, 0.66)
Canagliflozin 300mg	-1.20 (-1.61, -0.79)*	0.45 (-0.06, 0.97)
Empagliflozin 10mg	-0.71 (-1.08, -0.34)*	-0.04 (-0.52, 0.45)
Empagliflozin 25mg	-0.83 (-1.20, -0.45)*	0.08 (-0.41, 0.57)
Dapagliflozin	-0.75 (-1.08, -0.43)*	*Reference Treatment*

*indicates statistical significance. **CrI**=credible interval

Notably, such a difference in the relative change in HbA1c would also impact the cost-effectiveness analyses. Given the limited data informing the NMA, it is important for the committee to consider how influential a single trial is on the results; particularly considering the fundamental differences in study characteristics described above. Despite the above sensitivity analysis, AstraZeneca suggest it is still not possible to meaningfully compare between the SGLT2s based on the limitations and differences between trials.

1.2 The Plain English summary does not adequately communicate the challenges in the evidence base described above, and as such is misleading

Although the differences between trials are generally captured within the report, the implications of these differences have not been clearly communicated alongside the results. Specifically, given the heterogeneity of trial data, the following exert from the Plain English summary is misleading: *"…the flozins are good value for patients as a whole. The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins"*. The report is therefore currently at risk of eliciting conclusions on the data based on limited and incomparable trials.

In contrast, if a different yet clinically appropriate outcome is considered rather than relative change in HbA1C, then dapagliflozin appears at least as effective as canagliflozin 100 mg or empagliflozin 10 mg:

- Outcome: the proportion of patients able to achieve a target HbA1c <7%
- Results: A larger proportion of patients in dapagliflozin reached HbA1c <7% (48.8%-51.4%) across trials, including Kaku *et al.,* when compared with patients on canagliflozin 100 mg (31.5%-44.6%) or empagliflozin 10 mg (35.3%-38.8%; pg 52)

The aim of diabetes treatment is to reduce a patient's HbA1c to target (this is usually set on an individual patient level basis). Although the relative change in HbA1c versus placebo was lower in the dapagliflozin trials, likely impacted by the high placebo effect, it is clear that the active arm is still effective at achieving a reduction in HbA1c (in absolute terms, and in proportion of patients achieving HbA1c <7%).

1.3 Summary

Overall, the SGLT2 trials differ substantially in design and baseline characteristics (Kaku *et al.,* being a key example). It has previously concluded that if the distribution of characteristics is not balanced across trials, then this biases the indirect analyses [12]. Even at scoping stage of the MTA, the Warwick AG stated that "it is probably unsafe to conclude that any one flozin is best". Furthermore, NICE have considered the flozins to have a similar efficacy and safety profile in dual therapy, which has a larger evidence base (see Section 4.4 of the empagliflozin TA336 guidance).

A meaningful comparison between the individual SGLT2s is therefore not possible in monotherapy based on the currently available data, and it is not reasonable to compare between them in the NMA or cost-effectiveness results. On balance, Kaku *et al.,* may be an outlier in trial design and therefore should be excluded from any analyses.

AstraZeneca request that the text in the plain summary (*The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins***) is redacted, or is made more consistent with the executive summary. We ask that it is also clarified in both summaries that the ICERs for the SGLT2s are based on limited available data; any comparison is compounded by the differences between trials impacting the efficacy outcomes.**

2 SGLT2s in monotherapy are cost effective versus DDP4s

ICERs for the SGLT2s compared to gliclazide or pioglitazone appeared highly variable depending on the model type by the submitting company, and the associated assumptions. We therefore consider that there is uncertainty in the cost effectiveness of SGLT2s versus SUs or pioglitazone in monotherapy.

Nevertheless, all companies demonstrated cost effectiveness versus sitagliptin (or DPP4s) for their product. This is in agreement with the AG who also concluded that the SGLT2s may be cost-effective versus sitagliptin. Indeed, in the more clinically plausible scenarios presented by the AG, dapagliflozin proves cost effective versus sitagliptin (ICER range: £6,632-£19,787; see section 2.2 for AG scenario plausibility).

2.1 Additional analyses demonstrating the cost effectiveness of dapagliflozin versus DPP4s, pioglitazone, and SUs

Based on the limited evidence to enable a comparison between the flozins, AstraZeneca presented SGLT2s as a pooled class within the submission demonstrating cost effectiveness versus DPP4s. In alignment with the AG report, Table 3 demonstrates the cost-effectiveness of dapagliflozin versus comparator classes (based on the AstraZeneca model), to further show that dapagliflozin remains cost effective versus DPP4s.

Table 3: Cost-effectiveness of dapagliflozin versus SUs, pioglitazone, and DPP4s

	Total cost	QALY's	Δ Cost	Δ QALY	ICER
Dapagliflozin	£27,968.76	13.2			
Pioglitazone	£26,070.77	13.11	-£1,897.99	-0.0908	£20,896
SU	£26,551.38	13.18	-£1,417.38	-0.0227	£62,347
DPP4s	£27,883.04	13.19	-£85.72	-0.0113	£7,603

The QALYs and costs for dapagliflozin are similar to the pooled flozins results (table 31 in the AG report). The similarity in results is explained by the CDM design: monotherapy treatments are discontinued at intensification to the second sequence. This means that the effect of monotherapy (e.g. the SGLT2s) impacts only a couple of years out of a lifetime. As the time on the monotherapy and subsequent effect is short, small differences in efficacy do not translate to drastically different ICERs.

In contrast, the AG model continues the original compound for the whole modelling duration with new treatments being added in rather than switching. As such, the efficacy differences between treatments are carried over and have a much greater impact on the ICERs compared with the CDM. **Notably, any inaccurate results in the NMA are likely to have a significant effect on the demonstration of cost-effectiveness.**

- This approach to intensification is a fundamental difference between the AG analysis and the AstraZeneca analysis. It is debatable as to whether the most appropriate approach is to isolate cost-effectiveness in a single position or to model the clinical pathway (which will vary depending on the initial therapy)
- As described in the scoping discussions, and submission, we believe that the most appropriate positioning of SGLT2s in clinical practice is for patients who are unsuitable for an SU. As such, adding an SU as an intensification treatment would be inappropriate in clinical practice. Indeed, a clinical expert indicated that they would only use an SGLT2 if gliclazide were not appropriate; and therefore the next step of intensification may be to try a GLP1: whereas if a sulfonylurea is used at first line monotherapy, then the clinician may add a DDP4 or an SGLT2
- AstraZeneca recognise that intensification to NPH following monotherapy (as in the AstraZeneca model) may not fully reflect clinical practice: however believe it allows a fairer comparison between the monotherapies than comparing the intensification process described above

One other difference between the AstraZeneca and AG models is the assumptions in modelling weight. The AG recognised that weight is important for modelling the evolution of diabetes and therefore explored different scenarios (p176). The next section describes why some scenarios seem less clinically relevant than others.

2.2 A number of scenarios around weight, presented by the assessment group, are clinically implausible

The AG present six scenarios to model the impact of weight on QOL; however the assumption that weight does not have an impact on the model, and that weight rebounds after one year are not considered plausible clinical scenarios. Clinicians rather expect durability of weight loss when using an SGLT2 (Clinical Expert Opinion 2015).

Given the AG recognise the importance of weight loss (page 22-23) it does not seem appropriate to assume that weight has no impact on QOL, and the rationale for including this scenario is not clear. Weight loss has been shown to have a substantial impact on QOL in a range of studies and is associated with improved well-being [13], SF-12 Physical and Mental Component Summary scores and depression [14], and improvements in physical health, self-esteem, and overall HRQOL [15]. A recent review also identified a range of papers reporting utility values for weight: (disutility of -0.002 to -0.080) [16]. Additionally:

- NICE clinical guidelines (CG87) recognise the importance of weight loss by recommending body weight loss of 5-10% for overweight diabetic patients
- The impact of weight on QOL has been previously agreed as an important consideration by experts, and included in NICE technology appraisals for dapagliflozin (TA288)

Secondly, AstraZeneca do not consider it a plausible clinical assumption that weight loss rebounds after one year. This was also confirmed by a clinician who expects durability of weight loss based on trials and clinical experience:

- Data in the monotherapy study (Ferrannini *et al.*) demonstrated a sustained clinically meaningful reduction in weight with dapagliflozin over two years. At 102 weeks dapagliflozin monotherapy had a significantly greater reduction in weight compared to placebo + low dose metformin (-3.94 kg vs. -1.34 kg; P=0.016)[4, 17]
- Moreover, weight loss for SGLT2s has been demonstrated to be maintained over four years. Del Prato *et al*., found weight reduction with dapagliflozin (add on to metformin) at 52 weeks was maintained up to 208 weeks, whereas weight gain with glipizide plus metformin at 52 weeks remained stable at 208 weeks (−3.65 vs. +0.73 kg): difference −4.38 kg (95% CI: −5.31, −3.46)[18]

Overall, a number of scenarios in the AG cost-effectiveness analyses do not appear to appropriately account for clinical evidence on the impact and duration of weight loss. Excluding the less clinically relevant scenarios results in all flozins being cost-effective versus DPP4s: base case ICERs range from £2590 to £19,787 across the flozins versus sitagliptin.

We request that the scenario where weight has no impact on QOL is not included in future reports, or is highlighted as a clinically implausible scenario. The scenarios in which weight rebounds after one year are highly conservative: a further scenario where weight rebounds after two years may also be considered by the committee.

3 SGLT2s should be recommended where monotherapy treatment with metformin, SUs, and pioglitazone is inappropriate

As noted above, there appears uncertainty in the cost-effectiveness of SGLT2s versus pioglitazone or SUs. However, there is recognised remaining unmet need for patients who may be at risk of hypoglycaemia or additional weight gain (and are therefore unable to take such treatments).

Based on the clinical effectiveness in reducing hyperglycaemia, in addition to the benefits of "some reductions in blood pressure and weight", as stated by the AG, the flozins therefore seem an appropriate option for these patients. The AG report concludes that SGLT2s offer a cost-effective treatment option compared to DPP4s, and note that SGLT2s have the added benefit of weight loss. We anticipate this to be a very small population in monotherapy, whereby IMS data (MAT [moving annual total] Aug 2015) indicates that, over a year, less than 2000 prescriptions were written for the flozins: much less than for SUs or pioglitazone (Table 4).

Crucially, this positioning is also in agreement with current clinical practice; a clinician suggested they only use SGLT2s in monotherapy for patients unable to take both metformin and SUs (they do not prescribe pioglitazone due to the adverse effects).

Although repaglinide was included in the scope of the MTA, there is very little use of repaglinide in clinical practice (Clinical Expert Opinion 2015). Data additionally indicates there have been no prescriptions for repaglinide in monotherapy over the last year (IMS, MAT Aug 2015). Further, while repaglinide was included in the recent NICE type 2 diabetes draft guideline update, this suggestion was criticised: for example O'Hare *et al.,* judged repaglinide to have significant limitations, including the dosing of three times daily, increased risk of hypoglycaemia and weight gain [19]. AstraZeneca subsequently believe that repaglinide would not be an appropriate treatment option in monotherapy.

In conclusion, on balance of the report and the clinical and cost-effectiveness evidence presented, AstraZeneca believe that SGLT2s as a class should be recommended as an option for patients who are intolerant or unsuitable for monotherapy with metformin, SUs, or pioglitazone.

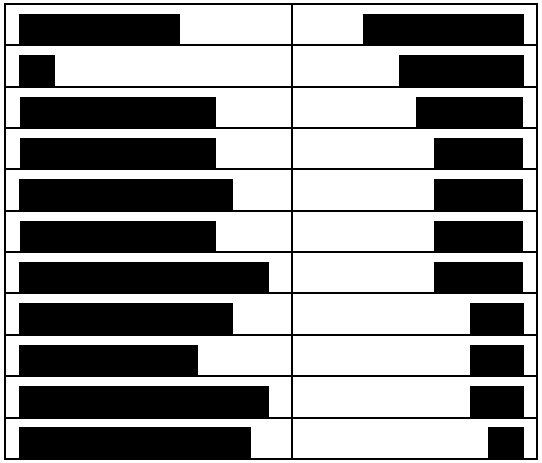
Table 4 below highlights some of the text specific responses AstraZeneca to the report, and Table 5 presents a response to some of the key questions posed by the assessment group.

Table 4: AstraZeneca proposed alterations to the report

Page	AG comment in report	AstraZeneca comment/ description of proposed amendment
11	If drug treatment is required to control high blood glucose levels when metformin cannot be used, the other options suggested in the NICE guideline include; - Sulfonylureas - Pioglitazone - The DPP4 inhibitors - Repaglinide	Although repaglinide was included in the recent draft of the guideline update, there was large clinical criticism to this suggestion. In response to the recent draft guidelines O'Hare 2015 judged repaglinide to have significant limitations, including the dosing of three times daily, increased risk of hypoglycaemia and weight gain. In addition, there is very little use of repaglinide in clinical practice (Clinical Expert Opinion 2015). Data additionally indicates there have been no prescriptions for repaglinide in monotherapy over the last year (IMS, MAT Aug 2015).
11	DPP4s have the advantage of being weight neutral.	Although weight neutrality of DPP4s is an advantage over current treatments in monotherapy, it should be clarified that this is not a benefit versus SGLT2s, which are able to reduce weight.
14	The reductions in HbA1c with pioglitazone and gliclazide were…	We suggest the AG also includes the reduction in HbA1c with sitagliptin
17	Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin	This statement is unclear as to what this is referring to, particularly given the earlier comments on cost. It should be clarified that this is over a lifetime horizon, when used as monotherapy Additionally, it is not clear why there is a discrepancy between these treatment costs (page 62). Please clarify why this may be the case
20	Plain English summary: However they are much more expensive than older drugs such as gliclazide and pioglitazone	AstraZeneca propose the addition of 'and are a similar cost to DPP4s'; however we are surprised that the assessment group have chosen to highlight cost in the opening paragraph when the focus of NICE is cost-effectiveness
20	Plain English summary: If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin…	As described above, this is an implausible scenario, and should not be included in the summary
20	Plain English summary: As a consequence, the flozins represent very poor value for patients as a whole compared pioglitazone, repaglinide and gliclazide	This text seems emotive and is unspecific. Suggested alteration: As a consequence, the flozins represent poor value for patients as a whole compared pioglitazone and gliclazide *in the monotherapy setting*
20	The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins. But if a patient's day to day living is affected …	As described above, this statement is misleading; we request that the text is redacted from the report, and the summaries should clarify that ICERs are based on limited available data with differences in study characteristics.

<table>
<tr><th colspan="3">Background</th></tr>
<tr><td>22</td><td>Progression [of diabetes] may be slow.</td><td>Note: progression may also be rapid.</td></tr>
<tr><td>24</td><td>Pioglitazone is recognised as causing weight gain but does not cause hypoglycaemia. Metformin does not cause either weight gain or hypoglycaemia.</td><td>For completeness, we suggest that heart failure, fractures, oedema, and risk of bladder cancer associated with pioglitazone are also mentioned</td></tr>
<tr><td>25</td><td>The first draft recommended that patients who cannot take or tolerate metformin should take repaglinide</td><td>Please note this was strongly criticised by commentators and the final version of the guideline is not yet released</td></tr>
<tr><td>29</td><td>[SUs] But they are very cheap, and have been used for so long that all their adverse effects are known.</td><td>It is worth noting the additional blood glucose monitoring and costs associated when patients are on tablets with a risk of hypoglycaemia, including sulfonylureas. The DVLA guidance requires monitoring of blood glucose at least twice daily and at times relevant to driving [20]</td></tr>
<tr><td>31</td><td>Despite its adverse effects, pioglitazone is still widely used, though its use may be declining, with new initiations falling in recent years. The Health and Social Care Information Centre Report gives figures for items prescribed in 2013/143

<table><tr><td>Table 1 Prescriptions 2013/14
Metformin</td><td>18,100,000</td></tr><tr><td>Sulfonylureas</td><td>8,400,000</td></tr><tr><td>Sitagliptin</td><td>2,020,100</td></tr><tr><td>Pioglitazone</td><td>1,408,600</td></tr><tr><td>Linagliptin</td><td>329,400</td></tr><tr><td>Vildagliptin</td><td>173,200</td></tr><tr><td>Repaglinide</td><td>83,800</td></tr></table></td><td>More relevant data for this report may be the prescribing of treatments in a monotherapy setting;

 
(Source: Patient data, IMS Information Solutions UK Ltd, MAT Aug 2015)</td></tr>
<tr><td>32</td><td>Box 1: CG87</td><td>Please clarify that in the most recent draft of the guidance (June 2015), the DPP4s had a more flexible positioning, [redacted] longside the generics</td></tr>
<tr><td>34</td><td>The amount blocked appears to vary amongst the different drugs, with dapagliflozin 10mg blocking only about a third of reabsorption.</td><td>This text may be misinterpreted to infer that the reabsorption of dapagliflozin is inferior to the other flozins: it should be clarified that the reference in fact states “none of these SGLT2 inhibitors are able to inhibit >30–50% of the filtered glucose load”.
Please note, one reference was in healthy volunteers</td></tr>
<tr><td>35</td><td>Box 2</td><td>It should be clarified that a partial update of TA288 is scheduled: due to</td></tr>
</table>

		additional available data NICE will review the triple therapy regimen. This indication has already been accepted by the SMC
36	Renal impairment	Please clarify the following: - Canagliflozin or empagliflozin should not be initiated in patients with GFRs < 60 ml/min. For patients on canagliflozin 300 mg or empagliflozin 25 mg with GFRs below 60 ml/min, dose should be reduced for o 100 mg and 10 mg respectively. - Initiation of empagliflozin is not recommended in patients over 85 years - A 5 mg dose of dapagliflozin is also available; this dose is recommended as a starting dose for patients with severe hepatic impairment
36	Where should SGLT2 inhibitors fit into the therapeutic pathway? Factors to be considered include:	Hypoglycaemic events should also be included as a factor to be considered
Chapter 2: clinical effectiveness		**Please clarify the following:**
48	Kaku and colleagues 2014 did not define hypoglycaemia.	Kaku 2014 defined hypoglycaemic events as: symptoms with confirmed plasma glucose <3.5 mmol/L (<63 mg/dL). Major hypoglycaemic episodes were counted as plasma glucose value <3 mmol/L (<54 mg/dL)
54	Ferrannini 2010 did not report on lipid levels.	Total cholesterol changed by +1.10 **mg/dl** in the dapagliflozin 10 mg am and + 0.63 **mg/dl** in the dapagliflozin 10 mg pm dose (Page 378 of CSR)
55	The definition of hypoglycaemia varied amongst trials with most using 4.0 mmol/l as the threshold, which seems a little high, when the lower limit of normal is 3.5 mmol/l	Please note, all three dapagliflozin trials used the 3.5 mmol/l limit for a hypoglycaemic minor event
58	We believe there are errors in the numbers reported for UTIs in Table 4. Please note this may also impact the text on page 66, and inputs into the AG model.	Please adjust **Ferrannini 2010/Bailey 2015** results to: **Dapa 10 mg**: 24 weeks: 4/70 102 weeks: 6/70 102 weeks (men): 2/34 (*correct in report*) 102 weeks (women): 4/36 **Placebo**: 24 weeks: 3/75 102 weeks: 3/75 102 weeks (men): 0/31 (*correct in report*) 102 weeks (women): 3/44 Please adjust **Kaku 2014** results to: **Dapa 10 mg**: 24 weeks: 2/88 (*correct in report*) **Placebo**:

		24 weeks: 2/87 <u>Please adjust **Ji 2014** results:</u> **Dapa 10 mg**: 24 weeks: 5/133 **Placebo**: 24 weeks: 4/132
65	Dapagliflozin has been shown to have a dose-dependent effect on glycosuria in patients with T2DM.	Please clarify, this study was conducted in healthy subjects.
71-77	EMPA-REG	Considering that the section that includes the EMPA-REG ends in a sentence stating the 'results are not applicable to people starting monotherapy with empagliflozin' it is our position that these results should not be considered in the monotherapy indication. [redacted]
87 vs. 169	Table 9 on page 87 shows a mean difference in HbA1c from baseline of -0.59 (-0.70 to -0.48) for dapagliflozin This differs greatly from table 52 on pg 169, and in the model (μ = -0.704), while results for empa and cana are similar to pg 87.	Please could the AG clarify why there are such differences
102	The weight gain after adding gliclazide to a SGLT2 inhibitor may be different – it may only restore weight to the baseline before weight loss on the flozin.	Strojek *et al.,* demonstrated that when dapagliflozin is added to sulfonylurea monotherapy, there is a significant improvement in HbA1c (-0.13% vs -0.82%) and in weight reduction (-0.72 kg vs. -2.26kg). This suggests that an SGLT2 in combination with an SU is still likely to have a beneficial impact on the patient's

		weight [21]
103	So similar proportions in each group had to move to rescue therapy, implying no difference in durability	This is not correct. At week 208 the coefficient of failure was significantly lower in the dapagliflozin treatment group than glipizide (0.19 [95% CI 0.12, 0.25] vs. 0.61 [95% CI 0.49, 0.72]), indicating a lower rate of increasing HbA1c when treated with dapagliflozin
103	For the effects of adding sitagliptin we have two useful trials with HbA1c baseline 7.7 and 7.8% which reported reductions in HbA1c of 0.67% and 0.79% (Scott 2007, Nauck 2007) giving a mean of 0.73%.	Please clarify: these are add on to metformin, active controlled trials.
Chapter 4: Clinical effectiveness from manufacturers		
104	Lilly now market a combination tablet with empagliflozin and linagliptin.	Please note that the empagliflozin and linagliptin combination is only currently marketed in the US
106 + 109	AG disagrees with assumption that the classes of drugs can be grouped	As described in section 1, there are inherent differences between the SGLT2 trials, and limited evidence available in monotherapy. Appendix 2 presents updated forest plots, denoting the individual agents used in each trial, to allow for a more informed evaluation of the distribution of effects for each agent. The decision to lump treatments depends on the clinical assessment that treatments have similar effects (this has previously been considered in dual therapy: see Section 4.4 of the empagliflozin TA336 guidance). Indeed, page 109 states the 'lumping' of evidence into treatment classes may have overcome the issue of sparse evidence networks or zero values.
106 117	AG disagrees with assumption that when monotherapy fails NPH will be used. The AG sequence is Dapagliflozin 10mg > dapagliflozin + gliclazide > dapagliflozin + gliclazide + NPH	See section 2.1 above
Chapter 5: Cost effectiveness		
180	the AG calculate the baseline utility by implementing the -0.0061 quality of life decrement when the patient BMI rises above 25mg/m2. The mean BMI from UKPDS is 27.7 hence the calculation is 2.7*0.0061 which is added to the baseline utility of 0.785	This may be a typo: as it is a disutility we would assume that it would be 2.7*(-0.0061), then it will be added (as a negative value) to the baseline utility equalling 0.7685 and not 0.8015 as assumed in the report.
178	The AG mentioned that the baseline BMI from the NICE draft guideline is 31.6kg/m2	In this case should we use the formula above with the BMI from the actual baseline in the UK of 31.6kg/m2? This would be 6.6*(-0.0061)= 0.6763 Also in table 49 with the NICE CG baseline characteristics, the BMI presented is 31.9kg/m2

AG Model	In the model, the utility input the Bagust effect of -0.0061 but we didn't find an input of +0.0061 associated with weight loss	Please confirm how the weight is modelled and if this works two ways, for weight gain and loss. It is unclear what assumptions are being applied in the AG model for extrapolation of weight effect (i.e. maintenance of weight effect and weight regain) over time. It would be helpful to see a plot on the average HbA1c and weight progression of the patients simulated in the model
	The model uses a baseline HbA1c value of ~8.4.	A large standard error is applied as patients are simulated with baselines varying from HbA1c 6-12; please note this may not represent current practice

Table 5: AstraZeneca response to AG questions in the report

Page	AG comment in report	AstraZeneca response
Chapter 4: Clinical effectiveness from manufacturers		
106 - 107	One problem with the AstraZeneca NMA is the data reported in the forest plot (Figure 4.6) for the pooled sulfonylureas, which include glibenclamide, glimepride, glipizide and one gliclazide trial. The net effect size in HbA1c lowering is 0.12%...	The error was only in the graphical presentation of the forest plots so there was no impact on the NMA. The forest plots were regenerated, correcting a previous error (please see Appendix 3).
	the primary analysis included the rescued patients and this is reflected in the one of the analyses, which reported a 0.09% reduction in HbA1c. (It is not clear where the rise of 0.03% in the AstraZeneca forest plot comes from.)	Please refer to updated forest plots in Appendix 3. The 0.09% reduction in HbA1c reported in the text was for change at 52 weeks. The data extracted for the AstraZeneca NMA looked at the primary endpoint at 26 weeks, and data was digitized from Figure 3a in Rosenstock *et al.,* (those patients who have a baseline and at least one post-baseline HbA1c assessment and no major protocol violations).
	It is not clear where the 0.1% figure used in the AstraZeneca meta-analysis comes from, though we note that the HbA1c difference between glimepiride and pioglitazone at 3 months as 0.1%.	The estimate of 0.1% represents the difference between glimepiride and pioglitazone arms at 6 months (not glimepiride and placebo); this was incorrectly labelled in the original forest plot. Please see updated plots in Appendix 3.
	The AstraZeneca forest plot reports a reduction in HbA1c of 0.14% compared to placebo. There was no placebo group in Erem 2014 which compared gliclazide with pioglitazone and metformin.	We confirm that there is no placebo group in Erem. Please refer to updated plots in Appendix 3.
106	N/A	Please note, in checking the NMA model, we have found an error in the results for hypoglycaemic events. Please see appendix 4 for updated results. We have therefore also re-run the base case analyses for DPP4, TZD and SU versus the grouped flozins to assess the impact on the ICER. There was very little impact on the results, with the main change being an increase in the ICER

		versus SUs from £52,047 to £59,013 (see appendix 4).
108	It specifies that vague priors were used for unknown parameters, however no details were provided as to the distributions or link functions used in the models.	For both continuous and binary endpoints, the NICE DSU code was used. Vague priors were: -Treatment effects had a vague prior of dnorm(0,.0001) -between-studies SD had a vague prior of dunif(0,5) (for RE models) Binary outcomes were modelled using the logit link.
108	Although it is not clear which treatment was the reference treatment in the network meta-analyses, results are presented for comparisons of the treatment classes with both placebo and SGLT2 only.	Placebo is the reference treatment throughout the analysis. In the tables, we realize that the term 'reference treatment' was used to label the treatment against which the relative effect measures were being compared to.
109	lacked details concerning the prior distributions and link functions used, its assessment of autocorrelation in MCMC models and sensitivity analyses concerning the elements of the models themselves (e.g. prior distributions, link functions and priors for parameters).	The analyses were run using a burn-in of 20,000, 100,000 iterations, and a thin parameter of 10 (i.e. retaining every tenth parameter in each of three Markov chains) to reduce the autocorrelation. Monte Carlo error was assessed (which reflects number of iterations and degree of autocorrelation) and was consistently less than 5% of the posterior standard deviation for all parameters of interest, in all models.
Cost effectiveness		
119	Only one paper was identified that addressed the cost effectiveness of flozin monotherapy in the patient group	A poster by Charokopu *et al.,* was also published last year on dapagliflozin monotherapy vs. DPP4 [22]
142	As far as the AG is aware the corollary of these has not been made available for the equations underlying the UKPDS OM2 model. As a consequence, it is not clear how the CDM of the AstraZeneca submission has implemented the probabilistic modelling.	Prior to UKPDS group making the bootstrapped regression coefficients available for the UKPDS OM1 equations the Cardiff model would sample risk probabilistically by using the published standard errors associated with each respective coefficient. This ignored information on covariance and the availability of the bootstrapped coefficients overcame this limitation. Bootstrapped coefficients for the UKPDS OM2 regression coefficients are currently available; consequently, only standard errors (ignoring covariance) are utilized.
142	During the STA of dapagliflozin the ERG noted various errors in the CDM implementation formulae for the evolution of the risk factors, which were subsequently corrected during the course of the STA. The AG assumption is that within the AstraZeneca submission these errors have been corrected.	This assumption appears correct. The following changes were incorporated: ○ [redacted]

		[redacted]
143	The submission did not present any analysis of model convergence over the number of patients modelled. The CDM only permits pair wise comparisons. As a consequence, the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion.	This is correct; the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion. (See below in response to pg 216 for comment on convergence)
144	The submission does not appear to state what the baseline prevalence of the complications of diabetes was. The submitted electronic model sets these to zero.	That is correct. The complication history was assumed to be zero. Since the occurrence of complications is not a model driver, the effect is negligible.
145	The AG does not know how these figures for "intensified NPH" were obtained. Usually if NPH was insufficient, short-acting insulin would be added at meal-times	Source for HbA1c and weight effect NPH: 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. 81, 184–9 (2008) Source for HbA1c effect intensified NPH: Waugh, N. et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol. Assess. 14, 1–248 (2010). Source for weight effect intensified NPH: Montanana et al. 2008, chosen as most recent study reporting weight effect
146	A patient is modelled as intensifying treatment, first to NPH and then to intensified NPH, when their HbA1c breaches the 7.5% intensification threshold. The AG assumption is that the monotherapies are withdrawn at treatment intensification, but this is not explicit within the Astrazeneca submission	This is correct..
	Patients may also discontinue due to adverse events. The AG was unable to identify what was assumed for these patients: whether they switched to an alternative monotherapy and if so which, or whether they intensified to NPH insulin.	Patients switch to next treatment in case of discontinuation.

<table>
<tr><td></td><td>The costs of the complications of diabetes in the first year and for subsequent years for blindness and amputation were based upon the UKPDS84. This is the same source as the AG though the AG arrives at somewhat lower values. … the source of the discrepancies is unclear.</td><td>Costs for blindness and amputation have been based on the UKPDS84 (cost year 2012). To inflate these costs to 2014, the hospital & Community health services (HCHS) index has been used.
Index value in 2012: 282.5
Index value in 2014 290.5</td></tr>
<tr><td>148</td><td>AG calculations suggest that the UKPDS84 average inpatient costs and outpatient costs for those without any of the modelled complications have not been included within the AstraZeneca modelling. If this is the case it would be a quite serious omission, and would tend to bias the analysis in favour of the more effective treatment.</td><td>It seems that inpatient and outpatient costs have not been included for patients without complications. However, the difference in life years between the treatment arm and the control arm is minor (-0.010 for TZD to 0.004 for DPP4). This means that patients in the treatment arm live at most 0.004 years longer, resulting in an additional 0.004 times the annual inpatient/outpatient costs compared to the control arm. The impact seems negligible.</td></tr>
<tr><td></td><td>Table 5.10 of the AstraZeneca submission also does not include a cost for fatal IHD events despite these being within the UKPDS84 and seeming to be associated with deaths in the UKPDS82 and the UKPDS OM2.</td><td>The CDM does not support cost inputs for fatal IHD, only for non-fatal IHD. As a consequence, costs for fatal IHD are automatically set to zero. However, the difference in fatal events between the treatment arm and control arm is minor (-0.00002 for SU to 0.00003 for DPP4), so the impact on results seems negligible.</td></tr>
<tr><td></td><td>For reasons that are unclear, AstraZeneca chose to revert to the costs of the UKPDS65 for the ongoing costs among those with a history of IHD, CHF and stroke, and probably MI as well.</td><td>It is unclear what this means. The history of IHD, CHF and stroke are set on zero.</td></tr>
<tr><td></td><td>ESRD was costed using the estimate of Baboolal et al. for continuous ambulatory peritoneal dialysis. Previous NICE assessments have also used this reference, though have also tended to use the higher cost estimates within Baboolal et al for hospital haemodialysis. Astrazeneca argued that the use of the peritoneal dialysis cost was conservative</td><td>ESRD events are more frequent in the treatment arm than the control arm for TZD and SU, so the lower ESRD price is <u>not</u> a conservative approach here. However, the difference is minor, so the impact is not expected to be considerable.</td></tr>
<tr><td>152</td><td>The scenario analyses around adverse events and discontinuations for the comparison with pioglitazone were reported as having the same values as the corresponding analyses for sitagliptin, so appear to be typos.</td><td>This is a typo in the report (p 79, table 5.14) the model results for pioglitazone should read:
<table>
<tr><td>No discontinuation</td><td>£ 1,901</td><td>0.1000</td><td>£ 19,001</td></tr>
<tr><td>No disutilities for AE</td><td>£ 1,912</td><td>0.0958</td><td>£ 19,961</td></tr>
</table></td></tr>
<tr><td>216</td><td>A concern with the Janssen and the Astrazeneca model is that there has been little presented on model convergence. The AG has relied upon the work of the draft NICE CG for diabetes, which resulted in deterministic model runs having 50,000 patients simulated with 1,000 inner loops for each patient to reduce the Monte-Carlo error. The draft NICE CG for diabetes could be read as suggesting that only 100 inner loops are necessary for convergence, but even this seems to be somewhat more model runs that any of the company submissions. As a consequence,</td><td>Please find below results for 500 and 1000 runs (using the new probabilities for hypoglycaemic events). Although more than 100 runs may have been appropriate, the ICER is improved whether 500 or 1000 runs are used:
<table>
<tr><td></td><td>Previous ICER (100 runs)</td><td>ICER (500 runs)</td></tr>
<tr><td>DPP4</td><td>6,125</td><td>3,995</td></tr>
<tr><td>TZD</td><td>20,639</td><td>19,513</td></tr>
<tr><td>SU</td><td>59,013</td><td>51,609</td></tr>
</table></td></tr>
</table>

	the AG is uncertain whether the company models have reliably converged	
218	Note that the baseline HbA1c of 7.5% of Astrazeneca is based upon the treatment intensification threshold rather than the Astrazeneca NMA, which had a mean of 8.2%. The Astrazeneca proportion who smoke has been taken from the electronic model, where it is ambiguous whether this is the proportion at diagnosis, the proportion at baseline, or both.	The proportion who smoke represent the proportion at diagnosis and has been derived from a 52-week NMA of RCTs of anti-diabetic agents added to metformin: Oxford Outcomes. *Network Meta-Analysis of Anti-Diabetic Agents in Type 2 Diabetes Mellitus: Metformin add-on therapy*. 139 (2011).
219	Given the recentness of the diagnosis of diabetes, the companies and the AG all suggest low prevalences of complications at baseline. But Astrazeneca assumes these to be zero.	No scenario was performed on history of complications. In the Metformin + Dapagliflozin STA, this analysis has been done. However the prevalence of complications is not an important driver of the model, so the impact is expected to be minor.
223	All the analyses have used the CODE-2 quality of life decrement for BMI above 25kgm-2. Astrazeneca may not have restricted this to when the patient BMI is above 25kgm-2, but given baseline BMIs the impact of this will not have been large. All analyses also rely upon the estimates of Currie et al (2005) for the quality of life impacts of hypoglycaemic events, though again it appears that Astrazeneca may have applied the coefficient for non-severe hypoglycaemia to the event rate rather than to its logarithm.	From section 5.7.3 of the original submission for TA288 is states that **"**The resultant disutility is calculated as follows: - Severe event (binary variable: if ≥1 event then [1], else [0]) * 0.047 + number of symptomatic events * 0.0142 + number of nocturnal events * 0.0084" If this is how hypo related disutility was calculated in the submission (rather than the model's in-built function) then no log transformation is required- the AG have not read all the Currie 2006 manuscript. The values of 0.0142, 0.0084 and 0.047 are taken directly from the text: - "Regarding the association between fear of hypoglycaemia (HFS) and the EQ5Dindex, a difference of one unit on the HFS would result in a change in the EQ5Dindex of 0.008 units, whereas a difference of 5.881 units on the HFS would result in a change of 0.047 units on the EQ5Dindex. Similarly, each symptomatic hypoglycaemic episode yields a 0.0142 (1.42%) decrement in utility, while each nocturnal episode is associated with a 0.0084 (0.84%) utility reduction." As the log transformation referred to in the Currie manuscript refers to the regression equations only (used to derive the above numbers) the AG's concern is unwarranted. If the submission used the Cardiff Model's in built equations from the Currie paper, then the log transformation is undertaken anyway (and applied to number of symptomatic events)

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Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes [ID756]

AstraZeneca Response: Appendices

Date of response: 9th November 2015

Appendix 1: Caterpillar plots of random effects model

Figure 1. Caterpillar plot of random effects model for mean change in HbA1c (%) in RCTs comparing each treatment versus placebo

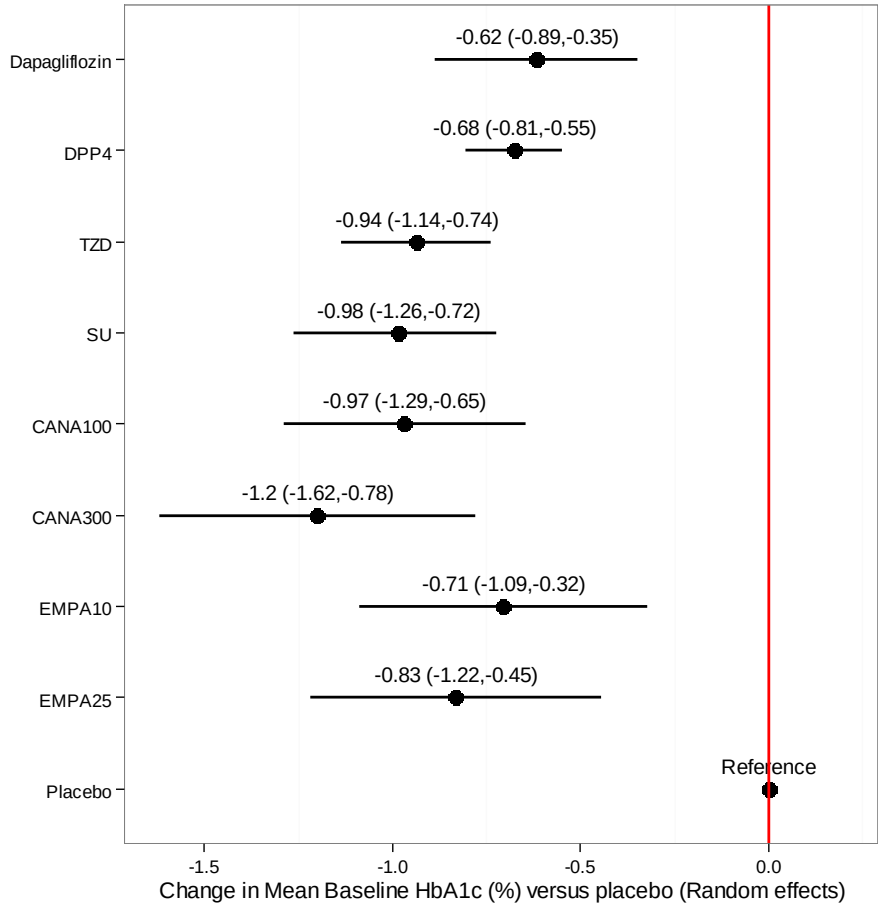
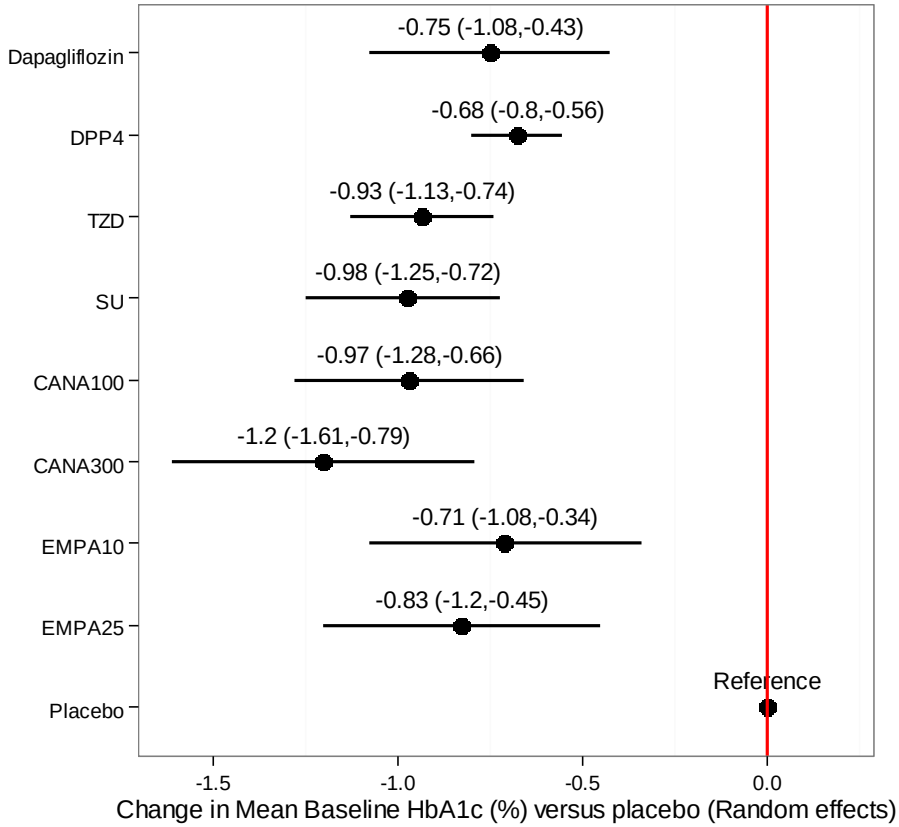


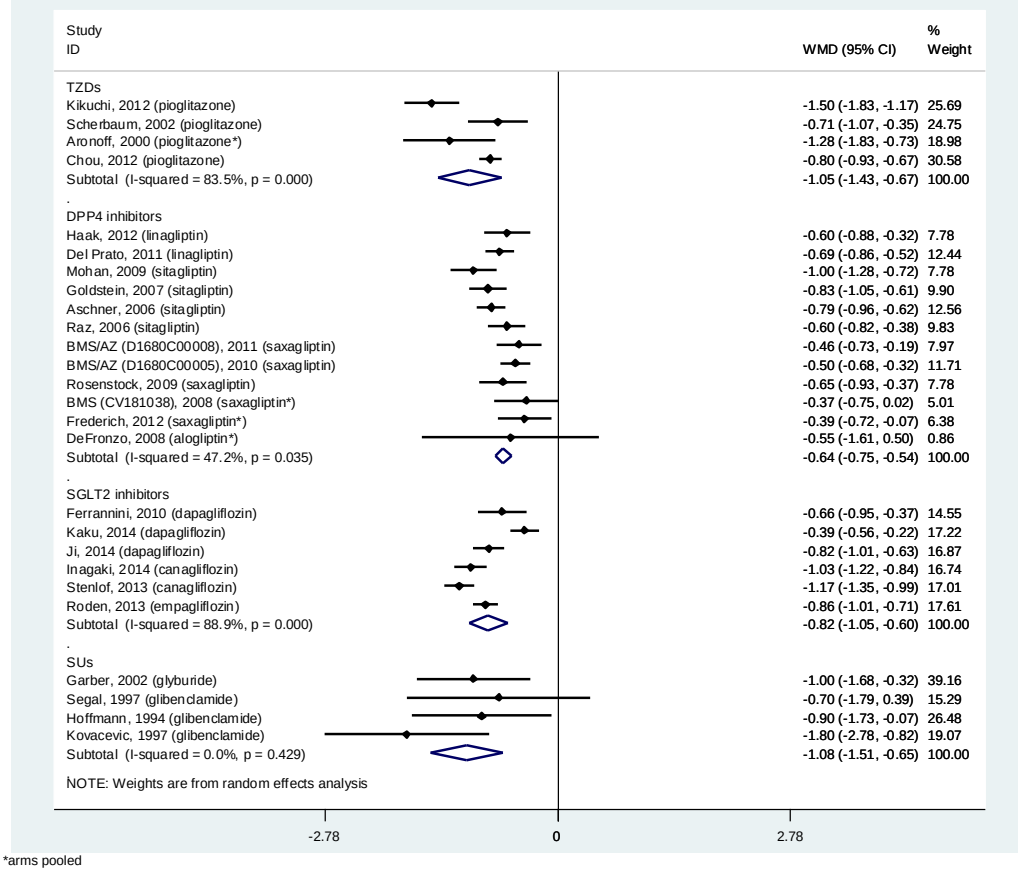
Figure 2. Caterpillar plot of mean HbA1c change from baseline, random effects model (All vs. placebo). Sensitivity analysis excluding study by Kaku *et al.*



Appendix 2: Updated forest plots

Below are updated and additional forest plots showing the pair wise comparisons for HbA1c, weight, systolic blood pressure, and hypoglycaemia. The placebo-controlled trials as well as active-controlled trials are shown, and active ingredient is noted, to support assessment of the heterogeneity of treatment effect within the class, as it relates to pooling of agents.

Figure 3 Pairwise comparisons of mean change in HbA1c (%): placebo-controlled trials



*arms pooled

Figure 4 Pairwise comparisons of mean change in HbA1c (%): active-controlled trials

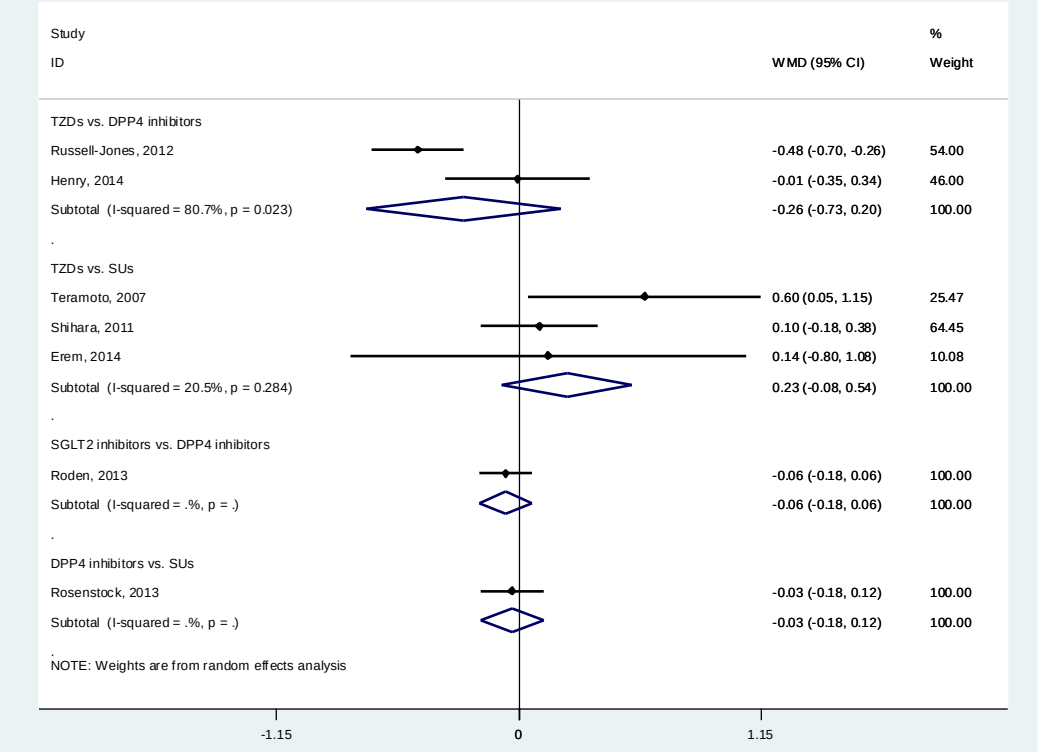


Figure 5 Pairwise comparisons of mean change in weight (kg): placebo-controlled trials

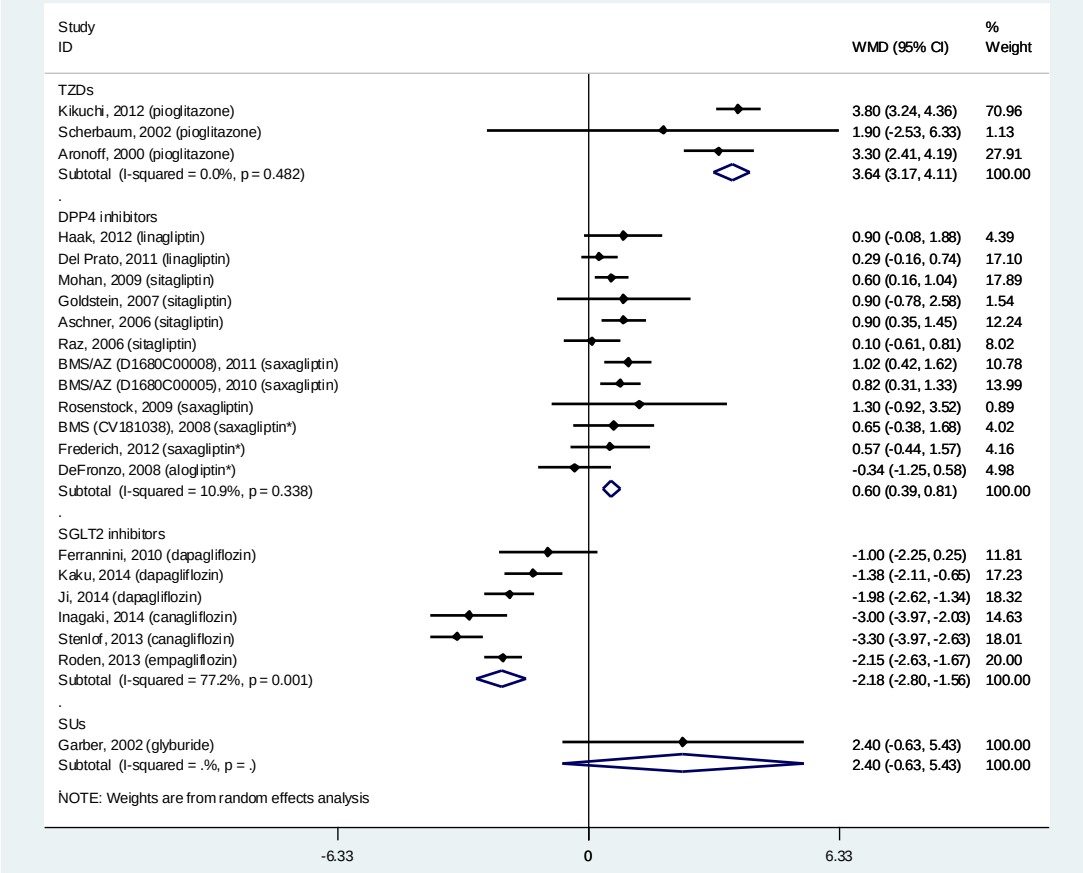


Figure 6 Pairwise comparisons of mean change in weight (kg): active-controlled trials

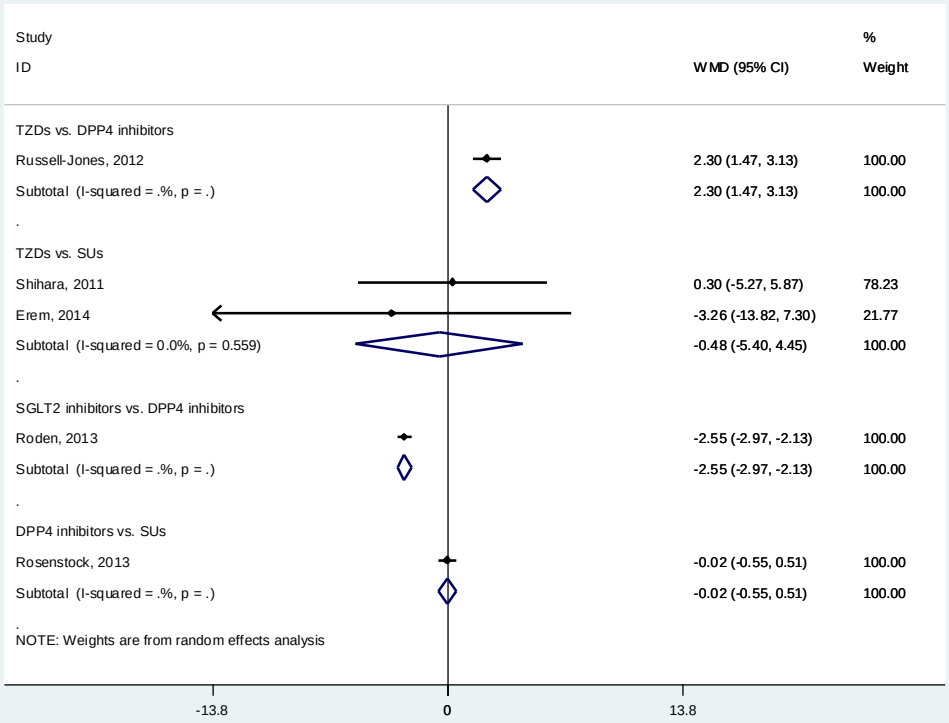


Figure 7 Pairwise comparisons of mean change in SBP (mmHg): placebo-controlled trials

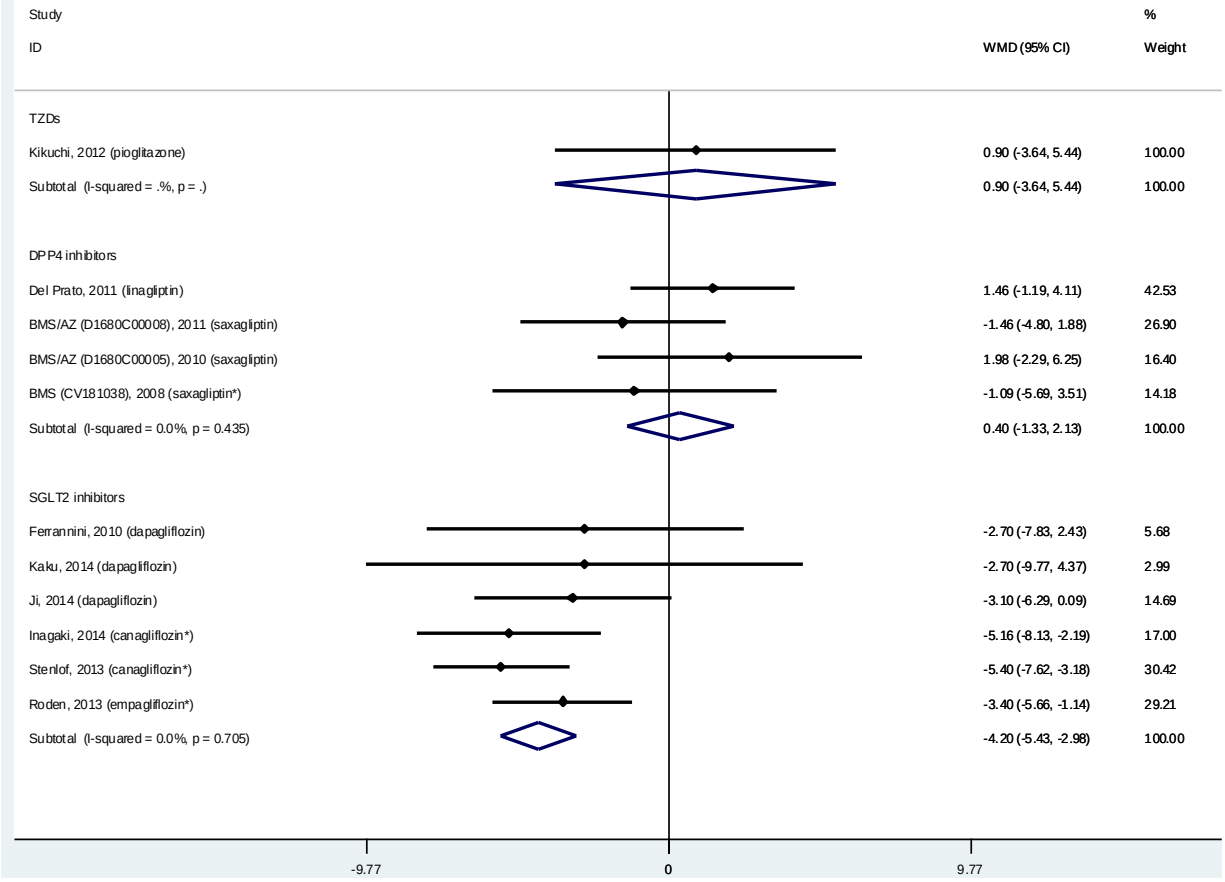


Figure 8 Pairwise comparisons of mean change in SBP (mmHg): active-controlled trials

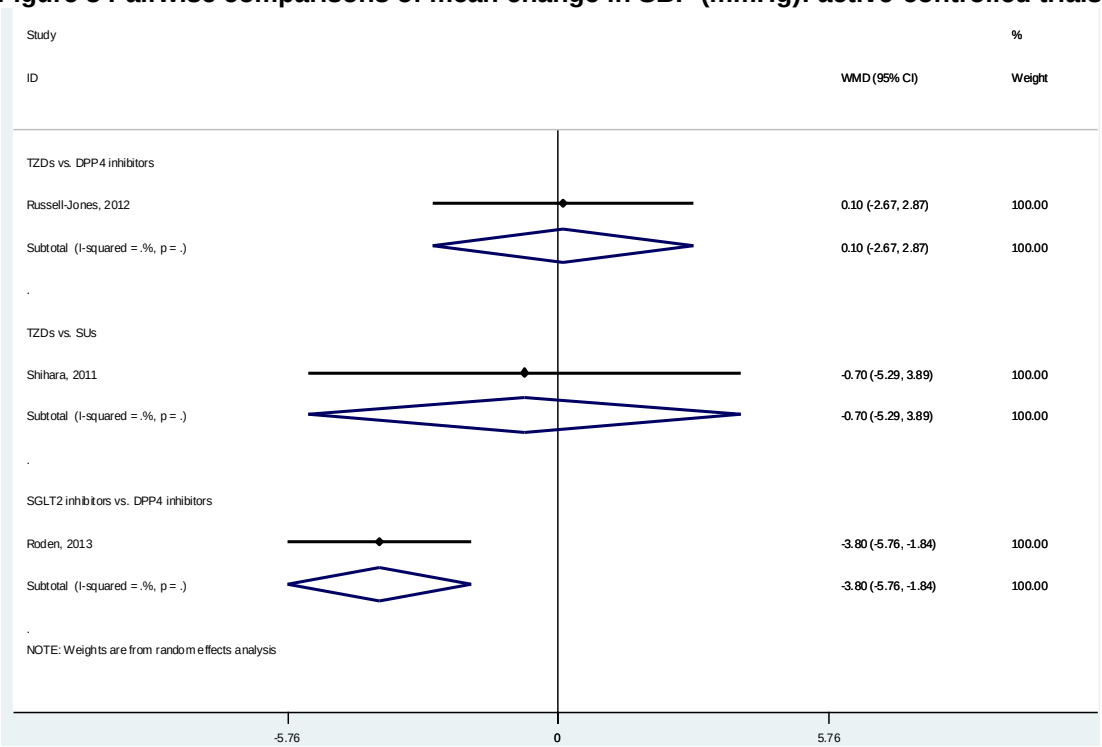


Figure 9 Pairwise comparisons of hypoglycaemia: placebo-controlled trials

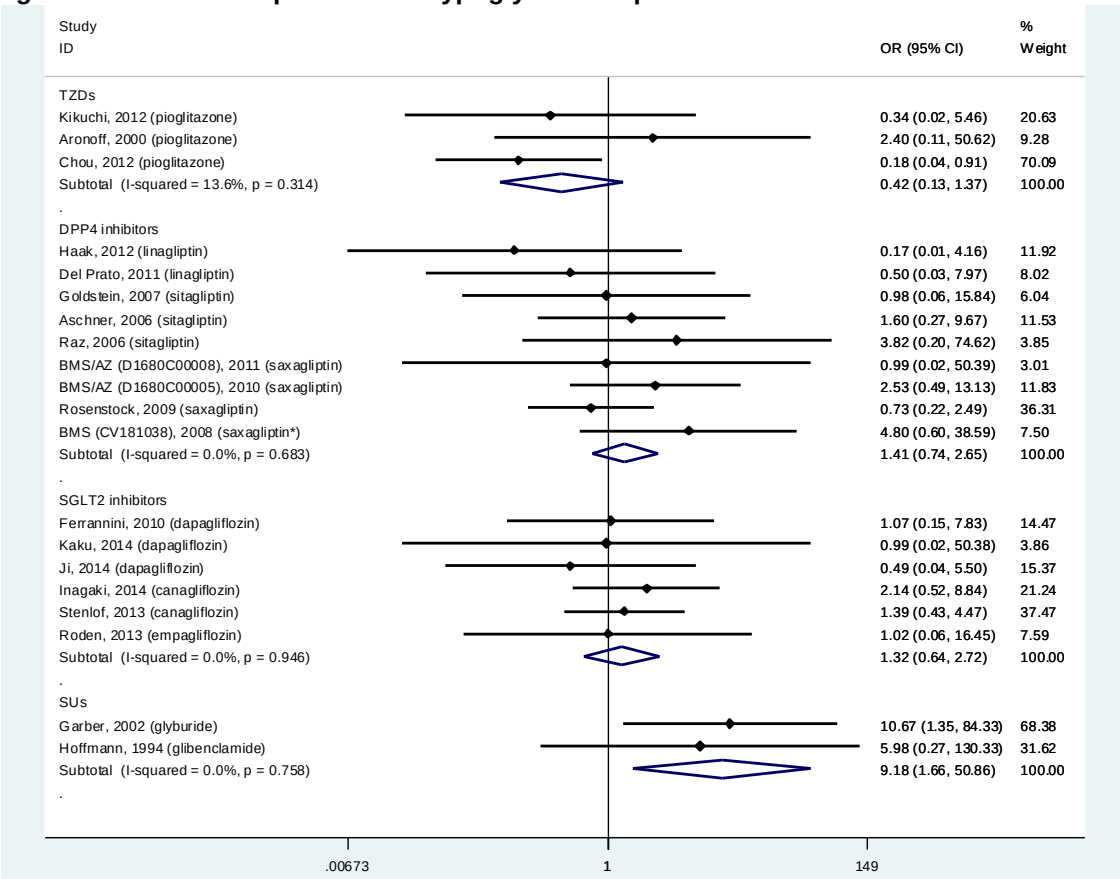
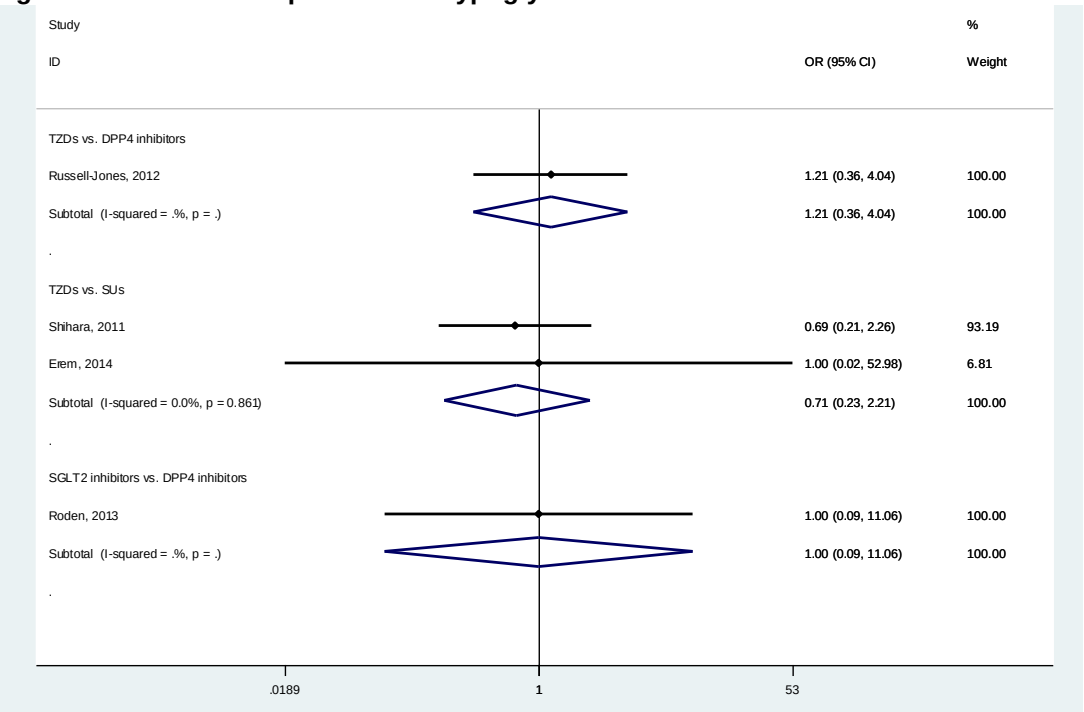


Figure 10 Pairwise comparisons of hypoglycaemia: active-controlled trials



Appendix 3: Updated results for the hypoglycaemia network

The below includes updated results for the hypoglycaemia network, with SGLT2s as a class.

Table 1. Risk of hypoglycaemia, fixed effect model.

Regimen	Odds of hypoglycaemic events	
	All vs. Placebo Mean (95% CrI)	SGLT-2s vs. ALL Mean (95% CrI)
Placebo	*Reference Treatment*	1.30 (0.67, 2.65)
DPP-4 inhibitors	1.33 (0.75, 2.38)	0.98 (0.41, 2.39)
TZDs	1.28 (0.53, 3.22)	1.02 (0.33, 3.11)
Sulfonylureas	3.69 (1.40, 10.52)	0.35 (0.10, 1.15)
SGLT-2 inhibitors	1.30 (0.67, 2.65)	*N/A*

CrI: credible interval; N/A: not applicable.

Figure 11. Caterpillar plot of risk of hypoglycaemia, fixed effect model (All vs. placebo)

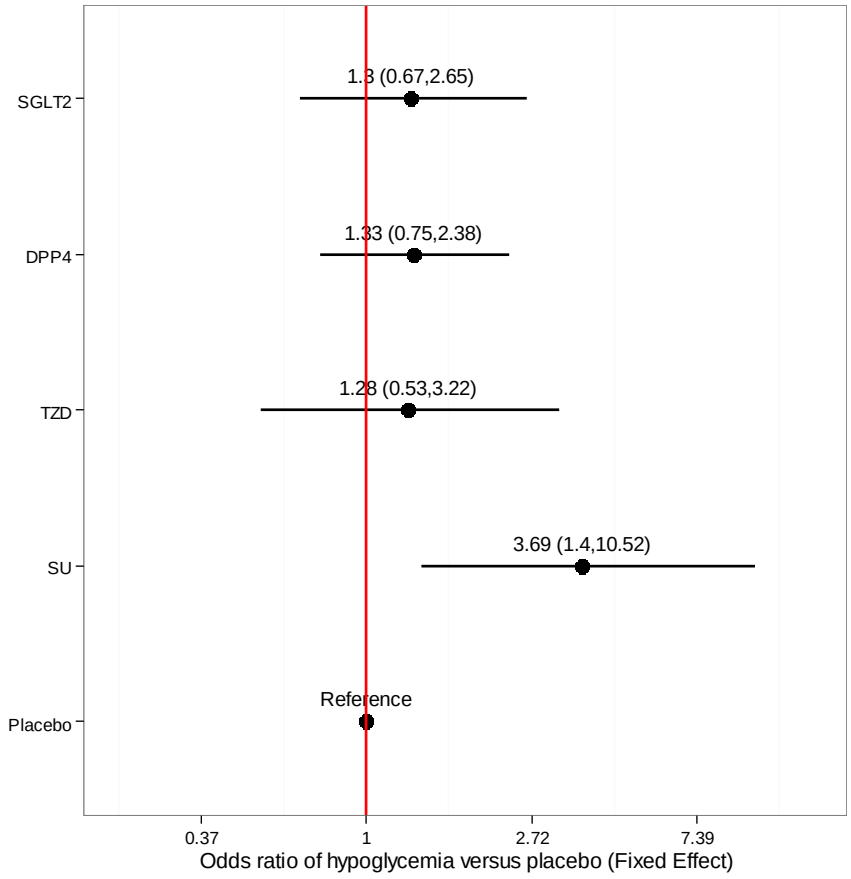


Table 2. Risk of hypoglycaemia, random effects model.

Regimen	Odds of hypoglycaemic events	
	All vs. Placebo Mean (95% CrI)	SGLT-2s vs. ALL Mean (95% CrI)
Placebo	*Reference Treatment*	1.28 (0.53, 3.00)
DPP-4 inhibitors	1.31 (0.66, 2.66)	0.97 (0.33, 2.82)
TZDs	1.20 (0.42, 3.50)	1.07 (0.27, 4.07)
Sulfonylureas	3.73 (1.14, 13.74)	0.34 (0.07, 1.50)
SGLT-2s	1.28 (0.53, 3.00)	*N/A*

CrI: credible interval; N/A: not applicable.

Figure 12. Caterpillar plot of risk of hypoglycemia, random effects model (All vs. placebo)

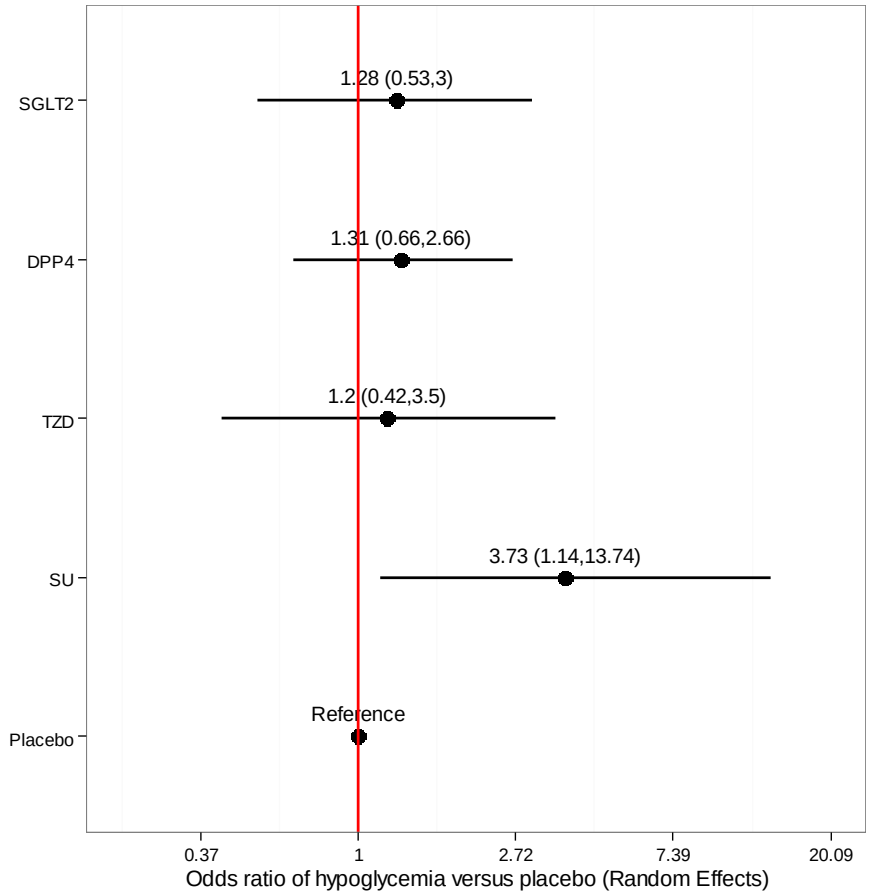


Table 3: Updated cost-effectiveness results based on the updated odds ratio of hypoglycaemia

Odds ratios hypo original NMA (May 2015)					Odds ratios hypo new NMA (Oct 2015)			
	Odds ratio vs. Placebo	Odds	Probability	**ICER**	Odds ratio vs. Placebo new	Odds	New probabilities	**ICER**
DPP4	1.46	0.0163	0.016	**5,904**	1.33	0.0148	0.0145	**6,125**
TZD	2.22	0.0246	0.024	**20,089**	1.28	0.0142	0.0140	**20,639**
SU	4.97	0.0582	0.055	**52,047**	3.69	0.0410	0.0393	**59,013**
Flozins	0.91	0.0101	0.0100	**-**	1.30	0.0144	0.0142	**-**
Placebo	-	0.0111	0.0110	**-**	-	0.0111	0.0110	**-**

Comments on Multiple Technology Appraisals (MTA)

Canagliflozin, dapagliflozin, empagliflozin monotherapy for treating type 2 diabetes [ID756]

Order number	Section Number	Page Number	Comments
1.	Summary	11	"Their [sulfonylureas'] safety record is well established." The most recent meta-analysis of CV outcomes (Monami et al, 2013) showed an increased risk of mortality (Mantel-Haenzel-OR: 1.22 [1.01–1.49], p=0.047). The authors concluded that CV safety cannot be considered unless it is evaluated in long-term cardiovascular outcomes trials. Therefore, while sulfonylureas are a well-established treatment for treating type 2 diabetes, there continue to be concerns about their long-term safety, particularly the potential increased risk of mortality.
2.	Summary	13	It is stated that *"Compared to placebo, empagliflozin 10 mg reduced HbA1c by 0.74% and empagliflozin 25 mg by 0.86%. Weight loss was about 2 kg, and SBP was reduced by 2.6 and 3.4 mm Hg."* However, in the previous sentence it is stated that *"One empagliflozin trial was carried out in 197 centres in 22 countries, and the other in 124 centres in 9 countries, mainly western countries but including China, India and Japan."*: The manner in which this is currently written implies that the numbers presented refer to both trials. Please either include information for both trials, or describe the trial to which you are referring. For reference, in the EMPA-REG-MONO study, compared to placebo, empagliflozin 10mg reduced HbA1c by -0.74% (95% CI: -0.88, -0.59) and empagliflozin 25mg reduced HbA1c by -0.85% (95% CI: -0.99, -0.71). Weight loss was about 2kg and SBP was reduced by 2.6 and 3.4 mmHg.
3.	Summary	13	*"The only significant adverse effects reported in the trials were increases in urinary and genital tract infections, mainly in women. Both UTIs and GTIs occurred in about 4% to 9% in women."* It is not clear if this is referring to the empagliflozin trial data or all SGLT2i data included in the monotherapy assessment report. Please make it clear which trial(s) this data has been reported from.
4.	Summary	13	*"The proportions of MIs reported as fatal were surprisingly low at 4.0% and 4.4% for placebo and empagliflozin respectively."* It is unclear where these values have come from. Figures for adjudicated fatal or non-fatal MI are 5.4% and 4.8% for placebo

			and empagliflozin (NEJM, table 1) respectively, and 0.5% and 0.3% for fatal MI (supplementary appendix table S5). Please correct these values to reflect the NEJM publication.
5.	Summary	13	*"Subgroup analyses showed that the primary outcome only reached statistical significance in Asians."* This statement is misleading as it indicated that there is only an effect in Asian patients. However, the trial has not been powered to demonstrate superiority in subgroups. The treatment-by-race interaction test (p=0.0872) is not significant, and the 95% CIs of the race subgroups include the overall effect. This p-value for interaction was not significant for ethnicity and multiple testing was not accounted for. In addition, due to the nature of tests for heterogeneity not being accounted for in the statistical analysis plan, these results would only ever be hypothesis generating and not confirmatory in nature. The HR for Whites (0.88) is almost identical to the overall HR (0.86). Please note that for CV death the effect is significant even in the separate subgroups of Whites and Asians.
6.	Summary and EMPA-REG OUTCOME	13 and 72	"The mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group." "Despite the addition of other glucose-lowering drugs, the mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group, a difference of 0.35%." These numbers are not in the NEJM publication.
7.	Summary	14	"However in some trials the untreated controls might also have had an increased risk of UTIs due to poor control and hence glycosuria." It should be clarified that this statement does not relate to the EMPA-REG-OUTCOME study because the design of the study did not include an untreated group. All patients were treated at the discretion of the investigator, including background glucose lowering medications.
8.	Summary	14	*"Only one dose of dapagliflozin is used, despite larger effects being reported with larger doses such as 20mg daily."* Only one dose of dapagliflozin is used. Larger effects have been reported with larger doses but this is outside the summary of product characteristics and is unlicensed. Please make it clear that 20mg is an unlicensed dose.
9.	Summary	19	"Only empagliflozin has long-term cardiovascular outcomes reported yet, showing a reduction in mortality. " Please consider including the reduction in hospitalisation for heart failure as well.
10.	Summary	20	*"If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin over the more traditional treatments of pioglitazone, repaglinide and gliclazide. The traditional treatments may even provide more patient benefits. The flozins and sitagliptin cost around £400 more each*

			year than the traditional treatments. As a consequence, the flozins represent very poor value for patients as a whole." Weight loss is intrinsic to reducing insulin resistance (a key driver of the type 2 diabetes process) and compared to treatments such as pioglitazone and gliclazide is a significant benefit to patients. It is unclear what additional benefits pioglitazone, repaglinide and gliclazide offer to patients over the DPP-4is and SGLT-2is. Please detail which additional benefits traditional treatments may provide patients over and above the gliptins and flozins? Please also amend the final sentence to included sitagliptin. We also question the conclusion given the potential benefits of lower hypoglycaemia, no weight gain and also potential CV benefits the flozins offer significant benefits to patients.
11.	1	33	"Due to their insulin-independent mode of action, they do this without weight gain or hypoglycaemia". The lack of weight gain may also relate to the loss of calories in the urine.
12.	1	34	*"There is also an SGLT1 transport mechanism, which is present both in the kidney and the gut. In the kidney, it is much less important than SGLT2. Inhibition of gut SGLT1 reduces absorption of glucose there, and it has been suggested that canagliflozin may have a dual action. This was reported first in healthy volunteers but has since been reported in a study of people with type 2 diabetes."* This was reported first in healthy volunteers but has since been reported in a study of people with type 2 diabetes. However, additional SGLT1 inhibition has not been shown to have a clinically meaningful effect. There are no head-to-head comparisons between the current licensed SGLT2 inhibitors. Please make this more complete by stating the additional inhibition of SGLT1 and relevance to HbA1c reduction remains uncertain and there are no head-to-head studies comparing SGLT2 inhibitors.
13.	1	34	"In addition to improving glycaemic control, the SGLT2 inhibitors also reduce blood pressure." Please note that weight loss is also seen with SGLT2 inhibitors.
14.	Study design	47	The studies were all double blind multicentre trials and only the two empagliflozin trials had active comparators (Roden 2013/4 and Lewin 2015)." It should be noted that the two studies were not primarily powered for the active comparison between the active monotherapies.
15.	2	General	Patients with Asian race (ethnicity) and patients from Asian countries (region) are used interchangeably. Please clarify which patient group (i.e. of Asian ethnicity or from Asian region) is being referred to enhance clarity.

16.	2	52	*"Empagliflozin at 10 mg/day reduced HbA1c by between 0.66 (Roden) and 0.83% (Lewin) from baseline, which amounted to 0.16% more than with linagliptin, no difference to sitagliptin, and 0.58% more than with placebo."* Can this commentary be amended to describe each trial i.e. the Monotherapy (Roden) and the Fixed Dose Combination (FDC) empagliflozin/linagliptin initial combination (Lewin). It could be confusing as the reader may think that this is referring to 1 study. This is difficult when comparisons are made between both sitagliptin and linagliptin.
17.	2	55	*"Empagliflozin at 10 or 25 mg/day reduced systolic blood pressure by between 2.1 and 3.7 mmHg from baseline, which amounted to between 1.7 and 3.4 mmHg more than in the control group. None of these differences were significant."* Can this be clarified that this is referring to the empagliflozin/linagliptin (Lewin et al) trial which involved an active comparator (linagliptin), as opposed to comparing against placebo. The statement "none of these differences were significant" is misleading as the monotherapy results are as follows: • 10mg: -2.6 (95% CI: -4.9, -0.4), p = 0.0231 • 25mg: -3.4 (95% CI: -5.7, -1.2), p = 0.0028
18.	2	70	Cardiovascular safety. "All three of the SGLT2 inhibitors reviewed in this report are in large, long-term cardiovascular studies" It should be clarified here that the CV trial for Empagliflozin has been completed and reported
19.	2	71, general	The official name of the study is EMPA-REG OUTCOME®
20.	2	71	*"72% were white, 21% Asian and 5% Black including African-Americans. The Asians were from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea."* Asian patients by race were 21%, patients from Asian region were 19%, so the sentence is technically not factually correct. Please clarify in the document either that "19% were Asian from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea" or that "21% were Asian" but remove the statement around which countries they were from. The two statements together are not referring to the same patient population and could result in confusion.
21.	2	71	When stating *"About 30% were on monotherapy, and 48% were on dual therapy implying **26%** were on more complex regiments with three drugs or more";* "More complex regimens" is being used here to refer to patients treated with three drugs or more. It is implied that 26% here is calculated by subtracting 30% and 48% from 100 (i.e. the total population) to give 26%. This is incorrect. The correct calculated value if subtracting both 30% and 48% from 100% would be 22%. In addition, given that 2% of patients included were drug

			naïve patients (the baseline paper: Cardiovascular Diabetology 2014, 13:102), this also needs to be subtracted from the total population to give 20% as the proportion of patients on "more complex regimens" (i.e. three drugs or more). Please correct this to state that 20%, rather than 26%, of patients were on three drugs or more.
22.	2	71	EMPA-REG-OUTCOME. The results demonstrating the reduction in the hospitalisation for heart failure should also be included.
23.	2	72	*"ACEIs or ARBs in 23.6%, which does not seem compatible with the 81% on these drugs at baseline"* At baseline, 81% of patients were on either ACEIs **and/or** ARBs, with a very small proportion on both ACEIs **and** ARBs. As the patients on both ACEIs and ARBs at baseline were very few, either ACEIs or ARBs could be added to the existing treatment if patients were not treated with either of those medications at baseline. In addition, "medication introduced post-baseline" is defined as new initiation or re-initiation of the medication. Therefore, this cannot be interpreted based on simple addition. Please remove statement "…which does not seem compatible with the 81% on these drugs at baseline".
24.	2	72	*"Similarly Table S12 reports statins being introduced in 22% of the empagliflozin group, which implies that at study end, 99% were on statins, with 14% also on fibrates"* "Medication introduced post-baseline" is defined as new initiation or re-initiation of the medication. Therefore, this cannot be interpreted based on simple addition. At baseline, 77% of patients were already being treated with statins, whereas 22% of patients had statins introduced post-baseline. Some of these patients may have stopped and resumed statin regimes during the trial, whilst others were newly initiated patients on statin treatment. A similar case exists for patients treated with fibrates at baseline and throughout the study duration. Please remove statement "…which implies that at study end, 99% where on statins, with 14% also on fibrates".
25.	2	72	*"The results were analysed by staff from Boehringer Ingelheim who co-funded it with Eli Lilly"* Please note, the outcome events were adjudicated by an independent blinded adjudication committee. The data was also analysed and validated by a group of independent external statisticians from the University of Freiburg in Germany.
26.	2	72	*"The two empagliflozin groups were pooled for the analysis, because event rates were almost identical…"* The EMPA-REG OUTCOME study is powered to show the superiority of pooled empagliflozin vs. placebo with 2:1 randomization. Therefore two doses were pooled according to the predefined statistical analysis plan in the protocol. This is

			because the study was designed on the assumption that the CV benefit of both doses of empagliflozin would be the same. It is incorrect to state that the groups were pooled because the event rates were the same. In addition, the HRs versus placebo was almost identical for both doses when analysed separately (0.85 for 10mg and 0.86 for 25mg). Please note that for CV death and all-cause mortality a significant superiority has been shown even for the individual dose comparisons vs. placebo. Please also remove statement "…because the event rates were almost identical".
27.	2	72	*"When the main outcomes were assessed for the 10mg and 25mg empagliflozin groups separately, the differences were not significantly different from the placebo group"* The EMPA-REG OUTCOME study is powered to show the superiority with pooled empagliflozin vs. placebo with 2:1 randomization. The pre-planned analyses of individual subgroup vs. placebo were conducted to assess whether the benefit size was consistent between two doses.
28.	2	73	*"Supplementary table S5 reports 11 deaths from acute MI in the placebo group and 15 in the pooled empagliflozin group, but these figures do not match those in table 1 in the main paper. The figures for fatal stroke also differ between main text and supplement 11 versus 9 for placebo, 16 versus 14 for empagliflozin"* It is unclear where these figures (i.e. 9 for placebo and 14 for empagliflozin) come from. Table 1 in the main NEJM publication does not report the number of deaths from acute MI. In addition, fatal stroke is also not presented in the main text. These numbers (i.e. 11 for placebo and 15 for empagliflozin) are correct as "fatal MI or stroke" were defined as death occurring ≤ 30 days after a MI or stroke event. Any death caused by MI or stroke occurring >30days after previous MI or stroke was defined as "CV death; caused by stroke"; this is standard way of capturing CV death, and fatal MI/stroke event.
29.	2	73 (table 6)	In Table 6 results of EMPA-REG OUTCOME trial – there are the following inconsistencies compared with table S5 of the supplementary appendix: • Fatal MI is 0.5% for placebo (as reported in Table S5), not 0.2%. Fatal stroke is 0.5% for placebo (as reported in Table S5), not 0.4%. Please also note that the true value for Non-cardiovascular mortality is 2.1% for empagliflozin, not 2.0%. This is because the values reported in the paper were rounded Please correct these values to reflect the supplementary appendix of the EMPA-REG OUTCOME study publication (DOI: 10.1056/NEJMoa1504720).
30.	2	73	*"The proportion of fatal to non-fatal MIs looks odd – 5 deaths out of 126 MIs. Similarly of 69 strokes, only 9 were fatal. This raises*

			the question of where the 137 cardiovascular deaths come from." In the placebo group, 126 patients had an adjudicated MI, 11 were adjudicated as resulting in CV death (main publication Table 1, and Supplementary appendix Table S5). Figures for both empagliflozin groups are 223 patients including 15 resulting in death. For strokes the figures are 69 including 11 resulting in death (placebo) and 164 including 16 resulting in death (both empagliflozin groups). Please correct these values to reflect the main EMPA-REG OUTCOME publication and accompanying supplementary appendix.
31.	2	73	*"The DKA rate in the empagliflozin was double that in the placebo group but the excess risk was only about 1 in 1500 per year, and numbers were very small."* With 1, 3, and 1 DKA events in the three arms (placebo, empagliflozin 10mg and empagliflozin 25mg), respectively, this does not support a statement of doubling the DKA rate. The summary by the safety committee and the NEJM authors was that there was no increase of DKA cases with empagliflozin in this study.
32.	2	74	*"The ill-defined "other cardiovascular deaths"* All fatal events were adjudicated by an independent adjudication committee. If the cause of death was definite non-cardiac origin such as trauma, end stage of cancer etc. it was classified as "non-CV death". If there was well documented definite cause of CV death then that event was captured as CV death with specific cause. If the cause of CV death was not clearly documented, then the event was classified as "other CV death", which is the standard adjudication procedure of a CV outcome trial.
33.	2	74	*"…with curious accelerations in the placebo group curves after 42 months"* The mean observation time was 3.1 years. After 42 months only a few participants were reflected in the Kaplan-Meier curves. Therefore, any change in the curves needs to be interpreted with caution.
34.	2	74	*Referring to the section "How were these cardiovascular benefits achieved?* ": Please note that this study was not designed to answer how the benefits could be achieved; this study was designed to be a "CV risk factors equipoise" trial. Patients in the placebo arm received more CV and glucose lowering medications.
35.	2	75	*"Discontinuation rates from study drugs due to adverse events are reported as 19.4% for placebo and 17.3% for empagliflozin in the paper but as 13.0% and 11.5% in appendix H."* Adverse event leading to discontinuation of a study drug"

			includes temporary discontinuation; whereas "prematurely discontinued from trial medication due to adverse event" in the patient's disposition only included permanent discontinuation.
36.	2	75	*"Of the 282 primary events in the placebo group 49% were cardiovascular deaths. Of 490 primary outcomes events in the empagliflozin group, 35% were cardiovascular deaths."* This is not correct; the contribution of CV deaths for the 3-point MACE is 107 patients (38%) for placebo and 143 patients (29%) for empagliflozin. Reason is that for 3-point MACE the first event counts.
37.	2	75, 77 Regarding subgroup analyses	One of the major objectives of subgroup analyses for the key CV endpoint is to investigate consistency of the result across the subgroups and whether the data suggests an interaction related to patient characteristics. Some heterogeneity was observed in primary outcome event but none in CV death. The subgroup analyses were not adjusted for multiple testing which increases type 1 error dramatically. Therefore we cannot conclude statistical significance using the results of subgroup analyses. For primary outcome subgroup analyses; - Ethnicity, BMI, Background antihypertensive therapy: there was no interaction between subgroups. - Age, HbA1c : Some heterogeneity was observed however multiple testing was not adjusted. The results would be hypothesis generating and not confirmatory.
38.	2	77	*"There was no evidence of overall mortality reduction in white people…"* This is incorrect. The HR for Whites for CV mortality is 0.64 and highly significant. The HR for Whites for all-cause mortality is not yet published.
39.	2	77	*"The subgroup analyses in EMPA-REG Outcome are interesting. Younger, lighter, better controlled patients did better, as did the Asian group. There could be overlapping features here in that the East Asians tend to be lighter. There was no evidence of overall mortality reduction in white people but some reduction in CVD mortality, which suggests that there were more non-cardiovascular deaths in white people on empagliflozin. Further details will no doubt be released but with such a very large study, further analysis is bound to take time."* As mentioned above this is seriously misleading and scientifically wrong. We cannot make conclusions such as the above based on the results of the subgroup analyses as there was no evidence of any significant interaction in CV death and multiple testing was not adjusted for.
40.	2	77	*"The differences observed do not seem sufficient to justify the very optimistic media coverage, such as reports that 'Lilly's Jardiance diabetes pill could be a $6 billion-a-year blockbuster'."* While we cannot speculate on future sales, the results from EMPA-REG OUTCOME study are clearly a breakthrough. The hardest possible endpoint in a clinical trial is all-cause mortality

			as there is no room for misinterpretation. A 32% relative and 2.6% absolute risk reduction is highly clinically relevant. The magnitude of the effect on CV death and all-cause mortality is fully in line with that seen in other landmark trials with statins and ACE inhibitors / ARBs. This was achieved despite the fact that the patients in EMPA-REG OUTCOME were very well treated as evident by their blood pressure and LDL cholesterol levels, as demonstrated by the use of co-comintant medication. The Number Needed to Treat to prevent one death over 3 years was 39 (calculated to be 25 over 5 years) and is therefore, again, in the same range as the aforementioned landmark trials. In addition, The Alliance would like to highlight that results such as these have never been demonstrated by diabetes treatments and, as such, warrant specific reference to empagliflozin within the document in this regard. Empagliflozin is the only glucose lowering agent in a completed dedicated cardiovascular trial to have demonstrated superiority in the primary composite cardiovascular endpoint. Studies involving metformin have demonstrated some cardiovascular benefit in historical studies, however, it should be noted that this was not in a prospective dedicated cardiovascular outcome trial of the design, size and robustness of EMPA-REG OUTCOME. It should be noted that these results cannot be extrapolated across the SGLT2i class until the other class members' cardiovascular outcome trials report in the coming years and that it is empagliflozin alone that has thus far demonstrated this important effect for patients with type 2 diabetes.
41.	2	77	*"It is worth noting that the Empa Outcome trial involved patients at high cardiovascular risk who had had diabetes for many years and who were on complex regimens for their diabetes. The results are not applicable to people starting monotherapy with empagliflozin*." Although few drug naïve patients were included in the EMPA-REG OUTCOME study, potential benefits of empagliflozin as monotherapy cannot be excluded. In a previous meta-analysis of 11314 patients on placebo and 2,395 patients on all empagliflozin (1,098 patients on empagliflozin 10 mg, and 1,297 patients on empagliflozin 25 mg) including a monotherapy study (published EPAR), the HR of 4P MACE was 0.48. Therefore the potential benefit of empagliflozin in the earlier T2DM patients might be even larger than what we observed in the EMPA-REG OUTCOME trial.
42.	5	116, general	It has to be noted that the cost-effectiveness model did not include any data from the EMPA-REG OUTCOME study. While the EMPA-REG OUTCOME study only included a small proportion of patients on monotherapy, it cannot be definitively concluded that empagliflozin has no positive effects on CV outcomes. Therefore, it would make sense to explore the potential impact of empagliflozin in monotherapy in patients at high CV risk. If only in sensitivity analysis to explore what potential impact this

			benefit could have on the cost-effectiveness results.
43.			
44.			
45.			

Please add extra rows as needed

Healthcare Improvement Scotland

NICE Health Technology Appraisal - Assessment Report

On

Canagliflozin, dapagliflozin and empagliflozin monotherapy for type 2 diabetes

TO: NICE **09 November 2015**	**FROM: Healthcare Improvement Scotland**

Comments provided to Healthcare Improvement Scotland by:

[redacted]

Sulphonylureas (SU) **do** (not "can") cause weight gain over time. Hypoglycaemia is an issue with SU therapy. Mild to moderate hypoglycaemia episodes are common in type 2 diabetes even if severe hypos are less common than indicated in the UK Hypoglycaemia Study Group paper. Hypoglycaemia in type 2 diabetes is a poorly researched area and has major quality of life issues. SU therapy lacks durability (see ADA guidelines). Cardiovascular outcome on SU therapy is contentious but remains a real concern. Home blood glucose monitoring should be used in conjunction with SU therapy. This will have a significant cost impact and quality of life consequences. Other medication (except insulin) do not require blood glucose monitoring particularly in relation to driving.

I appreciate that type 2 diabetes is a progressive disease with β-cell dysfunction, increase in insulin resistance etc but most patients started on SU therapy go onto require insulin therapy. I am sure a lot of this is due to the SU therapy. Although the cost of SU therapy is low the downstream costs are very significant. Gliclazide is commonly used at 160mg bd when there is little benefit in using more than 120mg per day.

The BMIs in the SGLT2i studies are low and do not reflect areas such as the West of Scotland where the mean BMI is much higher (males 31 kg/m^2, females $32kg/m^2$) so SGLT2i are much more likely to have a greater impact on weight loss than the studies suggest. "Real life" clinical practice reflects this.

Pioglitazone is not a medication in common use following the problems with rosiglitazone. It may or may not be time for its "resurrection" but pioglitazone is associated with weight gain and fluid overload making it an unpopular choice amongst clinicians. This will exacerbated if patients require regular urinalysis and BNP checks. Repaglinide, which is a weak SU, is likely to be associated with poor compliance/concordance particularly if it needs to be taken 2-3 times a day.

Ranking the SGLT2i in terms of efficacy must be open to criticism as there are no head to head trials, each cohort will be different, BMI etc.

Comment provided to Healthcare Improvement Scotland by:
Dr Alan Jaap, Consultant in Diabetes, Royal Infirmary of Edinburgh

I have now had a look at this report and would comment that it appears to be done to a high standard. I agree with the clinical conclusions and the extensive health economic modelling used seems reasonable to me (although I am not an expert in this).

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response
ERG Report

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes [ID756]

9th November, 2015

Issue 1 Incorrect clinical information presented

Description of problem	Description of proposed amendment	Justification for amendment
On page 53, when discussing weight for canagliflozin, while the reductions from baseline are correct, the reductions compared to placebo are incorrect.	For 100 mg, the reductions vs placebo should be 1.9 kg and 2.1 kg, instead of 3.0 and 3.1 kg. For the 300 mg dose, the reduction vs placebo should be 2.9 kg instead of 3.9 kg.	Janssen advocate that that these errors in the data are corrected. Janssen is unsure whether this error appears only in the text or has been pulled through into the modelling. Janssen has attempted to replicate the network meta-analysis (NMA) conducted by the Assessment Group (AG, further detail provided in a separate document by Janssen, titled “Additional Information”) and from this do not believe that this error features in any further analyses conducted by the AG.

Issue 2 Incorrect clinical information presented

Description of problem	Description of proposed amendment	Justification for amendment
On page 54, when discussing systolic blood pressure reductions with canagliflozin 300 mg, the Assessment Report (AR) states that a 0.5 mmHg was seen from baseline, which is 0.9 mmHg more than placebo.	For 300 mg, the reduction from baseline was 5.0 mmHg rather than 0.5 mmHg. And when compared to placebo this should be 5.4 mmHg.	Janssen attempted to replicate the network meta-analysis (NMA) conducted by the AG. While exact replication was not achieved as too few details were reported in the AR reported about how missing data were handled, near replication was achieved, which suggests a high likelihood that this error is not only a typographical error in the text, but an error that has been pulled through to the NMA and subsequent economic modelling (disadvantaging CANA 300 mg). For a summary of the replication analysis conducted, please consult the separate file, titled “additional information”.

		Janssen advocate that on page 54 this error is corrected.

Issue 3 Incorrect clinical information presented

Description of problem	Description of proposed amendment	Justification for amendment
In table 4, on page 57, of the AR the AG has presented inaccurate data for urinary tract infection (UTI) rates associated with the use of canagliflozin. It appears that GMI rates from Stenlof, et al (2013) were incorrectly extracted as UTI rates.	Note that values for UTIs need correction (genital mycotic infection (GMI) rates were mistakenly provided for UTI rates). The correct UTI rates at 26 weeks are: 14/195 (7.2%) for 100 mg, 10/197 (5.1%) for 300 mg and 8/192 (4.2%) for placebo. The correct UTI rates for the high HbA1c sub-study at 26 weeks are: 3/47 (6.4%) for 100 mg and 2/44 (4.5%) for 300 mg. The correct UTI rates at 52 weeks are: 16/195 (8.2%) for 100 mg, 14/197 (7.1%) for 300 mg and 12/192 (6.3%) for placebo/sitagliptin. These data are also summarised in Table 3, on page 19 of the submission made by Janssen.	It appears that the AG has presented figures for genital mycotic infections (GMIs) instead of UTIs. Janssen has provided the correct values for UTIs, and is unsure if this will have an impact on the modelling. Janssen advocate that Table 4 be corrected.

Issue 4 Misinterpretation of the SUCRA

Description of problem	Description of proposed amendment	Justification for amendment
On page 112, the AG have incorrectly summarised how the SUCRA was used by Janssen in the interpretation of the NMA results.	The AG correctly summarise that Janssen reported both the point estimates (and credible intervals) of the mean difference and odds ratios and the probability of the different treatments as being the most effective based on the Surface Under the Cumulative Ranking (SUCRA). Although the summary of the interpretation of SUCRA was correctly presented in the report, the way in which the SUCRA was described to be used by	Janssen has clarified the use of SUCRA in the interpretation of their NMA.

	Janssen to interpret the results is incorrect. The treatments were ranked based on the SUCRA, where treatments with the highest values have the highest probability of being most effective. The SUCRA is expressed as a percentage and ranges between 0% and 100%, with a SUCRA of up to 100% indicating treatments to be ranked first with the high certainty, while low SUCRA values indicate the opposite. Separately to treatments being ranked, the probability for canagliflozin to perform better than each comparator considering specific end point was calculated. This probability is a separate concept to the interpretation using SUCRA. There is no threshold reported in the guidelines to show the superiority of a treatment versus its comparators; therefore, these probabilities were interpreted as follows: - if the probability of performing better for treatment A compared to treatment B was >70%, then A was assessed as better than B - if this probability was between 30% and 70%, then A and B were reported as similar, and - if the probability was <30%, then B was described as better than A.	

Issue 5 Differences in inclusion of sulfonylureas in AG versus Janssen NMAs

Description of problem	Description of proposed amendment	Justification for amendment
On page 113, the report describes that all sulfonylureas were pooled in the Janssen NMA.	The Janssen analysis did not pool all sulfonylureas. All sulfonylureas (i.e. gliclazide, glipizide, glibenclamide and glimepiride) were considered separately and pooling was performed for the different doses of a same treatment. This was necessary as most identified trials allowed for the titration	Janssen has clarified the pooling of sulfonylureas and provided an explanation for the approach that was used. Differences by inclusion of additional SU trials

	of SU doses; as such, not enough data is available to investigate separate doses. In addition, the AG found no suitable trial of gliclazide vs. placebo, so they used 2 trials of gliclazide vs. pioglitazone (Lawrence, t al 2004 and Erem, et al 2014) and 1 trial of gliclazide vs. vildagliptin (Foley, et al 2009). The additional level of indirectness poses an additional source of uncertainty in the efficacy estimates of gliclazide in the NMA conducted by the AG. The Janssen analysis included one of these trials (Lawrence, et al 2004). Erem, et al 2014 was not included as it compared gliclazide to a titration of pioglitazone (and we considered different doses of pioglitazone separately) and Foley, et al 2009 (versus vildagliptin) was excluded from the Janssen NMA as numeric results were available at 104weeks only (data at 26 weeks could be estimated from a graph but exact numbers were not reported). Including sulfonylureas other than gliclazide could have the following effects on the Janssen NMA. Glimepiride and glipizide were not involved in loops in the network therefore deleting them would have no consequence on other estimates. Glibenclamide was linked to placebo, gliclazide, pioglitazone 30 mg, and pioglitazone 15 mg. Deleting it would predominantly impact the assessment versus gliclazide and would have a small impact on pioglitazone 30 mg and pioglitazone 15 mg estimates. DPP-4 estimates could potentially be affected through the loops via pioglitazone; however, effects are small because there are a number of other studies that inform these values, as well.	do not significantly change the treatment effect of gliclazide. Please consult Section 5 in a separate document provided by Janssen, titled “additional information” for further detail.

Issue 6 Inclusion of dapagliflozin 5 mg as a comparator in the Janssen NMA

Description of problem	Description of proposed amendment	Justification for amendment
On page 112, it was noted that Janssen NMA included comparators that the AG considered irrelevant (such as dapagliflozin 5 mg).	Janssen identified 4 trials assessing dapagliflozin, only one of which (Bailey, et al 2012) assessed only dapagliflozin 5 mg. Its size was comparable, if smaller to the other studies. Therefore, it would be expected to have a minor impact only on the comparison versus dapagliflozin 10 mg and no impact versus other comparators.	Janssen has provided an explanation of the anticipated impact for the inclusion of dapagliflozin 5 mg as a comparator included in the NMA.

Issue 7 Differences in studies included in Janssen NMA

Description of problem	Description of proposed amendment	Justification for amendment
On pages 112, the AG notes that the Janssen NMA includes some studies that it does not find relevant.	The Janssen NMA planned to include more comparators than the AG NMA, and in this sense it is broader and has found more studies that matched its inclusion criteria (details of which may be found in Table 3 of the study report). In some cases, the inclusion of comparators on this occasion not considered relevant by the AG can benefit the network of evidence by providing studies that link 2 relevant comparators indirectly.	Janssen has provided justification for including a greater number of studies in the NMA supporting Janssen's submission.

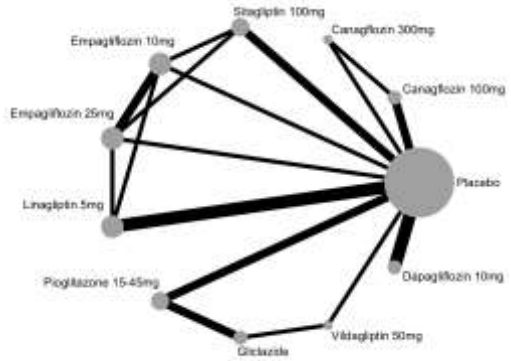
Issue 8 Differences in inclusion criteria between AG and Janssen NMAs

Description of problem	Description of proposed amendment	Justification for amendment
On page 79, the report notes that studies included in the AG NMA were restricted to those of 24 or 26 weeks in duration but Janssen included studies of 26 +/- 4 weeks [page 113].	Note that only one study included in the Janssen NMA did not report results at 24 or 26 weeks. This study, NCT01183013, assessed linagliptin vs. pioglitazone with data at 30 weeks.	Janssen has identified only 1 the study which was included due to the differences in inclusion criteria related to the time of trial reporting and do not believe that the inclusion of this study impacts the results of the Janssen NMA in a significant manner.

Issue 9 Differences in AG and Janssen NMA results

Description of problem	Description of proposed amendment	Justification for amendment
Tables 106, 107, and 108 illustrate differences in the results from the AG and Janssen NMAs, specifically related to comparisons to pioglitazone and sulfonylureas.	Note that there are some examples where the results were similar between the 2 analyses: • HbA1c change of -1.20 with canagliflozin 300 mg in the Janssen submission and -1.153 in the AG; Table 106 • HbA1c change of -0.64 with dapagliflozin 10 mg in the Janssen submission and -0.704 in the AG; Table 106 • SBP change of -3.40 with empagliflozin 25 mg in the Janssen submission and -3.743 in the AG; Table 107 • Weight change of -3.42 with canagliflozin 300 mg in the Janssen submission and -3.577 in the AG: Table 108. However, there are some marked differences for some efficacy results. In particular: • In a recently updated analysis by Janssen, HbA1c change with sulfonylurea is reported as -1.04, however the AG report this change as -1.301 (Table 106). Janssen are unsure how this input parameter was generated. In Table 9 of the assessment report, the change in HbA1c reported more closely matches that found in the Janssen analysis, at -0.95. • AG also had much more favourable HbA1c lowering for pioglitazone. HbA1c change with pioglitazone in the updated analysis conducted by Janssen is reported as -0.76 and the AG report this value to be -1.200 in Table 106. Again, Janssen are unsure as to how the AG determined this value as the input parameter for the economic modelling as in Table 9 of the	Janssen has clarified the potential differences in the NMAs that may have resulted in the observed differences in the results, some of which may be reflected also later in the economic outcomes.

	Assessment Report the AG report the change in HbA1c with pioglitazone to be -1.13. • SBP change of -5.41 with canagliflozin 300 in the Janssen submission and -1.338 in the AG; Table 107. AG had worse SBP lowering for canagliflozin than that from Janssen NMA; this may be as a result of the AG wrongly extracting SBP data from the CANTATA-M study. Please consult Section 2.4.3. in the separate document supplied by Janssen, titled "additional information" for further clarification. • SBP change of +0.88 with pioglitazone in the Janssen submission and -1.400 in the AG; Table 107. Janssen understand that this is an assumed effect by the AG, as no SBP value was determined by the NMA conducted by the AG for pioglitazone; however, Janssen are unsure as to how this assumed effect has been determined. • Weight change of +0.62 with sulfonylurea in the Janssen submission and +1.397 in the AG: Table 108 Differences in the results for pioglitazone can be explained by the choice of dose specific nodes. The AG NMA pooled pioglitazone doses together, whereas the Janssen NMA considered separately pioglitazone 15, 30, and 45 mg. Moreover, the studies assessing pioglitazone included in the AG NMA and Janssen NMA differed to an extent. The Janssen NMA excluded the study with pioglitazone titration (Erem 2014) that was included in the AG analysis. Some pioglitazone trials with high drop-out rates were excluded from the AG NMA but included in the Janssen NMA (e.g. Aronoff 2000, Chou 2012 and Scherbaum 2002). A trial that assessed pioglitazone versus glibenclamide (Watanabe 2005) was excluded from the AG NMA and included in the Janssen NMA. As described above, the NMAs differed in how sulfonylureas	

	were included. Janssen considered multiple sulfonylureas, but the AG considered that the only sulfonylurea of relevance was gliclazide. Accordingly, the evidence base on sulfonylurea differed between the two NMAs. The AG evidence on the relative efficacy of canagliflozin vs. sulfonylurea was obtained from a double-indirect link (canagliflozin <-> placebo <-> (pioglitazone or vildagliptin) <-> gliclazide; see figure below). Regardless, within the updated NMA conducted by Janssen, the reduction HbA1c for sulfonylureas closely matched that determined by the AG.  **Figure 4** Network plot – glycated haemoglobin (HbA1c) Differences in hypoglycaemia event rates were also seen between the 2 NMAs that likely resulted from the differences in inclusion of sulfonylurea studies. The gliclazide studies included in the AG NMA reported low hypoglycaemia rates, which may have driven the low rates seen in the AG NMA: • Lawrence 2004: did not report the hypoglycaemic events • Erem 2004: 0 patient in both arms (gliclazide and pioglitazone) had an hypoglycaemic event • Foley 2009: did not report hypoglycaemia data at 24-	

	26 weeks but at the end of the study (104 weeks), the rates of patients with at least one grade 1 hypoglycaemic event were: vildagliptin = 0.7% and gliclazide = 1.7% (0 patient had a grade 2 hypoglycaemic event in both arms) The high amount of uncertainty associated with the HbA1c effect estimates for pioglitazone, vildagliptin and gliclazide in the AG NMA (see for example Figure 5 within the AR) indicate a possible heterogeneity or lower information content in this part of the evidence network. This is confirmed in the results on weight gain (Figure 7 of the AR) that also show a large uncertainty for the estimates associated with vildagliptin and gliclazide. In light of differences in the efficacy estimates for sulfonylurea and pioglitazone between the Janssen submission and the AG NMA, it would be interesting to see how the AG NMA efficacy estimates would change with their removal. Janssen have conducted such an analysis, please see separate document, titles “Additional Information”. Moreover, the AG assumed some efficacy estimates that were unavailable from the NMA. In particular, the values for SBP change with pioglitazone and sulfonylurea were based on assumptions. Janssen was able to source these estimates from the NMA used to inform the submission, which was conducted in line with NICE Guidelines 2008 and DSU 2011.	

Issue 10 Lack of statistical details for the Janssen NMA

Description of problem	Description of proposed amendment	Justification for amendment
On pages 112-115, the report noted a lack of statistical details for the Janssen NMA.	As stated by the AG, the Janssen NMA was conducted appropriately and thoroughly. Janssen summarised only the fundamental elements of the NMA within the submission as to	Janssen has provided a brief summary of key statistical information related to the NMA,

	allow for space for the full reporting of results within this size restricted document. Thus, in places for contributing analyses such as the NMA, Janssen refer the reader to consult the study report for more technically specific information and within which on this occasion the required information can be found on page17. In brief, the AG is correct in finding that both random- and fixed-effects analyses were carried out. In a sparse network of evidence, the inclusion of treatments that are informed by only one study should pose no problem in terms of estimating the rest of the evidence network unless convergence in the variance estimator becomes a problem. The efficacy estimate for that treatment with sparse evidence will, however, be subject to more uncertainty than the treatments informed by multiple studies. The Gelman-Rubin plots were examined in case of doubts on the convergence. The convergence was good for all analyses, except for the analysis of hypoglycaemic events. Due to this non-convergence, the number of iterations was increased only for the analysis hypoglycaemic events where we have used 100,000 burn-in and 100,000 iterations for the estimate for the fixed effect model. More information on the convergence of the modelling may be found in the NMA report from Janssen, on page 16 and in Appendix 8. Results for treatment efficacy were presented as the efficacy relative to canagliflozin, because this was the treatment of interest in the Janssen submission. As the purpose of the NMA is to establish a network of evidence, it is also possible to present the results relative to any other comparator, the way the AG did in Figures 5, 7, etc.	which may be found in the original study report, as signposted within the Janssen submission.

Issue 11 Question regarding differences between 2 Janssen NMAs

Description of problem	Description of proposed amendment	Justification for amendment
On pages 124, the AG questions the differences in the rates of severe and non-severe hypoglycaemic events for pioglitazone and sitagliptin observed in the NMAs with and without repaglinide.	The Janssen base case did not include comparison vs. repaglinide; therefore the NMA without repaglinide was used in the base case. The AG is correct that for pioglitazone and for sitagliptin, the hypoglycaemia rates are lower when the two Jovanovic studies assessing repaglinide were included: (Jovanovic et al. 2000)(repaglinide vs. placebo) and (Jovanovic et al. 2004) (repaglinide vs. pioglitazone 30 mg). The inclusion of these 2 trials added an indirect link to pioglitazone 30 mg via placebo – repaglinide – pioglitazone 30 mg. Moreover, pioglitazone 30 mg is linked to sitagliptin via the (Henry et al. 2014). This explains why the inclusion of repaglinide in the network had an impact on the results of pioglitazone and sitagliptin. This difference is further explained in the analysis of the hypoglycaemic events as there were fewer studies in the analysis for this endpoint. Therefore, the estimates are less robust as they are based on less evidence (for example, for HbA1c there were 4 studies on linking placebo and sitagliptin while there are only 2 studies for the analysis of hypoglycaemia). Moreover the analysis of hypoglycaemic events is less stable in a more general point of view as the model experiences some convergence issues due to low number of events in most trials included in the NMA and standard approach adjustments were necessary to reach convergence (this limitation has been explain in detail in the NMA report on page 30 and Table 34 in Appendix 8). The trial by Jovanovic 2000 was excluded by the AG due to a high drop-out rate, but Janssen could not identify the rational for the exclusion of Jovanovic 2004. In scenario analyses 1 through 4, repaglinide was used as a	Janssen has provided an explanation of the differences observed in the NMAs with and without repaglinide.

	comparator and the full set of treatment effects (for all comparators) were sourced from the NMA that included the 2 repaglinide studies, including rates of hypoglycaemic events. The alternative parameter inputs did not demonstrably alter the results for pioglitazone and for sitagliptin, for example reducing the ICER for canagliflozin 100 mg vs. sitagliptin from £1,407 in the base case to £1,254 in scenario 1 and increasing the ICER for canagliflozin 100 mg vs. pioglitazone from £78,518 in the base case to £84,048 in scenario 1 (though remember that scenario 1 includes differences, albeit much smaller, in the other NMA treatment effects as well).	

Issue 12 Inconsistencies in the AG efficacy estimates

Description of problem	Description of proposed amendment	Justification for amendment
Janssen has identified inconsistencies between the reporting of treatment effects between Table 9 and Tables 51-53, in the AR.	The AG explains in considerable detail in the Section 3 ("Network meta-analysis") of the AR how the NMA was conducted. Janssen believe that the methods used by the AG are adequate and were in most part able to replicate the analysis (as explained in a separate document provided by Janssen, titled "Additional Information"). Janssen were able to achieve very similar results to those presented in Table 9 of the AR. However, in the cost-effectiveness modelling section, different estimates are presented in Tables 51 and 52. It is unclear how the estimates in Tables 51 and 52 have been derived. The AG states on Page 166 that "Clinical effectiveness was sampled within the NMA" and that a check was made that the subsample of 1000 draws for the HE modelling had the same means. From comparing across the above mentioned tables it is apparent, though, that the means do not match. One possible reason may be the sentence on Page 118 stating	Janssen has highlighted inconsistencies in the reporting of treatment effects that are a crucial element of the economic analysis. Janssen is unclear as to how these inconsistencies may have arisen and would advocate that the AR includes further information to allow for the full understanding of the AG analysis.

	that “we need to be selective in the trials from which we extract data, rather than using the effect sizes from broad-spectrum meta-analysis”. This sentence suggests to Janssen that the AG did not use the network meta-analysis presented in this AR to inform the efficacy parameters of economic assessment. However, Janssen are unable to identify another source for the efficacy estimates that were used in the economic evaluation conducted by the AG. Additionally, on Page 169, the AG writes that “For the intensifications, due to a lack of data the addition of a treatment is assumed to have the same clinical effectiveness regardless of what it is being added to”. These efficacy estimates are shown in Table 53. It is unclear which studies informed these estimates as they match neither the AG’s meta-analysis nor the earlier Table 51 (gliclazide HbA1c, PIO and gliclazide weight, etc.).	

Issue 13 AG Misunderstanding

Description of problem	Description of proposed amendment	Justification for amendment
On page 122, there appears to be a misunderstanding that only pairwise comparisons are permitted in the ECHO-T2DM model. Consequently, the AG is unclear whether the characterisation of uncertainty within the probabilistic sensitivity analyses (PSAs) across all the comparators is correct (i.e., whether each treatment arm used the same sampled parameter values across the various pairwise comparisons).	Details about the way in which the ECHO-T2DM model runs comparisons can be found on page 48 in the Janssen submission and in its accompanying Appendices, Appendix 4. In brief, the results submitted were based on multiple comparison methods, in which the same hypothetical patients and the same PSA parameters were applied for each of the treatment alternatives. This means that for each simulation run, canagliflozin and comparator were simulated with identical patients and PSA parameter values, so agents cannot be stochastically favoured or disfavoured relative to the others. However, although the patients and PSA parameter values are	The approach used was consistent with NICE expectations and appropriate for addressing the study question.

	identical for all agents within each simulation run, they did vary across simulation runs (e.g., the base case versus scenario analysis 1 and scenario analysis 2, etc.).	

Issue 14 AG Misunderstanding

Description of problem	Description of proposed amendment	Justification for amendment
On pages 125-127, there appear to be misunderstandings with regard to the treatment effect rebound assumptions.	The AG is correct in finding that the Janssen economic modelling includes a rebound of treatment effects whenever a treatment is discontinued. This rebound is applied regardless of the reason for discontinuation (e.g., adverse events, failure to meet HbA1c targets, and eGFR-related stopping rules). While the ECHO-T2DM model supports different assumptions, the magnitude of the rebound always equalled the magnitude of the initial treatment effect itself in the simulations supporting the current submission. That is, the initial treatment effect is reversed (rebounding to “natural history” and not to “baseline”). This rebound mechanism is applied equally to all covariates (HbA1c, BMI, SBP, LDL, HDL, triglycerides, and total cholesterol). Rebound is applied regardless of the position in the treatment sequence of the treatment being withdrawn, and regardless of the treatment that follows the discontinued treatment. The AG is correct that the additional “effect” of having applied a differential annual drift during the treatment is not reversed (although this would not apply once patients have altered treatment) and thus becomes permanent (even when an agent is discontinued). For the simulations submitted, this advantages pioglitazone and disadvantages sulfonylurea. Discussion at a clinical advisory board suggested that the ADOPT study would be the most suitable source for HbA1c drift parameters. This same panel of experts that	As noted on page 40 in the submission, Table 12 specifies rebound as immediate reversal of the treatment effect; further clarification appears in the in the neighbouring text.

	recommended the SBP and weight drift approaches as well. Rebound effects are strictly related to the discontinuation of agents. Whenever an agent is discontinued, the ECHO-T2DM model will assign the next indicated agent in the treatment sequence as needed to reach glycaemic control. Thus, the AG is incorrect in the following statement “It is not obviously reasonable to assume that there will be rebound when patients start insulin”, where the AG is trying to associate the “rebound” to the agent being started, not to the agent being discontinued. It is true, that the net effect of the rebound and treatment effect associated with rescue medication (insulin in the above case) would logically not be associated with an increase in HbA1c (i.e., worse control), since ECHO-T2DM would intensify the rescue medication by increasing the dose or add additional agents as needed to achieve glycaemic control.	

Issue 15 AG Misunderstanding

Description of problem	Description of proposed amendment	Justification for amendment
On page 218 (Table 104), there is an incorrect value reported for patient characteristics	In Table 104 of the AR, the duration of diabetes for Janssen canagliflozin trials is listed as 0.0. This is not correct. The ECHO-T2DM model uses a uniform distribution for this parameter where the min/max ranges are set. Specifically, we applied a range of 0 to 9.358, which is presented in the Appendix, Table 13, page 36. This range is based on the pooled monotherapy RCTs for canagliflozin. The mean value is 4.679.	Janssen advocate that Table 104 be corrected.

Issue 16 Incorrect description of modelling of uncertainty and convergence

Description of problem	Description of proposed amendment	Justification for amendment
On page 122, when describing the Janssen economic model, Janssen are unsure of the definition used to describe deterministic analyses and calls into question whether characterisation of uncertainty within the PSAs across all the comparators is correct and robust.	Janssen is unsure about the terminology regarding "deterministic" (which the AG define as including no second order sampling, but presumably allowing for 1st order stochastic uncertainty). ECHO-T2DM does have the capability to inactivate second order sampling of parameter values, and thus does qualify as "deterministic" modelling; however, it includes only Monte Carlo based micro-simulation sampling of patient cohorts and ultimate outcomes (i.e., a cohort-level deterministic analysis is not supported). As for inactivating second order uncertainty, we did not present such simulation results because Janssen believe they would be fundamentally flawed for analysis of complex, multi-factorial diseases like T2DM with complex, inherently non-linear models. The clinical trial results provide a distribution, but the sample mean is only a point estimate of the true value. To the degree that T2DM models are constructed with many interdependent, highly non-linear equations, assuming a true parameter value rather than using the distribution of possible values generated by the trials (and other data sources) themselves will lead to biased estimates of the outcomes (Claxton 2008) (Claxton, 2008). With regard to the AG's characterization of simulation results as having a high degree of Monte Carlo error, we disagree. The number of patient cohorts is directly related to the parameter uncertainty, and the large number of patients per cohort ensures that uncertainty due to patient heterogeneity can be captured adequately. The choice is, essentially, one of simulating a given number of heterogeneous patients once each or simulating a smaller number of heterogeneous patients multiple times. While it is always desirable to reduce Monte Carlo error, in the face of this trade-off, capturing as much of the between-patient variation as possible by simulating a larger	While we did not perform deterministic analyses, we posit that these types of analyses are inappropriate given the inherent nonlinearity arising from the complex pathophysiology of T2DM

	number of different individual patients per cohort was preferred. This captures more patient heterogeneity and thus eliminates more uncertainty in the cohort means than if a Monte-Carlo loop had been added.	

Issue 17 Incorrect description of treatment algorithm

Description of problem	Description of proposed amendment	Justification for amendment
On page 122, of the AR, the AG question the credibility of the ECHO-T2DM model on the basis that no convergence analysis was presented as part of the Janssen submission.	It is correct that we did not present an analysis of model convergence across patients modelled due to space constraints. Such data were presented to NICE during the course of a previous single technology appraisal (STA) submission for the use of canagliflozin in combination therapy, however, and the results were deemed stable at lower sample sizes than those used during this multiple technology appraisal (MTA) (1,000 x 1,000 for the base case). The doubling of patients for this submission (1,000 x 2,000) was done intentionally to give confidence in the stability of the results. A convergence analysis similar to the convergence analysis run for the STA od canagliflozin has retrospectively been conducted. Scenario 1 (identical key assumptions as the base case with the inclusion of repaglinide as a comparator) was simulated ten times, with a 1,000 x 1,000 sample size, and with different seed values. The variation of the following outputs was assessed: • Absolute costs • Absolute QALYs • Incremental Costs • Incremental QALYs • ICERs	Janssen has justified why no model of convergence for ECHO-T2DM was presented as part of the original submission made by Janssen.

	• Net Monetary Benefit Please note that the variability in the ICER cannot be assessed here because there are no comparators for which at least two quadrants of the cost-effectiveness place were not covered. Therefore, we present the variability in the NMB, which is invariant to those problems, and the variation is relatively stable across comparators and relatively modest (between about £70 and £100). Perhaps more interesting, however, is the variability surrounding the Δcost and ΔQALY. Again, the sample size here seems sufficiently robust, the variation of Δcost and ΔQALY (between about £20 to £35 for Δcost and around 0.005 for ΔQALY). Remember that the base cases were simulated with 2,000 x 1,000 sample size and will have even less variation.	

Issue 18 Incorrect description of treatment algorithm

Description of problem	Description of proposed amendment	Justification for amendment
On pages 123, 126, and 133, the report indicates that there is ambiguity regarding the modelling of oral rescue medication upon treatment discontinuation.	On page 48 of the submission made by Janssen, it is explained that three arms of canagliflozin use are modelled, where canagliflozin 100mg is defined as the base case and canagliflozin 300 mg, and canagliflozin 100 mg dose increase as two further comparator arms. Thus far, canagliflozin is investigated in clinical trials only as 100 mg and 300 mg separately. However, a recently completed trial, DIA4004, investigates the efficacy, safety, and tolerability of canagliflozin (100 mg, up-titrated to 300 mg, if applicable) in the treatment of patients with T2DM with inadequate glycaemic control on metformin and sitagliptin therapy. No results are as yet available. The AG correctly noted that canagliflozin 100mg is followed by gliclazide rescue medication in the <u>intervention</u> arm but by canagliflozin 300 mg prior to gliclazide rescue medication in the canagliflozin dose titration <u>comparator</u> arm. The intervention arm of	Janssen has provided clarification of the treatment algorithms used. Janssen believe that this information has been provided in the submission materials.

	canagliflozin represents the clinically plausible scenario in which patients are treated initially with canagliflozin 100 mg are tolerating canagliflozin 100 mg once daily and have an eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, as a result the dose can be increased to 300 mg once daily orally. On page 38 of the Janssen submission the structure of the titration scenario is explained in full. Furthermore, all treatment pathways are clearly described in Appendix 4.2.4 of the submission made by Janssen. The three different arms are: ○ Intervention Arm: Just canagliflozin 100mg, which was naturally followed by the addition of gliclazide as rescue therapy (like most of the other comparators) ○ Intervention Arm: Just canagliflozin 300mg, which was naturally followed by the addition of gliclazide as rescue therapy (like most of the other comparators) ○ Canagliflozin Dose Titration Arm: Begins with canagliflozin 100mg and increases to canagliflozin 300mg as needed to maintain control, which is followed by the addition of gliclazide rescue therapy as needed. The treatment algorithm is correctly reflected in AG Table 16, but needs to be corrected in Table 103. The correct treatment algorithm is reproduced in the Table below to correct this misunderstanding. To clarify, unlike when patients simply lose HbA1c control, if patients discontinue their monotherapy treatment due to adverse events or contraindications, they switch to the next agent in the treatment sequence (as the details are presented in Appendix 4.2.4. The rescue therapy profile (i.e., treatment effects and adverse events) is the same regardless of whether the patient discontinued the monotherapy treatment or not (i.e., the effect is “incremental”). The AG is correct that repaglinide was included as a comparator only in scenario analyses 1 through 4 (as mentioned in Table 13 on page 47 of the submission). Further details about repaglinide as a	

	comparator can be found in Appendix 8.1.1. Repaglinide was not included in the base case for a number of reasons: current market share of repaglinide stands at <0.16% by volume; there is limited clinical experience with the drug within U.K.; and there are few relevant clinical studies on which to build a robust analysis. **Actual Janssen Modelling of Treatment Sequence** <table><tr><th>Initial Therapy (Start of Mono)</th><th>First Rescue</th><th>Second Rescue</th><th>Third Rescue</th><th>Fourth Rescue</th></tr><tr><td>Cana, Empa, Dapa</td><td rowspan="3">+SU (Gliclazide)</td><td rowspan="2">+NPH - Cana, Empa, Dapa, DPP-4i, Gliclazide</td><td rowspan="2">+Aspart</td><td rowspan="2">n/A</td></tr><tr><td>DPP-4i (Sitagliptin)</td></tr><tr><td>Pioglitazone 30mg</td></tr><tr><td>Sulfonylurea (Gliclazide)</td><td>+DPP-4i (Sitagliptin)</td></tr><tr><td>Repaglinide</td><td>+Pioglitazone 30mg - Repaglinide</td><td>+ Gliclazide</td><td>+ NPH - Pio 30mg, Gliclazide</td><td>+Aspart</td></tr></table>	

Issue 19 Clarification needed for source estimates

Description of problem	Description of proposed amendment	Justification for amendment
On page 125, there is confusion regarding the source of the clinical effectiveness estimates used for insulin rescue medication in Table 18.	Because of its flexible delivery schedule (and many possibilities for titrating dose), insulin therapy is more complicated to model than conventional oral (or other injectable) agents. While the ECHO-T2DM model can simulate insulin as a fixed-dose conventional agent like oral medications (with a one-time treatment effect), ECHO-T2DM also supports the more realistic scenario, in which insulin doses can be titrated upwards on an annual basis in order to maintain glycaemic control. This was the approach used in the simulations underlying this submission. The relevant details of this approach are provided in Table 12, on	Janssen has provided clarification on the sources for insulin rescue medication.

	page 33 in the Appendix supporting the submission made by Janssen. Additionally, details of the parameterization are discussed in Appendix 4.2.4; below is a brief summary.	

Issue 20 Incorrect assumption that needs to be clarified

Description of problem	Description of proposed amendment	Justification for amendment
On page 124, the report states that based on the electronic input sheets submitted by Janssen and the model having an annual cycle, the 26-week estimates were assumed to apply at the end of the first cycle.	There is concern over the application of 26-week data over the 52-week 1st cycle. As the ECHO-T2DM model operates with a Markov cycle length of one year, the ERG is correct in noting that 26-week treatment effects are not applied at 26 weeks. They are instead applied in the first year, which is the level of detail in time resolution available in ECHO, though it should be noted that patients experience ½ cycle of upward drift in HbA1c and the other bio-markers to counter the omission of data for weeks 26 to 52 in the NMA.	Janssen has provided clarification on the incorrect assumption regarding treatment effects.

Issue 21 Clarification needed on hypoglycaemia event rates

Description of problem	Description of proposed amendment	Justification for amendment
On page 133 regarding the hypoglycaemia event rates, clarification is needed on whether these rates were adjusted to be annual rates, to align with the annual model cycle.	To clarify, the ECHO-T2DM model simulates hypoglycaemic event rates (per year) and so rates are annualised. The 26 week data represents the time horizon of the trials underlying the NMA, the event rate endpoints in the trial were however calculated as rates per patient-year (i.e., on an annualised basis). For example, 100 events in trial with 400 patients over 26 weeks would imply 100 events over 200 patient-years (and an annual rate of 0.5 events per patient-year). In ECHO-T2DM, the hazard of hypoglycaemic events is modelled to	Janssen has provided clarification on hypoglycaemia event rates and their incorporation into the ECHO-T2DM model.

	match the mean rates of events observed in the clinical studies of each AHA. These hazards are modified to take into account the increased risk of hypoglycaemic events at lower values of HbA1c. The AG correctly notes that the relationship between HbA1c and the hypoglycaemic event rate (a hazard ratio of 1.43) comes from the large and long-term DCCT (DCCT 1991)study of Type 1 diabetes mellitus (T1DM). This is currently believed to be the most appropriate available data on this relationship (77), where multivariate adjustment for confounding factors and a large sample size engender relatively high confidence in the results. As explained in Appendix Section 4.2.3, results specific to insulin-treated T2DM patients based on a meta-analysis of 82 studies (155 trial arms) were presented at the ISPOR European Congress in 2013 (McEwan et al. 2013). While the methods used differed somewhat from those used in the DCCT analysis, for example the DCCT analysis was estimated from long-term patient-level data and the recent analysis was estimated using (presumably much shorter) aggregated trial data, exponentiation of the reported coefficients from the new meta-analysis generated hazard ratios that are similar, if not slightly larger (1.53 for non-severe and 1.89 for severe hypoglycaemic events) than the DCCT figure of 1.43. Differences in the choice of covariates and timing of the HbA1c measurement may explain the difference in part (the new analysis included both baseline HbA1c and achieved reduction, whereas DCCT used the current HbA1c value only). . Because rescue medication leads generally to convergence of HbA1c curves, the exact value of this hazard ratio is unlikely to be a major driver of the results and Janssen has interpreted the new evidence as confirmatory of the DCCT estimate used in the model. Additional supporting evidence on the relationship for T2DM comes from (Pontiroli, Miele, and Morabito 2012). The authors analysed clinical correlates of HbA1c, and of overall, nocturnal and severe hypoglycaemia in T2DM patients receiving insulin, and confirmed that lower HbA1c values are associated with a higher incidence of	

	hypoglycaemia.	

Issue 22 Clarification needed on adverse event rates

Description of problem	Description of proposed amendment	Justification for amendment
On page 134 regarding adverse events, clarification is needed on whether the UTI and GTI event rates were adjusted to be annual rates and so to be in line with the annual model cycle.	The UTI and GTI event rates are indeed defined as events per patient-year. The average length of time for which an event is experienced was estimated, using online resources such as NHS Direct, and the appropriate annual rate derived. The 26- week duration refers to the time horizon of the clinical trial, and not to the time period over which the rate applies. Thus, they are in line with the annual model cycle.	Janssen has provided clarification on adverse event rates.

Issue 23 Factual inaccuracies that need to be corrected

Description of problem	Description of proposed amendment	Justification for amendment
On pages 129-131, there are factual inaccuracies in the report regarding estimates for the evolutions of HbA1c and convergence between treatments.	In the ECHO-T2DM model, the evolution of HbA1c is determined by treatment effects, reversals associated with treatment withdrawal, and annual drift. Because treatments are intensified when a patient's HbA1c value exceeds the specified target value, which results in an application of treatment effects, convergence occurs in the simulations. This convergence was noted by the AG and is depicted in the plot showing mean HbA1c over time (Figure 11 on page 130 of the Janssen submission), which shows a convergence to values near the target value for all treatments during a large part of the simulation time horizon. While ECHO-T2DM does model events on an annual Markov cycle, treatment intensification of more than one escalation in a given cycle	Janssen has provided clarification on the evolutions of HbA1c and convergence between treatments.

	can occur if required to reach glycaemic control. The portion of patients escalating from the starting canagliflozin dose to the next treatment in the first year explains why the observed average drop in HbA1c in the first year for patients started on canagliflozin can exceed the treatment effect of canagliflozin obtained from the NMA, a question raised by the AG. Whilst the convergence in HbA1c is probably more pronounced for patients modelled to be receiving insulin, because their doses can be increased, this convergence is already evident earlier in the simulation, due to patients' escalation from the first treatment to the next treatment at different time points according to requirements to meet HbA1c; i.e. Patients with higher HbA1c (overrepresented in the control arm) reach the intensification threshold sooner, so they get the additional HbA1c lowering sooner, so on average the two HbA1c curves are pushed closer together (convergence). Heterogeneity in the timing of treatment escalation is modelled in ECHO-T2DM. As evident from Figure 10 within the AR, there is large-scale convergence in HbA1c evolution in the Janssen simulations. The AG question whether the linear rates of annual drift derived from Kahn et al. reflect reality adequately is, therefore, secondary. Of note, the plot on HbA1c evolution (Figure XX, in the AR) shows the population means averaged over many patient cohorts, i.e., individual steps such as clear saw tooth patterns, would be masked by heterogeneity in the timing of intensification due to patient heterogeneity and second-order uncertainty in treatment effects.	

Issue 24 Factual inaccuracies that need to be corrected

Description of problem	Description of proposed amendment	Justification for amendment
On page 132, the AR incorrectly states that using the ECHO-T2DM model, the absolute difference in SBP will be maintained even after insulin therapy is started.	Just as with HbA1c, antihypertensive rescue medication forces convergence over time in SBP values. Treated patients that worsen or do not improve SBP values will over time be prescribed more antihypertensive medicines than patients who had lower SBP values. Thus, patients with higher SBP will receive treatment (and experience SBP reductions) sooner than those with lower SBP values.	Janssen has provided clarification of the misunderstanding of convergence with the model.

Issue 25 Missing sources for QALY decrements

Description of problem	Description of proposed amendment	Justification for amendment
On page 134 (including Table 21), the AG was unable to identify the proper sources for QALY decrements.	The QALY decrements for GMI and UTI complications were sourced from Fordham et al (2013a) and Fordham et al (2013b) which correspond to reference 99, and 124, respectively, in the submission (please see page 43 of the Janssen submission and Table 30 in Appendix 6.2). Furthermore, these figures have also been published in (Shingler et al. 2015).	Janssen has provided the appropriate references for the QALY decrements.

Issue 26 Question on rate of neuropathy adverse events (AEs)

Description of problem	Description of proposed amendment	Justification for amendment
On page 137, the AG questions the reported rate of neuropathy with gliclazide and pioglitazone, indicating that it is not clear how this was handled in the ECHO-T2DM model.	The AG did a commendable job in trying to analyse the source of differences in QALY disutility. However, when a comparator has some categories with QALY gains and others with QALY losses, the AG appears to have summed the absolute values, thus giving a denominator that has no relationship to the total difference in QALYs between canagliflozin 100 mg and the comparator. Given that this unnatural summing was pronounced only for pioglitazone, Janssen do not find it odd that there were differences between pioglitazone and many of the other comparators (in particular gliclazide, which the AG pointed out specifically). In addition to this mathematical feature, it is important to note that the proportion of QALY differences between the comparators and the intervention (canagliflozin 100 mg) depend on individual treatments relative strengths and weaknesses. Because neuropathy rates are primarily steered by the degree of HbA1c control, treatment arms with relatively poor HbA1c control will experience greater differences in neuropathy when compared with canagliflozin 100 mg than agents with HbA1c control much more similar to canagliflozin 100 mg. Not surprisingly, the QALY disutility associated with neuropathy is almost identical for pioglitazone and canagliflozin and the QALY differences between pioglitazone and canagliflozin are primarily associated with other factors. It is important to consider that just as RCT's are typically powered primarily for specific outcomes and not for secondary outcomes and AE's, small stochastic differences in these particular outcomes in the modelling may occur, as such small absolute differences for individual items are of lesser importance.	Janssen has provided clarification of how neuropathy AE rates were handled in the model.

Issue 27 No eGFR stopping rule <<*Placeholder to be completed by Pierre*>>

Description of problem	Description of proposed amendment	Justification for amendment
On page 165, the AG expressed an interest in understanding the impact that turning off eGFR-influenced discontinuation would have upon the cost effectiveness estimates of the Janssen modelling.	Janssen have provided a full description of this analysis in a separate document provided by Janssen, titles "Additional Information". In brief, Janssen agree with the AG that evaluating the impact of the flozin-specific modifications supported in ECHO-T2DM provides useful information. An exploratory analysis was conducted utilising the assumptions and inputs of the base case simulation submitted by Janssen with the eGFR stopping rule and the eGFR treatment effect multipliers deactivated. The sample size was 1,000 cohorts of 1,000 patients. The direct consequences of this scenario are that time on flozins will increase in proportion to the number of patients with eGFR drifting below the discontinuation thresholds and that initial treatment effects will be maintained for the time for which a patient's HbA1c remains controlled with the flozins. Please be aware that the simulations here are based on the current price of canagliflozin 300mg. The results show: • Only small stochastic differences for the non-flozins (which were unaffected by the stopping rule) • Drug acquisition costs for canagliflozin 100mg increased from £3,184 in the base case to £3,279 in this scenario (since patients take them on average longer), but insulin medication costs decreased from £5,553 to £5,528. o Note: the relatively small differences between the two scenarios for canagliflozin 100mg are due to the low proportion discontinuing due to low eGFR • Drug acquisition costs for canagliflozin 300mg increased	Janssen have conducted an analysis whereby the functioning of the eGFR modules has been removed.

	from £3,407 in the base case to £3,681 in this scenario (since patients take them on average longer), but insulin rescue medication costs decreased from £5,296 to £5,095. • The same pattern was true for the other flozins as well • LYs and QALYs for all of the flozins increased in general from the base case to this scenario, with the exception of empagliflozin 25 in the canagliflozin 300 BC. Again this is due to the fact that it is a small proportion that discontinues due to low eGFR and the influence of stochastic differences. The relative difference to the non-flozin comparators for canagliflozin 100mg and canagliflozin 300mg increased in general as well, with the exception of pioglitazone vs. canagliflozin 100mg and gliclazide vs. canagliflozin 300mg. • Summary of the cost-effectiveness results are presented for canagliflozin 100mg and canagliflozin 300mg in the Tables of the additional Information document provided separately by Janssen. As can be seen, while the mean costs and mean utilities varied slightly, the HE verdict is qualitatively (and indeed almost numerically) identical.	

Issue 28 Disagreement with progression rates used for sulfonylureas

Description of problem	Description of proposed amendment	Justification for amendment
On page 128, the report suggests that applying the glibenclamide progression rate to gliclazide may not be appropriate, citing (Satoh et al.	The Satoh et al. study referred to by the AG was a non-randomised chart review of Japanese patients on sulfonylureas: • 65 patients on gliclazide only	Janssen has provided justification for the progression rates which were used.

2005).	• 168 patients on glibenclamide only • 41 patients who crossed-over The authors found that start of insulin was delayed in the gliclazide group. Grouping together the patients who used glibenclamide or crossed over, they found a mean duration from start of sulfonylurea until start of insulin of 8.0 years, compared with 14.5 years in the gliclazide-only group (P <0.0001). While this is an interesting finding, there are a number of reasons why it may not with certainty support the claim that gliclazide has a better coefficient of durability than glibenclamide in actual practice. First, the study was non-randomised and the sample sizes in each study arm are relatively small. Non-measured confounding factors, such as selection biases in which patients are given gliclazide or glibenclamide, may partly explain the results. Also, the authors present no calculation of required sample size and do not state what methods have been used to adjust for multiple testing. It is, thus, possible that some statistically significant results were observed purely due to chance. The study researchers noted imbalances between the two patient groups at baseline. Gliclazide patients also had on average lower n patients' fasting plasma glucose (FPG) at the start of the first oral anti-hyperglycaemic agent; lower HbA1c at the start of both the first oral AHA and at the start of sulfonylurea; and their average HbA1c during all treatment periods was lower than in the glibenclamide patients. The authors attempted to correct these biases by combining the patients receiving glibenclamide only and those that switch between the sulfonylureas into one group, but this did not resolve the differences in the patient baseline characteristics. In defence, the advantage of insulin-delay for gliclazide vs. glibenclamide did persist even when correcting for these baseline imbalances (see the Cox proportional hazard model in Table 3 of this publication) but it is still unclear whether any other unmeasured confounding factors could explain this observed difference.	

	Moreover, the study fails to state whether this attempted adjustment using the Cox proportional hazard model was applied to the time from diabetes diagnosis to start of insulin, time from start of first oral agent to insulin, or time from start of sulfonylurea to insulin, all of which have been studied. Perhaps even more importantly, Janssen is unclear how the results from the Satoh et al. study can be used to support the modelling of upward HbA1c drift in this kind of health-economic model because time to insulin is not exclusively determined by the annual drift. Indeed, other factors influence time to insulin initiation as well, including the magnitude of the initial treatment effect, compliance, and early discontinuation (e.g., due to AEs). All of these are handled explicitly in ECHO-T2DM (and presumably the UKPDS OM1); annual drift has to be parameterised separately from these. A scenario analysis (#2) was conducted within the Janssen submission, in which gliclazide was given an identical glycaemic drift to the other AHAs (described in Table 13, p. 47 and results presented in Table 19, p. 58). The ICER of canagliflozin 100 mg vs. gliclazide increased from £2,377 in the base case to £29,186 in scenario analysis 2, a value that remains below an acceptable threshold of £30,000 and one that is likely quite conservative given the low likelihood that gliclazide has the same drift. It should also be noted that the price used for the gliclazide comparator in the Janssen submission is about 2.5 times lower than the price used by the AG, which would artificially inflate the ICER.	

Issue 29 Dismissal of relevance of Mt. Hood assumptions

Description of problem	Description of proposed amendment	Justification for amendment
On pages 121-122 and 215, the report	The AG is correct that the simulations conducted for Mt. Hood	Janssen has provided an explanation of why

states that modelling assumptions used in the Janssen submission were likely different than those used for the Mt. Hood challenges.	challenges and the simulations conducted for external validity testing differ (e.g. model inputs and treatment pathway assumptions) from the simulations conducted for this submission (monotherapy treatment with the flozins and key comparators). However, that is the nature of simulations to address different study questions. The purpose of Mt. Hood challenges and external validation is to test the ability of the models to replicate the results of long-term trials and observational data in settings where the true results are known and we can evaluate how well the models perform, so each of the individual validation exercises is customised to model the patients and intervention in the study being considered. If during the validation the models can reproduce results of a large number of quite different studies reasonably well, then it increases the chances (and our confidence) that it will perform well even in a new setting for which long-term data are not available. The references to the Mt. Hood Challenges and to external validation were to inform the AG of previous validity testing so that the AG can interpret the results with an appropriate degree of confidence. The AG is correct, however, in assuming that bio-marker evolution has been modelled differently in some of these validation settings than in the Janssen submission, however, the approach is the same, matching drift to the best available data. For some studies, the long-term biomarker progressions are publically available and can be use directly from the study. For many others, the evolution has not been available, as such the best available matches are sources, often resulting in the use of the results of the ADOPT study in the same manner as in this submission.	the modelling assumptions would be expected to be different in part but also how a number of the modelling approaches have been used in validation setting previously.

Issue 30 Mistake in eGFR discontinuation rules

Description of problem	Description of proposed amendment	Justification for amendment
On page 133, the report notes some issues with the eGFR discontinuation rules used for empagliflozin	The discontinuation of empagliflozin 25 mg if eGFR drops below 60ml/min/1.73m^2 was correct; however there was a mistake in the modelling for empaglifozin 10 mg, which should have been continued until eGFR dropped below 45 ml/min/1.73m^2.	Janssen has provided updated base case results to correct this mistake. Greater detail of these results have been presented in in a separate document provided by Janssen, titled “Additional Information”,

Issue 31 Canagliflozin 300 mg results were omitted from scenario analysis 2

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>On page 140, the report notes that canagliflozin 300 mg results were omitted from scenario analysis 2.</td><td>We apologise that canagliflozin 300mg was inadvertently omitted from Table 51 in the Janssen submission appendices. We have reproduced this Table below and included the correct estimates from the original submission for canagliflozin 300 mg from scenario analysis 2. The correct ICER for canagliflozin 300 mg is slightly lower.
<table>
<tr><th>Therapy</th><th>Mean Costs</th><th>Mean QALYs</th><th>Cost per QALY (ICER)</th></tr>
<tr><td>Repaglinide</td><td>£20,982</td><td>10.03</td><td>-</td></tr>
<tr><td>Pioglitazone</td><td>£21,485</td><td>9.95</td><td>Dom</td></tr>
<tr><td>Gliclazide</td><td>£22,589</td><td>10.01</td><td>Dom</td></tr>
<tr><td>Sitagliptin</td><td>£23,615</td><td>9.99</td><td>Dom</td></tr>
<tr><td>Cana. 100</td><td>£23,732</td><td>10.05</td><td>£137,500</td></tr>
<tr><td>Empa. 25</td><td>£23,732</td><td>10.03</td><td>Dom</td></tr>
<tr><td>Empa. 10</td><td>£23,739</td><td>10.02</td><td>Dom</td></tr>
<tr><td>Dapagliflozin</td><td>£23,786</td><td>10.02</td><td>Dom</td></tr>
<tr><td>Cana. 100/300</td><td>£23,853</td><td>10.06</td><td>£95,700</td></tr>
<tr><td>Cana. 300</td><td>£24,460</td><td>10.09</td><td>£57,967</td></tr>
</table>
Recall, however, that the price of canagliflozin 300 mg has changed</td><td>Janssen has provided an updated table to correct this inadvertent mistake.</td></tr>
</table>

	and the following Table below reflects this new price change. Canagliflozin 300 mg (and canagliflozin dose titration) naturally become cheaper, rendering a new ICER of £42,517. \	

Issue 32 Differences in AG versus Janssen modelling

Description of problem	Description of proposed amendment	Justification for amendment
On page 121, the report describes differences in the Janssen modelling compared with that of the AG and other companies. Janssen has recognised that some differences identified by the AG may have arisen due to misunderstandings of the ECHO-T2DM model and are in fact similar between the two modelling approaches.	In a separate document, titled “additional Information”, Janssen has provided a summary to demonstrate the potential misunderstanding of the ECHO-T2DM model, which led the AG to believe that the model differs considerably from OM1. This summary aims to highlight the number of similarities between the models and also highlights the steps Janssen took to align the assumptions and modelling approaches as closely to those proposed by the AG in the original protocol document.	Janssen has provided a separate detailed explanation of the ECHO-T2DM model to illustrate similarities to the AG modelling approach.

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

Pro-forma Response

Additional Information

CANAgliflozin, DAPAgliflozin and EMPAgliflozin monotherapy for treating type 2 diabetes [ID756]

1. Comparison of ECHO-T2DM and AG's OM1

To assist the Assessment Group (AG) with this comparison and contrast with the Janssen submission, we have summarised the key elements of the AG and the Janssen analyses. This summary aims to highlight the steps taken by Janssen to conduct the economic analysis in line with the AG protocol and thus the similarities between the 2 models' inputs and assumptions.

It should be noted that although Janssen are not certain what precisely was simulated by the AG, our closest description is summarised in Table 1 below. On inspection, it is clear that there are many more similarities than differences in the simulation specifications.

At a general level, the key differences in the Janssen and AG's analyses are:

- Model employed (UKPDS OM1 vs. ECHO-T2DM)
- Cardiovascular disease (CVD) and mortality risk equations modelled (UKPDS 68 vs. 82)
- Method for simulating biomarker evolution (UKPDS OM1 equation vs. ADOPT-style coefficient of determination approach)
- Granularity of microvascular health states in UKPDS OM1 vs. ECHO-T2DM
- eGFR discontinuation was simulated for the flozins by Janssen but not by the AG. This is further explored in Section 3, below.

Table 1. Economic model comparison: model inputs and assumptions

	ASSESSMENT GROUP MODELLING (UKPDS-OM1)	***JANSSEN MODELLING (ECHO-T2DM MODEL)***
Simulation run details		
Time horizon	*40*	*40*
Cycle length	*1 year*	*1 year*
# patients simulated	*1,000 PSA iterations each with a patient cohort of 50,000 with 100 inner loops. For deterministic model runs, i.e. those without any second order sampling, number of inner loops increased to 1,000*	*2,000 (1,000 in SA)*
# cohorts		*1,000*
Discount rate (health and costs)	*3.5%*	*3.5%*
Macrovascular Risk equation	*UKPDS 68*	*UKPDS 82*
Key Baseline Patient Characteristics		

Main source of data	*Current draft NICE CG --> THIN database, additional data from Health Survey for England*	*POOLED DIA3005 and Inagaki 2014*
Age (years)	*59.80*	*56.20*
Disease duration (years)	*2.00*	*4.68*
Smokers (proportion)	*0.18*	*0.09*
HbA1c (%)	*8.40*	*8.02*
SBP (mmHg)	*137.50*	*127.72*
LDL Cholesterol (mg/dL)	*N/A, embedded within the total cholesterol ratio within UKPDS OM-1*	*118.01*
HDL Cholesterol (mg/dL)	*45.56*	*48.33*
BMI (kg/m^2)	*31.90*	*29.69*

Efficacy, safety and tolerability data:

Main source of data	*AG NMA + assumptions*	*Janssen NMA + assumptions*
NMA details	*See AG report, chapter 3 starting at p. 78*	*See Janssen submission, chapter 6, starting at p. 23*
Treatment Effect Details	*See table 51 and 52 in AG report, p. 168-169. For comparison of the efficacy data, please see tables 106-108 on p. 219-221*	*See table 17, p. 41 of the Appendix*

Treatment sequence

HbA1c intensification threshold	*7.50%*	*7.50%*
<u>When drugs are discontinued</u>		
Discontinuation in first cycle due to AEs	*Yes*	*Yes*
Discontinuation due to rescue? therapy	*CANA, DAPA, EMPA, DPP, PIO not discontinued. SU discontinued first when adding bolus insulin*	*CANA, DAPA, EMPA, DPP, PIO, SU discontinued when initiating basal insulin*
Discontinuation due to lower values of eGFR		
CANA	*No*	*CANA 100mg: <45 mg/mi/1.73m^2; CANA 300mg: <60 mg/mi/1.73m^2*
DAPA	*No*	*DAPA: <60 mg/mi/1.73m^2*
EMPA	*No*	*EMPA: <60 mg/mi/1.73m^2 (NB. corrected to <45 N/A, embedded within the total cholesterol ratio for EMPA 10mg in post-submission simulations)*

Consequences for discontinuing a treatment

Rebound of treatment effects upon discontinuation?	*"rebound is to the baseline value rather than to the baseline value plus annual drift" (AG report, p. 127)*	*Full and immediate rebound **<u>of initial TEs</u>** on all biomarkers*

Rescue therapy following HbA1c failure on CANA and comparator:

Oral Rescue	*See table below*	*See table below*

Insulin Rescue	*NPH then Bolus*	*NPH followed by adding Aspart*
Insulin treatment		
First insulin rescue agent	*NPH (TEs are applied as one-time effects)*	*Titrate NPH from 10 IU/day to 60 IU/day, as needed to maintain glycaemic control (TEs are applied according to the assumption that they are proportional to dose (i.e., the dose-response is linear)*
Second insulin rescue agent	*Bolus (TEs are applied as one-time effects)*	*Titrate Aspart from 5 IU/day to 200 IU/day, as needed to maintain glycaemic control (TEs are applied according to the assumption that they are proportional to dose (i.e., the dose-response is linear)*
Drift assumptions		
Type of progression	*Non-linear (UKPDS 68 equations for HbA1c, SBP and Tot:HDL ratio). Linear for BMI*	*Linear, drug-specific (based on ADOPT (for HbA1c), using UKPDS (for SBP and lipids), from previous submissions (for BMI)*
HbA1c	*UKPDS 68 eq. 11 (non-linear), excluding parameter for second year since diagnosis*	*Linear: CANA, DAPA, EMPA, SITA: 0.14; SU 0.24; PIO: 0.07; Repaglinide 0.24, Insulin 0.15. NOTE: The impact of using UKPDS 68 equation for HbA1c evolution was examined in scenario analysis 14*
SBP	*UKPDS 68 non-linear equation*	*0.3 mmHg*
Lipids	*Constant Total:HDL ratio of 3.0 mmol/L (approx. 116mg/dL)*	*0.03 mg/dL*
BMI	*Linear*	*0.1kg/year converted into BMI*
Adverse events included		
Hypoglycaemia	*Yes, non-severe symptomatic and severe hypoglycaemic events*	*Yes, non-severe symptomatic and severe hypoglycaemic events*
Genital Mycotic Infections (GMI)	*GTI*	*Yes, male GMI and female GMI*
UTIs	*UTI*	*Yes, Upper and lower UTI*
Peripheral Oedema	*No*	*Yes (elevated risk for pioglitazone, base risk for others)*
Treatment targets for starting anti-hypertensive and -dyslipidemia treatment		
SBP (mmHg)	*Unclear if modelled*	*140 mmHg*
T:Chol	*Unclear if modelled*	*193.1mg/dL (5.0 mmol/l)*
LDL (mg/dL)	*Unclear if modelled*	*54.1mg/dL (1.4mmol/l)*
HDL (mg/dL)	*Unclear if modelled*	*77.2mg/dL (2.0mmol/l)*
TGR (mg/dL)	*Unclear if modelled*	*398.2mg/dL (4.5mmol/l)*
Drug costs (£)		
CANAgliflozin 100mg	*476.93*	*477.26*
CANAgliflozin 300mg	***476.93*** *(as of 1st August 2015)*	***608.63*** *(price at launch)*
DAPAgliflozin 10mg	*476.98*	*477.30*
EMPAgliflozin 10mg	*476.98*	*477.30*

EMPAgliflozin 25mg	*476.98*	*477.30*
SU (Gliclazide) 80mg	*62.18*	***25.81***
AG Comment	*Gliclazide MR cost used*	*"It seems likely that Janssen assumed the costs for gliclazide rather than the costs for gliclazide modified release"*
DPP-4i (Sitagliptin) 100mg	*433.57*	*433.86*
TZD (pioglitazone) 30mg	***93.25***	***20.48***
Repaglinide 2mg	*71.91*	*71.10*
State and event costs		
Main source of data	*UKPDS 84 for macrovascular and microvascular (MI, IHD, CHF, stroke, blindness, ESRD, Amputation)*	*UKPDS 84 for macrovascular (MI, IHD CHF, stroke)*
More info	*AG Report, table 111-112, p. 224*	*AG Report, table 111-112, p. 224*
QALY set		
QoL Values		
No Complication	*0.801*	*0.843*
Macrovascular	*UKPDS 62 [MI, IHD, CHF, Stroke]*	*CODE-2 [MI, IHD, CHF, Stroke). NOTE: The impact of using UKPDS 62 QOL values was examined in scenario analysis 16*
Microvascular	*UKPDS 62 [blindness, ESRD, amputation]*	*CODE-2 (accounting for different severity)*
ESRD	*-0.263*	*-0.175*
Obesity (per BMI>25)	*CODE-2*	*CODE-2*
Hypoglycaemia	*(Currie et al. 2006)*	*(Currie et al. 2006)*
UTI, GMIs	*(Shingler et al. 2015)*	*(Shingler et al. 2015)*

BMI, body mass index; CANA, canagliflozin; EMPA, empagliflozin; DAPA, dapagliflozin; ESRD, end-stage renal disease; MR, modified release; TE, treatment effect; QoL, quality of life;

Based on different NMA's, there were specific differences for some treatment effects associated with PIO and SU (see Table 2). Furthermore, the AG simulated only canagliflozin 300 mg, whereas Janssen simulated canagliflozin 100mg, canagliflozin 300mg, and canagliflozin 100mg->300mg dose titration separately.

Table 2. Economic model comparison: treatment pattern

Initial Therapy (Start of Mono)	***First Rescue***		***Second Rescue***		***Third Rescue***		***Fourth Rescue***	
	Janssen	*AG*	*Janssen*	*AG*	*Janssen*	*AG*	*Janssen*	*AG*
CANA, EMPA, DAPA	*+Gliclazide*	*+Gliclazide*	*+NPH - CANA, EMPA, DAPA, DPP-4i, Gliclazide*	*+ NPH*	*+Aspart*	*+Bolus - Gliclazide (if applicable)*	*N/A*	*N/A*
Sitagliptin								
Pioglitazone 30mg								
Gliclazide	*+ Sitagliptin*	*+PIO*						

Repaglinide	*+PIO* *- Repaglinide*	*+ PIO +* *Gliclazide* *- Repaglinide*	*+ Gliclazide*		*+ NPH* *- PIO,* *Gliclazide*		*+Aspart*	

Janssen is unclear about which interventions the AG have included within their economic analysis, as it appears that not all interventions considered in the NMA have been modelled. Specifically, it seems that only CANAgliflozin 300 mg and EMPAgliflozin 25 mg have been modelled, however there is some misalignment with this assumption in the text, e.g., in Table 50 it clearly states for canagliflozin 100 mg to be used as the ff starting agent in treatment sequence, however it reports the treatment effects associated with canagliflozin 300 mg in Table 52 of the Assessment Report (AR).

Interpretation of the results

*The Janssen analysis was intentionally conservative from the perspective of canagliflozin. For example, a*ll AE rate assumed for alternative flozins were assumed similar to those associated with the use of canagliflozin 100 mg and for other AHAs placebo rates were used; not all additional resource use costs have been accounted for, e.g. one off initiation costs associated with nurses educating patients starting on insulin; immediate weight rebound at treatment discontinuation; and the treatment effects for flozins are modified with decreasing eGFR.

The AG emphasised the results featuring no BMI-related disutility, which favours sulphonylurea and pioglitazone, which both increase weight. Evidence suggests to the contrary. Treatment impacts such as improved glycaemic control, low incidence of hypoglycaemia, and weight loss have been associated with an improvement in HRQL and healthy behaviours indicating a shorter-term feedback loop between HRQL and outcomes (Grandy, Fox, and Bazata 2012; Davies and Speight 2012). Researchers have proposed that patients are more likely to adhere to treatment regimens that offer benefits from the patient perspective, such as convenience, avoidance of hypoglycaemic episodes, and weight loss, vs. those regimens that do not (Davies and Speight 2012; Pi-Sunyer 2009) Furthermore, recent long-term data (EMPA-REG??) suggests patient weight-loss is prolonged, whilst receiving flozin treatment and does not support the transient weight loss assumptions investigated by the AG in their BMI driven scenario analyses.

In the submission and appendices (Appendix 4.2) Janssen give a detailed account of why ECHO-T2DM was chosen rather than an alternative. In brief, the SGLT-2-inhibitors (flozins) class of drugs is relatively new in the treatment of T2DM, and class members have a MoA, therapeutic profiles and adverse event profiles that differ from other AHAs. While there are no head-to-head data comparing canagliflozin with other SGLT2 inhibitors in patients with T2DM, a study comparing the pharmacodynamic effects of canagliflozin versus dapagliflozin in healthy individuals demonstrated that canagliflozin 300 mg provided greater reductions in RTG and postprandial glucose (PPG) excursions and increases in UGE compared with dapagliflozin 10 mg; the reductions in PPG excursions with canagliflozin are likely related to the nonselective inhibition of sodium glucose co-transporter 1 (SGLT1) in the intestine. (Sha, et al 2015) As the mechanism of action for canagliflozin is primarily through inhibition of SGLT-2, it is important that the renal function (marked by eGFR) is accounted for in the estimation of efficacy and in the discontinuation of canagliflozin treatment when the patient's eGFR falls below 45 mL/min/1.73 m2 or 60 mL/min/1.73 m2 for canagliflozin 100mg and 300mg, respectively. This functionality specific to SGLT-2 is accounted for in the ECHO-T2DM model. A number of AEs potentially related to excretion of glucose in the urine were also included for simulations, including UTIs and GMIs (each allow for gender-specific rates, costs, and QALYs and there are separate event rates for the first cycle on agent

and subsequent cycles). ECHO-T2DM also allows for simulation of flexible and comprehensive AHA treatment algorithm as well as algorithms for the often key co-occurring conditions of hypertension and dyslipidaemia. Additionally, the ECHO-T2DM model includes functionality to include a many number of complications, for example less severe though still debilitating AEs, which more traditional T2DM modelling do not.
Janssen recognises that the need for validation of models in T2DM is particularly high given their level of complexity. ECHO-T2DM has been developed in line with the International Society for Pharmacoeconomics and Outcomes Research/Society for Medical Decision Making (ISPOR/SMDM) Modelling Good Research Practice Task Force good practice recommendations and has been through extensive review and validation exercises, including at the 4th and 5th Mount Hood Challenges in 2010 and 2012 (Caro et al. 2012; 'Mt Hood Challenges - Home Page'). The results of a comprehensive test of predictive validity were published in Willis et al. (2013) (Willis, Asseburg, and He 2013), and further detail is also presented in Appendix 10 of the original submission.

ECHO-T2DM was recently used for the modelling presented in the CANAgliflozin NICE single technology appraisal (as well as a number of HTA submissions in other countries), and was accepted by NICE as a valid and robust model (NICE 2014. 06/2014).

2. Summary of replicated AG network meta-analysis

Using the information provided by the AG, Janssen have explored the possibility of replicating the NMA conducted by the AG.

The following studies were included in this analysis:

- Aschner P 2006
- Chen Y 2015
- Dejager S 2007
- Del Prato S 2011
- Erem C 2014
- Ferrannini E 2010
- Foley JE 2009
- Haak T 2012
- Inagaki N 2014
- Ji L 2014
- Kaku K 2014
- Kikuchi M 2012
- Lawrence JM 2004
- Lewin A 2015
- Miyazaki Yoshinori 2002
- Roden M 2013
- Stenlof K 2013

2.1. Methods

Fitting the “typical” NICE NMA with uninformative priors and running both a fixed-effects and a random-effects analysis. GeMTC v0.7.1 using JAGS v4.0.0 under R3.2.2 was used to fit the models.

Few calculations were required to bring the data set into a form suitable for analysis with the “typical” NICE NMA instructions. For example, studies by Erem and Foley did not report HbA1c change; thus, HbA1c changes were calculated as 7.5 minus reported HbA1c. Moreover, the standard errors for some endpoints in studies that did not report standard errors are calculated from the standard deviations and sample size, or from the stated confidence intervals.

Placebo is selected as the “reference treatment”.

Diagnostics specifics: Running 4 parallel chains with 5,000 iterations discarded as burn-in, and collecting every 10th iteration (thinning parameter =10) from the next 20,000 iterations. This gives a sample of 4x2,000 = 8,000 iterations. The Raftery and Lewis diagnostic was used to estimate the number of iterations required for estimating the 95% credibility intervals with accuracy 0.5% and probability 95%. Convergence was assessed using the Gelman-Rubin diagnostic, the Geweke diagnostic and the Heidelberg and Welch diagnostic.

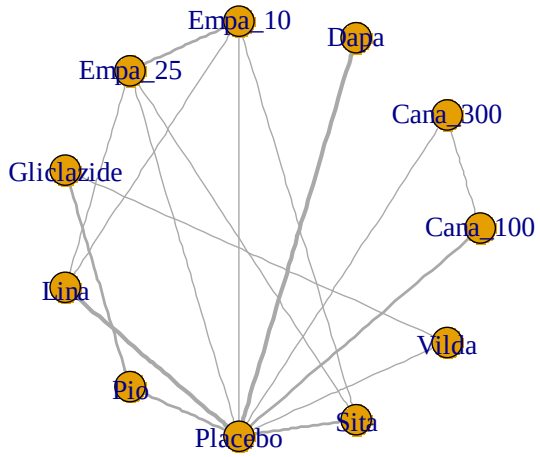
2.2. Delta HbA1c

Data preparation:

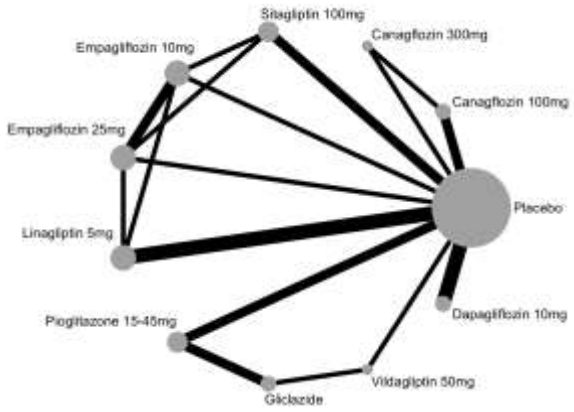
- 17 studies selected, with 38 arms in total.
- The pioglitazone 30 mg arm from Miyazaki was used (pioglitazone 45 mg was excluded).
- The qAM DAPAgliflozin arm from Ferrannini was used (qPM DAPAgliflozin was excluded).

2.3. Evidence network

Replicated analysis by Janssen:



AG:



2.4. Results

The Gelman and the Heidelberg and Welch diagnostics indicated that convergence was poor for the contrast of pioglitazone to placebo, so the sample size was increased to 4x 250,000 iterations = 1,000,000. This alleviates the problem, but didn’t completely resolve it.

The DIC on the random-effects model was 73.6, and the DIC on the fixed-effects model was 78.5. Accordingly, the random-effects model is selected and presented below.

Table 3 NMA Replication results comparison table

Replicated results					NICE AG	
Effects versus Placebo	Mean	SD	Naive SE	Time-series SE	Table 9	Tables 51+52
CANA 300	-1.2011	0.18079	0.000572	0.000574	-1.19	-1.153
PIO	-1.1316	0.27537	0.000871	0.009843	-1.13	-1.200
CANA 100	-0.9706	0.13951	0.000441	0.000454	-0.95	N/A
Gliclazide	-1.1226	0.25707	0.000813	0.006405	-0.95	-1.301

EMPA 25	-0.8768	0.13909	0.00044	0.000449	-0.88	-0.870
Sita	-0.7648	0.13012	0.000412	0.000435	-0.76	-0.723
EMPA 10	-0.7551	0.16296	0.000515	0.00083	-0.76	N/A
Vilda	-0.7051	0.20473	0.000647	0.003323	-0.72	N/A
Lina	-0.6018	0.1002	0.000317	0.000354	-0.61	N/A
DAPA	-0.6127	0.11756	0.000372	0.000386	-0.59	-0.704
Parameter	0.1498	0.08315	0.000263	0.001453		

SD, standard deviation

Using the information provided by the AG, Janssen have explored the possibility of replicating the NMA conducted by the AG. Specifically, for the outcome of HbA1c change, summary-level data was extracted from the seventeen studies included in the AG NMA, and a network meta-analysis was carried out in line with the NICE DSU guidelines. In general, the results on HbA1c agreed quite well with the AG's results. The replication of this analysis indicated, however, a large amount of heterogeneity in the evidence on gliclazide (the "loop" in the evidence network that involves placebo, vildagliptin, gliclazide and pioglitazone). In fact, breaking this loop by removing a single study reduces the estimated between-study standard deviation from 0.16 to 0.11, a considerable reduction. Given that special justifications had to be made to widen the study inclusion/exclusion criteria for the extension of the network to include gliclazide, this large amount of heterogeneity (and the strong effect of study inclusion on estimated efficacy) casts doubts on the comparability of these studies and the validity of the comparison to gliclazide as a whole.

2.4.1. A comprehensive overview of the effect of the non-flozin studies on the results

Each study (Erem, Foley, Lawrence, Kikuchi, Miyazaki) was removed in turn, to understand the impacts on the results. Table 4 below shows the mean values vs. placebo only.

Table 4 Exploratory analysis of study driven heterogeneity and impact on the NMA

		Glic vs. PIO	Glic. vs. Vilda	Glic. vs. PIO	PIO vs. Placebo	PIO vs. Placebo	CF NICE
vs. placebo	FULL RESULTS	w/o Erem	w/o Foley	w/o Lawrence	w/o Kikuchi	w/o Miyazaki	Table 9
CANA 100	-0.97	-0.97	-0.97	-0.97	-0.97	-0.97	-0.95
CANA 300	-1.20	-1.20	-1.20	-1.20	-1.20	-1.20	-1.19
DAPA	-0.61	-0.61	-0.61	-0.61	-0.61	-0.61	-0.59
EMPA 10	-0.76	-0.75	-0.75	-0.75	-0.75	-0.75	-0.76
EMPA 25	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88
Gliclazide	-1.12	-1.15	-1.98	-0.96	-0.97	-1.00	-0.95
Lina	-0.60	-0.60	-0.60	-0.60	-0.60	-0.60	-0.61
PIO	-1.13	-1.12	-1.76	-1.36	-0.89	-0.94	-1.13
Sita	-0.76	-0.77	-0.76	-0.76	-0.76	-0.76	-0.76
Vilda	-0.71	-0.72	-0.50	-0.61	-0.62	-0.64	-0.72
SD.D	0.15	0.16	0.11	0.12	0.13	0.13	

Excluding only one in five studies at a time has no effect on the estimates in HbA1c reduction for the flozins, linagliptin or sitagliptin. This is to be expected as the five studies excluded are not in the network of these comparators. In summary:

- Removing Foley: Generates a super SU, and makes PIO better, vildagliptin weaker, and reduces the between-study SD considerably.
- Removing Erem: Makes Gliclazide marginally stronger.
- Removing Lawrence: Makes gliclazide weaker, PIO stronger, vilda somewhat weaker, and reduces between-study SD
- Removing Kikuchi: Makes gliclazide weaker, PIO weaker, makes vilda somewhat weaker, and reduces between-study SD
- Removing Miyazaki: Makes gliclazide weaker, makes PIO weaker, vilda somewhat weaker, and reduces between-study SD

The exploratory analysis demonstrates that all studies except Erem et al introduce a strong heterogeneity that increases the between-study standard deviation considerably. Erem et al has a small effect on the evidence network, probably due to its small sample size of 19 patients informing the HbA1c outcome on each arm. The fact that the Foley study, which does not include pioglitazone, has such a strong effect on the estimate of pioglitazone, suggests that there is a very large amount of heterogeneity in the placebo-pioglitazone-gliclazide-vildaglitpin network, and is reason for concern. The Foley study indicates that gliclazide leads to an incremental change in HbA1c of -0.27 compared to vlidagliptin, and with 546 patients in each arm, it is very influential on this part of the network. The impact of each of the Lawrence, Kikuchi and Miyazaki studies on overall network imbalance and on the estimates for gliclazide and vildagliptin appears to be similar amongst them. Removing Lawrence, however, leads to a greater HbA1c reduction estimate for pioglitazone, whereas removing Kikuchi or Miyazaki leads to a smaller estimate. This indicates that the Lawrence study is less similar to the rest of the evidence network than the Miyazaki and the Kikuchi studies.

Further analysis, considering the comparison of the relative treatment efficacy inputs on the placebo-pioglitazone-gliclazide-vildagliptin loop is demonstrated an obvious imbalance on that loop (Table 5). Removing any of the studies, especially Foley or Dejager will overcome this phenomenon, as then the loop is weakened or broken.

Table 5. Treatment efficacy inputs effect on the placebo-pioglitazone-gliclazide-vildagliptin loop

Links	Delta on that lastly-added link	Delta cumulative
Placebo-PIO	-2.00 (Miyazaki; N small) -1.64 (Kikuchi; N medium)	about -1.7
Placebo-PIO-Glic	-0.40 (Lawrence; N small) -0.07 (Erem; N small)	about -1.9
Placebo-PIO-Glic-Vilda	+0.27 (Foley; N large)	about -1.6
Placebo-PIO-Glic-Vilda-Placebo	+0.5 (Dejager; N medium)	about -1.1

If the link to gliclazide is broken by removing some of the PIO studies, gliclazide and vildagliptin will have efficacy “nearer” placebo (via vildagliptin), i.e., they will be less effective by about 0.6 to 1.1 on the HbA1c %. Alternatively, if the link to gliclazide was broken by removing one of the vildagliptin studies, then gliclazide (and PIO) efficacy will be “nearer” placebo via pioglitazone, i.e., it will be

more effective by about 0.6 to 1.1 on the HbA1c. Moreover, the comparison of the flozins to gliclazide is driven heavily by the three studies Kikuchi, Dejager and Foley, and to a lesser degree by Lawrence, et al.

2.4.2. Accounting for trial design

To allow for the successful running of the NMA analysis a number of studies needed to be excluded and exploratory analyses were necessary to determine the impact of alternative approaches. Ultimately, these analyses made it very clear to Janssen that the studies on gliptins and flozins are newer and of higher quality as well as being much more comparable to one another (e.g. placebo-controlled, mostly two arms, double-blinded). The studies on gliclazide appear to differ. For example, with respect to the starting HbA1c figures highlighted, the fact that some of them are not blinded can have a much more significant impact on the results which the NMA derives.

2.4.3. Error in the AG NMA

In the review of the AG report, an error was noticed in the SBP lowering of Canagliflozin 300mg (-0.5 mmHg instead of the correct -5.0 mmHg). To evaluate the likelihood that this error extended to the full economic analysis, Janssen have attempted to replicate the AG NMA for SBP. Quite close results to those presented by the AG were able to be replicated; suggesting a high likelihood that the error extended to the NMA results that were included in the economic analysis. This estimate will have resulted in an underestimate in the benefits of canagliflozin 300mg.

3. eGFR stopping rule deactivated

On page 165 of the AG report, the AG write "While the AG has a number of issues with the Janssen modelling, the use of the ECHO-T2DM model did permit this to be explored though the AG has not reviewed the implementation of this in any detail. It would be interesting to know the impact that turning off these discontinuations would have upon the cost effectiveness estimates of the Janssen modelling. If this is significant enough to affect the conclusions that would be drawn from the Janssen modelling it could suggest additional modelling uncertainty from the AG use of the OM1 "

Response:

We agree with the AG that evaluating the impact of the flozin-specific modifications supported in ECHO-T2DM provides useful information, so we re-ran the base case simulation with the eGFR stopping rule and the eGFR treatment effect multipliers deactivated for 1,000 cohorts of 1,000 patients (the largest sample sizes that could be completed in the time available).

The direct consequences of this scenario are that time on flozins will increase in proportion to the number of patients with eGFR drifting below the discontinuation thresholds and that initial treatment effects will be maintained so long individuals are treated with the flozins. Note: the simulations are based on the current price of canagliflozin 300mg.

The proportion of patients affected by the stopping rule in the correct BC (in which empagliflozin 10mg was correctly parameterized) are presented in Figure 1, between 9% and about 14% for canagliflozin 300mg, dapagliflozin 10mg, and empagliflozin 25 mg which have a stopping rule of eGFR<60 and about 3% to 4% for canagliflozin 100mg and empagliflozin 10mg which have the stopping rule of eGFR<45. We found:

- Only small stochastic differences for the non-flozins (which were unaffected by the stopping rule)
- Drug acquisition costs for canagliflozin 100mg increased from £3,184 in the base case to £3,279 in this scenario (since patients take them on average longer), but insulin medication costs decreased from £5,553 to £5,528.
    - Note: the relatively small differences between the two scenarios for canagliflozin 100mg are due to the low proportion discontinuing due to low eGFR
- Drug acquisition costs for canagliflozin 300mg increased from £3,407 in the base case to £3,681 in this scenario (since patients take them on average longer), but insulin rescue medication costs decreased from £5,296 to £5,095.
- The same pattern was true for the other flozins as well
- LYs and QALYs for all of the flozins increased in general from the base case to this scenario, with the exception of empagliflozin 25 in the canagliflozin 300 BC. Again this is due to the fact that it is a small proportion that discontinues due to low eGFR and the influence of stochastic differences. The relative difference to the non-flozin comparators for canagliflozin 100mg and canagliflozin 300mg increased in general as well, with the exception of pioglitazone vs. canagliflozin 100mg and gliclazide vs. canagliflozin 300mg.
- Summary of the cost-effectiveness results are presented for canagliflozin 100mg and canagliflozin 300mg in the Tables below

eGFR module active (BC with current canagliflozin 300mg price and correct eGFR stopping rule for empagliflozin 10mg)

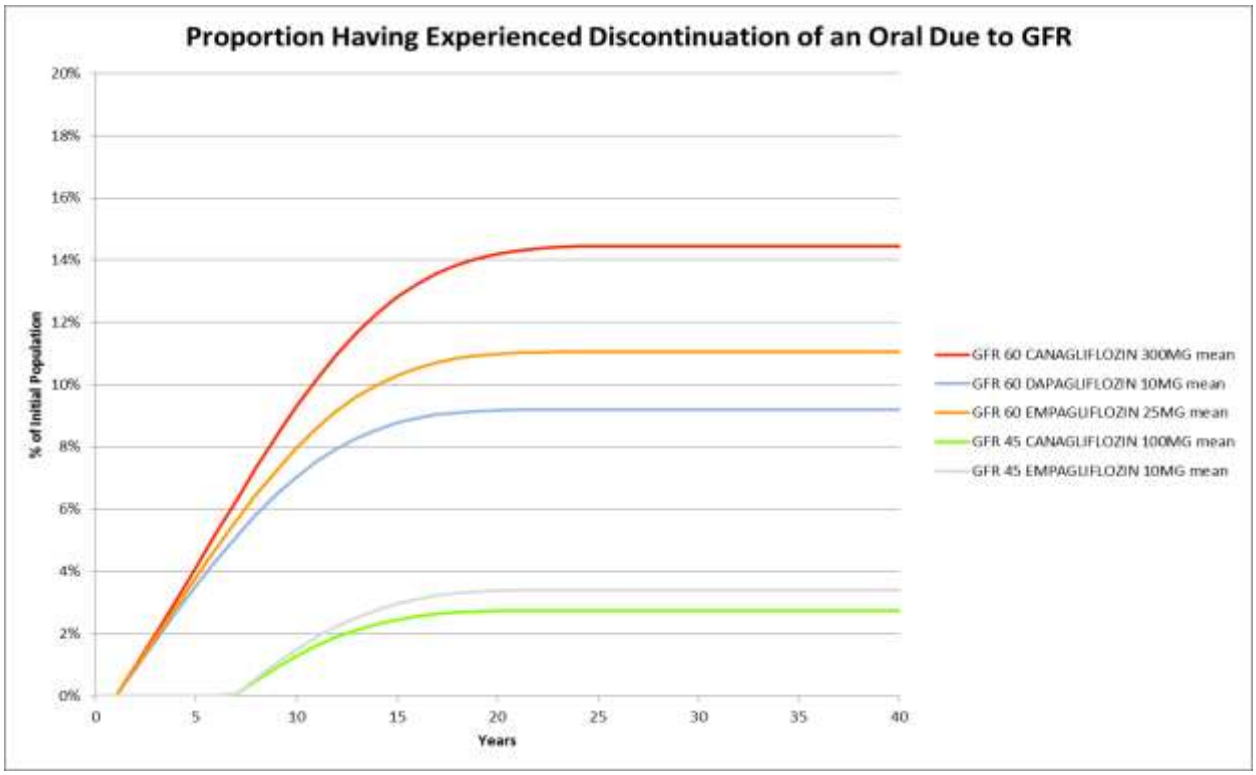
Arm	Mean Costs	Mean Utilities	HE Verdict
PIOGLITAZONE 30MG	20 175	9.95	Cheapest
SU (GLICLAZIDE 80MG 2X DAILY)	23 129	9.91	Dominated by PIOGLITAZONE 30MG
CANAGLIFLOZIN 300MG	23 284	10.03	ICER 37913 to PIOGLITAZONE 30MG
DPP-4I (SITAGLIPTIN 100MG)	23 317	9.94	Dominated by CANAGLIFLOZIN 300MG
EMPAGLIFLOZIN 25MG	23 410	9.98	Dominated by CANAGLIFLOZIN 300MG
CANAGLIFLOZIN 100MG DOSE INCREASE	23 421	10.01	Dominated by CANAGLIFLOZIN 300MG
CANAGLIFLOZIN 100MG	23 441	10.00	Dominated by CANAGLIFLOZIN 300MG
DAPAGLIFLOZIN 10MG	23 495	9.96	Dominated by CANAGLIFLOZIN 300MG
EMPAGLIFLOZIN 10MG	23 513	9.97	Dominated by CANAGLIFLOZIN 300MG

eGFR module deactivated

Arm	Mean Costs	Mean Utilities	HE Verdict
PIOGLITAZONE 30MG	20 350	10.01	Cheapest
SU (GLICLAZIDE 80MG 2X DAILY)	23 310	9.96	Dominated by PIOGLITAZONE 30MG
DPP-4I (SITAGLIPTIN 100MG)	23 532	10.00	Dominated by PIOGLITAZONE 30MG
CANAGLIFLOZIN 300MG	23 534	10.10	ICER 35614 to PIOGLITAZONE 30MG
CANAGLIFLOZIN 100MG DOSE INCREASE	23 619	10.06	Dominated by CANAGLIFLOZIN 300MG
CANAGLIFLOZIN 100MG	23 636	10.05	Dominated by CANAGLIFLOZIN 300MG
EMPAGLIFLOZIN 25MG	23 685	10.03	Dominated by CANAGLIFLOZIN 300MG
EMPAGLIFLOZIN 10MG	23 710	10.02	Dominated by CANAGLIFLOZIN 300MG
DAPAGLIFLOZIN 10MG	23 741	10.01	Dominated by CANAGLIFLOZIN 300MG

As can be seen, while the mean costs and mean utilities varied slightly, the HE verdict is qualitatively (and indeed almost numerically) identical.

Figure 1: Proportion of patients discontinuing flozins because of eGFR in the updated BC



4. eGFR discontinuation rule correctly applied for EMPA 10mg.

The AG correctly identified an error in the Janssen model inputs. The eGFR stopping rule was applied incorrectly for empagliflozin 10mg only (<60 ml/mg/1.73m^2 instead of <45 ml/mg/1.73m^2). This has now been corrected and the base case has been re-simulated and presented below. Because the price of canagliflozin 300 mg has changed since the original submission, this was also updated. Two sets of results are presented below: (1) the original base case with the incorrect empagliflozin stopping rule but with the current canagliflozin 300mg price (Table 6) and (2) the results using the current canagliflozin 300mg price and correct empagliflozin 10 mg stopping rule (Table 7). The differences between them correspond to the effect of the error in the empagliflozin 10mg stopping rule. Janssen did not alter the prices for pioglitazone or sulfonylurea in these analyses but did not significant differences in the costs reported as inputs between Janssen and the AG. Janssen is however unsure as to where these differences in input cost come from in both analyses these are reported to be the generic.

The results are stable with only minor stochastic noise. With the incorrect eGFR discontinuation for empagliflozin 10 mg (Table 7), canagliflozin 100mg dominates empagliflozin 10mg. This dominance is maintained when the correct eGFR stopping rule for empagliflozin 10mg is applied.

Table 6. Base case incremental cost-effectiveness results for all T2DM monotherapies (updated price change for canagliflozin 300mg)

	Mean Costs	Mean Utilities	Cost per QALY (ICER)
PIO	£20,264	9.998	-
SU (GLIC)	£23,220	9.949	Dominated by PIO
CANA 300	£23,370	10.083	£36,541
DPP-4I (SITA)	£23,443	9.981	Dominated by CANA 300
CANA 100 DOSE INCR.	£23,521	10.051	Dominated by CANA 300
CANA 100	£23,525	10.039	Dominated by CANA 300
EMPA 25	£23,528	10.024	Dominated by CANA 300
EMPA 10	£23,580	10.010	Dominated by CANA 300
DAPA	£23,594	10.006	Dominated by CANA 300

Table 7. Base case incremental cost-effectiveness results for all T2DM monotherapies (corrected for eGFR discontinuation rule per summary of product characteristics for empagliflozin 10 mg and price change for canagliflozin 300mg)

	Mean Costs	Mean Utilities	Cost per QALY (ICER)
PIO	£20,175	9.950	-
SU (GLIC)	£23,129	9.908	Dominated by PIO
CANA 300	£23,284	10.032	ICER £37,913 to PIOGLITAZONE 30MG
DPP-4I (SITA)	£23,317	9.937	Dominated by CANA 300
EMPA 25	£23,410	9.975	Dominated by CANA 300
CANA 100 DOSE INCR.	£23,421	10.006	Dominated by CANA 300
CANA 100	£23,441	9.999	Dominated by CANA 300
DAPA 10	£23,495	9.958	Dominated by CANA 300
EMPA 10	£23,513	9.967	Dominated by CANA 300

Abbreviations: CANA100, CANAgliflozin 100 mg; CANA300, CANAgliflozin 300 mg; DAPA, DAPAgliflozin 100 mg; DPP-4I (SITA); DPP-4i (Sitagliptin 100 mg); EMPA10, EMPAgliflozin 10 mg; EMPA25, EMPAgliflozin 25 mg; PIO; pioglitazone 30 mg; SU (GLIC), sulfonylurea (Gliclazide 80 mg 2x daily

The primary difference is naturally for empagliflozin 10 mg, for which total costs are reduced; however, the interpretation of the evaluation is unchanged. Pioglitazone is the least expensive and it dominates gliclazide. Canagliflozin 300mg has a nearly identical ICER versus pioglitazone and because of the now lower price dominates all of the remaining comparators.

5. Janssen error identified and corrected

In reviewing the AG report, a mistake in the inputs for gliclazide within the Janssen NMA was identified. The following data were initially extracted from the publication by Lawrence 2004 for the mean change from baseline in HbA1c: gliclazide= 1.21 and pioglitazone= 0.81, while the true results

are: gliclazide= -1.21 and pioglitazone= -0.81. This misreading of data had an impact predominantly on the NMA results for gliclazide. After running an update of the NMA, the median differences between gliclazide and canagliflozin for the mean change in HbA1c are:

- Canagliflozin 300 versus gliclazide: -0.16 [SD=0.28], P*=72% (previously reported as: -0.61 [SD=0.28], P=99%);
- Canagliflozin 100 versus gliclazide: +0.07 [SD=0.26], P=39% (previously reported as: -0.38 [SD=0.26], P=93%)

**P = probability for canagliflozin to perform better than the comparator.*

Janssen recognises that these are quite significantly different results and has thus re-run the base case simulations in ECHO-T2DM. The results of which have been presented below.

As there were not sufficient time to re-run the entire base case comparison, the simulation was limited to analyse canagliflozin 100mg and canagliflozin 300mg versus the affected agents (Gliclazide and pioglitazone), respectively. Note: the current price of canagliflozin 300mg were applied. The sample size was 1,000 cohorts with 2,000 patients each. The results are presented in the tables below.

For comparison purposes, the original ICERs of canagliflozin 100mg vs. Pioglitazone and vs. Gliclazide submitted to NICE were £78,518 and £3,377, respectively. The ICERs for canagliflozin 300mg (using updated price for canagliflozin 300mg) vs. pioglitazone and gliclazide were £38,156 and £1,360, respectively.

Table 8 Results of Canagliflozin 100mg vs. Pio and Gliclazide using the updated NMA results

Agent	Canagliflozin 100mg	Pioglitazone	Gliclazide
Mean Cost	23 682	20 452	22 997
Mean QALYs	10.006	9.967	9.919
ICER canagliflozin 100mg vs comparator	--	83 334	7 875

Table 9 Results of Canagliflozin 300mg vs. Pio and Gliclazide using the updated NMA results and price for Canagliflozin 300mg

Agent	Canagliflozin 300mg	Pioglitazone	Gliclazide
Mean Cost	23 468	20 380	22 980
Mean QALYs	10.091	10.007	9.963
ICER canagliflozin 300mg vs comparator	--	37 019	3 820

The effect of the error on the ICERs were each relatively small in absolute terms, and did not alter the qualitative interpretations that can be draw. For the comparison vs. PIO, the small differences reflect the small magnitude of the error in the NMA (0.01). The larger correction in the NMA estimates for gliclazide (-1.04 instead of -0.59) lead to an approximate doubling to tripling of the ICER, though the magnitude of the ICER remains low.

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MSD Response

9th November 2015

MSD welcomes the opportunity to comment on the assessment report for "Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes". However, MSD believes that it is imperative that the final updated NICE clinical guideline CG87 is published before the 1st Committee meeting for the assessment of this MTA. The latest published version of CG87 is from May 2009, with an update to the guideline currently in progress (2 draft versions have since been circulated; however, we are awaiting the final published update to CG 87). The report does not use a specific version of the guideline consistently, referring either to CG87 2009 or to one of the draft versions circulated in 2015.

More specifically, on page 11, the report states that the DPP-4 inhibitors (DPP-4i) are suggested in the NICE guideline if metformin cannot be tolerated or is contraindicated, whilst on p. 24, the report states that DPP-4i are not currently recommended by NICE for monotherapy. Also, on p. 22, the report cites the recommendations made in the CG87 2009. Nevertheless, in p. 26, the report reproduces the flowchart from the second draft version of CG87 (June 2015). Moreover, on p. 32 (Box 1) the report cites the recommendations of the CG87 2009, but the statement underneath "*The current draft of the updated guideline has at present omitted the stopping rule 1.6.1.4*" is misleading, as a number of other changes have been made in the draft guidelines concerning DPP-4i that have not been highlighted here.

The way that the guideline CG87 is used to support the evidence across the document is problematic and could undermine the results of this report. Various issues arise from the fact that the updated CG87 has not been finalised and published yet, and that this report cross-refers to different versions:

- Statements regarding DPP-4i use are based on CG87 2009. The current draft of the guideline is recommending DPP-4i in monotherapy for patients for whom metformin is contraindicated or who cannot tolerate metformin.
- DPP-4i monotherapy is not recommended in the CG87 2009 guideline, and thus MSD believes it is inappropriate to demonstrate that SGLT-2i are cost-effective vs sitagliptin (rather than a sulphonylurea [SU] which is recommended for monotherapy when metformin in not appropriate).
- The report should focus on the scope of this appraisal, which is to assess the clinical and cost-effectiveness of SGLT-2i vs. the relevant comparator(s).
- On p. 24 the report states "*The NICE guideline (CG87) on the management of T2DM is currently being revised. The first draft recommended that patients who cannot take or tolerate metformin should take repaglinide, a meglitinide analogue*." And then again on p. 27 "*The rational for choosing repaglinide was two-fold…*" Nevertheless, the second draft of CG87, the flowchart of which is presented on p. 26, has removed the preferential use of repaglinide in patients who are contraindicated to or cannot tolerate metformin, recommending equally DPP-4i, pioglitazone or SU. Additionally, if the report wants to base the analyses on the 2009 published CG87, which does not recommend repaglinide, the clinical cost-effectiveness data related to repaglinide would also not be relevant to the decision making process, and should be removed from the main body of this assessment report.

Additionally, MSD has a number of additional comments on the assessment report.

1. Vildagliptin's price

On p. 37, Figure 2, the price of vildagliptin is not reflective of its current, up to date price. The current price of vildagliptin is £434.74 annually, according to the September 2015 pricing from the National Drug Tariff (a pack of 56 vildagliptin is £33.35).

2. Reasons for sitagliptin not recommended for monotherapy

On p. 24, the report states: "*The dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as the 'gliptins', not currently recommended by NICE for monotherapy (because of cost).*" MSD believes that cost is not the same as cost-effectiveness – we would appreciate a clearer reason for the rejection, as well as the use of a reference.

3. Use of the term "gliptins"

On p. 116 the use of the term "gliptin" instead of "DPP-4i" may be confusing to the reader. MSD would welcome consistency across the report and use of the "DPP-4i" term.

4. Relevance of Asian populations

Three of the seven studies included in the systematic review *(Inagaki 2014, Ji 2014, Kaku 2014)* were conducted in East Asian populations. East Asians have different disease specifications: they suffer mainly from lack in insulin secretion (beta cells dysfunction) and their BMI tends to be lower; for these reasons treatment dose can differ for East Asian patients (e.g. DPP-4i will be given as half dose for Asians). In general, studies in East Asian population cannot apply to the overall population and will need to be replicated in Caucasian population as well (see Kim et al. 2012).

MSD is concerned that East Asian population data are not representative of the UK population. Additional information in the Caucasian population may be required in order to support the evidence.

5. Roden et al. 2013

MSD is concerned about the robustness of the conclusions of the assessment report regarding empagliflozin versus sitagliptin due to the use of the Roden et al. 2003 study.

Firstly, sitagliptin was not prescribed in line with its UK license (restricted monotherapy in patients who are not controlled or who cannot tolerate metformin). As it is also mentioned in the actual study, "*in most countries treatment with metformin is the recommended first-line therapy for patients who are not controlled with diet and exercise*".

Secondly, MSD is concerned that the study applied open-label regime in its study design and that might bias the results of the study.

Thirdly, study duration of 24 weeks is relatively short and MSD believes that firm conclusions cannot be drawn from this length of study and that this does not allow the durability of the study drugs to be fully assessed.

Finally, caution should be exercised when interpreting the results, as the authors themselves state that "*The comparisons between empagliflozin and sitagliptin were only exploratory and therefore no firm conclusions to be made about the comparative efficacy of these drugs*".

6. Misleading information on SGLT-2i

In the Conclusions section (p. 233), the authors state "*The SGLT2 inhibitors are effective in improving glycaemic control, promoting weight loss and reducing blood pressure – the first oral drugs for diabetes to do so*". MSD would argue that this is definitely not the first drug for diabetes that improves glycaemic control: all glucose lowering agents do.
Moreover, MSD is concerned that this statement may suggest that SGLT-2i are indicated as weight-lowering or blood pressure-lowering agents, which is inconsistent with their UK license. It could be conveyed as a biased statement and therefore MSD would welcome its removal from the report.

7. The EMPA-REG study

MSD is concerned about the interpretation of the EMPA-REG study in the report. On p. 76 the report states "*This study has attracted world-wide interest. It contrasts with the equivalent studies with the DPP-4 inhibitors, which did not show any reduction in cardiovascular outcomes…..*". MSD is concerned about the EMPA-REG outcome study being characterised as *equivalent* to SAVOR, EXAMINE and TECOS studies. MSD would suppose that the term "equivalent" is used by means of following FDA guidance to industry from 2008 "*…about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk*". However, EMPA-REG was done in a particular population, which is fundamentally different from the population of any of the DPP-4i studies, different in baseline characteristics as well as in study duration.

Similarly to the DPP4i studies, the EMPA-REG study was designed to demonstrate cardiovascular (CV) safety of empagliflozin on top of usual care vs usual care. MSD is concerned that the definition of "outcome study" is inaccurate. In outcome trials the risk factor (e.g. HbA1c) is not adapted and CV benefit may be therefore derived from a reduction in the risk factor level. On the other hand, CV safety trials, as required by the FDA, need to maintain the risk factor (HbA1c) similar between study arms (glycaemic equipoise) to demonstrate CV safety, which is not related to glycaemic control.

Finally, MSD is concerned that the EMPA-REG population is not representative of the overall type 2 diabetes patients in the UK. There are 920k metformin monotherapy patients in the year to June 2015 of whom 125k (14%) are treated for CVD. The number of patients who use metformin along with other oral anti-diabetic drugs and are treated for CVD is similar (13%) (IMS data).

8. 25mg empagliflozin and 300 mg canagliflozin dosing

MSD believes that the use of both 300mg (canagliflozin) and 25mg (empagliflozin) doses could be problematic. The report has escalated to higher doses, whereas the previous technology appraisals looked at the doses separately – this is not consistent. It would also be useful to add that cost-effectiveness analyses for canagliflozin 100mg are also relevant to the decision making as not all patients are able to be uptitrated to 300mg. The STA for canagliflozin evaluated cost-effectiveness evidence for both doses vs. the comparators. The same applies for empagliflozin, which has 2 licensed doses (10mg and 25 mg). MSD would welcome consistency with the license, and comparison between the lower doses.

9. Diabetic ketoacidosis

On p. 70, the report states "*Late reporting of adverse events is not unusual. The FDA has also recently issued a safety alert on the gliptins, the DPP-4 inhibitors, after reports of severe joint pain*" – MSD is concerned that there is no clinical relevance of this statement to DKA.

10. Tables 52 and 53

The GTI levels in Table 52 by the Assessment Group seem surprisingly low in comparison with the levels reported in the STAs for dapagliflozin and canagliflozin:

- UTIs levels placebo (4.0%); Cana 10/.l0mg (5.5%) and Cana 300mg (4.1%)
- GTIs levels placebo (3.2%); Cana 100mg (10.4%) and Cana 300mg (11.4%)

Additionally, UTIs are usually higher among female population and the AG does not report male and female data separately.

MSD is also concerned that Table 51 looks at monotherapy clinical-effectiveness estimates annually, whereas Table 52 looks at them half-yearly. This seems inconsistent.

11. Age restriction in empagliflozin use

MSD is concerned that the statement on p. 37 "*Dapagliflozin is not recommended in people over 75 but there is no such restriction for canagliflozin or empagliflozin"* is misleading as in the UK label for empagliflozin (SPC January 2015) 4.2 states that "*In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience".* Therefore, using >75 is misleading as it includes the >85 population as well.

12. Use of Scott 2007 and Nauck 2007 trials

On p. 103 the report states "*For the effects of adding sitagliptin we have two useful trials with HbA1c baseline 7.7 and 7.8% which reported reductions in HbA1c of 0.67% and 0.79% (Scott 2007, Nauck 2007) giving a mean of 0.73%.*"
The Scott study (monotherapy, PN010) from 2007 is a dose finding study where sitagliptin was used as twice daily in the following doses: 5mg bid, 12.5 mg bid, 25 mg bid, 50mg bid. The maximum reduction noted is -0.77% in the 50mg bid from HbA1c baseline of 7.8%. MSD believes that this is not an appropriate study as sitagliptin is licenced as 100mg once daily so no conclusions can be made based on this publication.
In regard to Nauck 2007 (PN024), the reduction in HbA1c was 0.67% from HbA1c in baseline of 7.5%. This study was sitagliptin add-on to metformin vs. SU add-on to metformin.

These are two completely different studies and MSD is concerned that they should not be included for the purpose of monotherapy. MSD believes that the only appropriate monotherapy study for sitagliptin is Aschner 2010 where the baseline was much lower (7.2%) and therefore the reduction observed in HbA1c was only 0.43%. Another appropriate study is Aschner 2006, which the Assessment Group rightly includes in the NMA.

Comments [redacted] on the SGLT-2 Assessment Report (AR).

It seems odd that the Plain English Summary makes no mention of hypoglycaemia and is focussed largely on 'a few kilograms gained or lost'.

It also makes no mention of the recently documented cardiovascular (CV) and all-cause mortality benefits reported for empagliflozin, unique for antidiabetic agents other than metformin (for which the evidence base is much weaker). One can argue that it was the perceived CV benefits of metformin that led to it's primacy in current guidelines following the UKPDS report of 1998.

On page 29 of the AR, the authors state that sulfonylureas 'have been used for so long that all their adverse effects are known.' And yet there continue to be published metanalyses suggesting that they may increase both CV and total mortality, compared with other anti-diabetes therapies.

Page 30: the use of BNP monitoring when using pioglitazone is not standard practice and would not usually be accounted for in cost-effectiveness analyses (although I note the AG attempts to do this). The increased risk of myocardial infarction with rosiglitazone remains contentious.

Page 34: I believe that 'glycosuria' has been renamed 'glucosuria' (possibly by the Americans.

P36: the continued use of cana- and empagliflozin in patients with eGFR between 45-59 mL/min should be at the lower dose of each drug (a slightly bizarre recommendation, given that their efficacy falls as the GFR reduces).

P37: In PICO, the population is those intolerant of Metformin AND who have an eGFR greater than 59 mLs/min….

P38: In terms of Outcomes, empagliflozin already has better evidence for good cardiovascular outcomes than (almost) all other anti-diabetes drugs. This is not acknowledged in the text.

P38: I believe that Metformin does increase lactate levels but is not associated with lactic acidosis. The comment stating that it does not increase lactate either needs to be referenced or removed.

P40: The comment that patients who have not developed diabetic retinopathy after 20 years 'are unlikely to do so' is unreferenced and, I believe, has no evidence to support it.

P56: The comment "The definition of hypoglycaemia varied amongst trials with most using 4.0 mmol/l as the threshold, which seems a little high, when the lower limit of normal is 3.5 mmol/l (Amiel S. Diabetic Hypoglycemia 2013/5/issue 3)." is inappropriate – there is no strictly defined 'lower limit of normal'.

P62: I believe that the mycotic genital and urinary tract (typically bacterial) infections should be dealt with separately. There is no doubt that superficial mycotic (fungal) infections are seen more frequently when patients take SGLP-2 inhibitors; the situation for UTIs is less clear-cut.

P70: The AACE/ACE Scientific and Clinical Review: Association of SGLT2 Inhibitors and DKA (October 24-25, 2015) felt it was still unclear as to whether there is any relationship between SGLT-2 inhibitor use and DKA.

P75: If blood pressure reduction was the major driver for the mortality benefit in EMPA-REG, one might have expected to see this impacting on non-fatal stroke, which was not the case.

The systolic blood pressure (BP) reduction in HOPE was almost certainly bigger than that reported in the main study (due to the timing of the BP recording (confirmed by a continuous BP monitoring sub-group analysis in HOPE).

The various subgroup analyses need to be treated with caution, and this should be acknowledged in this report.

P80: The Saleem and Jibran manuscripts are identical and neither should be considered until the authors respond to queries regarding their independence. Similar considerations apply to the Shah manuscript, which includes authors from the other two publications.

P82: Most clinicians who have any understanding of network meta-analysis (a small minority) have significant doubts about their veracity.

P101: Almost all diabetologists recognise weight gain as a common side-effect of sulphonylurea treatment – to suggest that it is not, based on a single reference, is questionable…

P103: I am puzzled as to why there is discussion of GLP-RA agonists at this point?

P118 (and elsewhere): the document assumes that practitioners follow NICE guidelines with therapy intensification at HbA1c of 7.5% but this is not the case in the UK. Insulin initiation is typically at 10% or more and treatment inertia is widespread throughout the therapy algorithm…

P212 (and elsewhere); I am perplexed as to why the AG would expect the SGLT-2 weight gain to disappear after a year or in cases whom continue to take it?

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes [ID756]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

October, 2015

Issue 1 Repaglinide dose titration schedule

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Repaglinide dose schedule based on glycaemic response does not reflect likely use – initial recommended dose is 500 mg tds up to maximum titrated dose of 16 mg – potential 5-6 titration steps with costs of extra GP visits and blood glucose monitoring	Modelling needs to take account of extra costs of higher doses , extra visits and costs of blood glucose monitoring .	ICER – QALY comparisons will show less cost benefit analysis of repaglinide that originally stated

Issue 2 Metformin intolerance

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Stated as 5-15% and mitigated by use of slow release Implication is develops initially or not at all In reality may develop with increased exposure as well after time	Statement to consider impact of later GI issues after initial use of metformin and impact of cost benefit analysis may need to be considered	May impact of developing models as need to consider alternatives may follow period of 1 year or more on metformin BEFORE GI side effects develop

Issue 3 Empagliflozin outcome study

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
More information on study cohort numbers if any who received sole empagliflozin monotherapy as relevant to current TA	If there were patients in EMPA-REG study with empagliflozin monotherapy did numbers permit sub group analysis re safety outcomes etc ?	CV outcomes on monotherapy would impact beyond current projections of benefit based solely on glycaemia +/- body weight changes

(please cut and paste further tables as necessary)

20th November

Assessment group responses to comments received during consultation

The volume of comments and pressure of work means we cannot reply to all of them so some prioritisation is required.

Responses to comments from clinical experts advising NICE

Professor Bain

Comments from Professor Bain in italics.

It seems odd that the Plain English Summary makes no mention of hypoglycaemia and is focussed largely on 'a few kilograms gained or lost'.

Accepted and revision will mention hypoglycaemia

P118 (and elsewhere): the document assumes that practitioners follow NICE guidelines with therapy intensification at HbA1c of 7.5% but this is not the case in the UK. Insulin initiation is typically at 10% or more and treatment inertia is widespread throughout the therapy algorithm…

This is one of the most important comments because it has implications for effect sizes in the modelling.

In past appraisals, we have commented on clinical inertia, citing research by Calvert and colleagues and Rubino and colleagues. We did so in this assessment report (page 118) but speculated that inertia might be less now because of the QOF.

"In past studies, patients with type 2 diabetes were often left poorly controlled for several years before intensification[181, 182] but this may be happening less nowadays, with improved control promoted by the Quality Outcomes Framework (QOF) of payments to general practices for demonstrating performance against HbA1c control indicators[183], including DM007 for the HbA1c indicator. The three bands are now 59, 64 and 75 mmol/mol. All of them (not just the tightest) probably encourage initiation of insulin in practice."

The Calvert and Rubino studies are references 181 and 182. They used data from 1995 to 2005 (Calvert) or 1985 to 2004 (Rubino). In summary, they found that patients were not monitored sufficiently closely, and that many were allowed to remain poorly controlled for years before treatment was intensified. This applied particularly with intensification to insulin.

However, the delays in starting insulin were not all due to clinical inertia. As noted in a previous assessment report (Waugh et al 2010) produced to support the CG87 update, patients and their physicians were reluctant to start insulin. The DAWN (Diabetes Attitude Wishes and Need) study found that 55% of patients who have never had insulin treatment had negative views about it. Peyrot and colleagues (2005) noted that patients believed that "taking insulin:

• leads to poor outcomes including hypoglycaemia, weight gain and complications
• means that the patient's diabetes is worse and that the patient has failed
• means life will be more restricted and people will treat the patient differently
• will not make diabetes easier to manage."

Hayward and colleagues in a very large study (8668 patients with type 2 diabetes) found that "insulin therapy was rarely effective in achieving tight glycaemic control". Two years after starting insulin therapy, 60% still had HbA1c levels of 8% of greater, 25% had levels between 8.0 and 8.9%, 20% between 9.0 and 9.9%, and 15% had levels over 10%.
Yki-Jarvinen and colleagues came to similar conclusions in people with type 2 diabetes who were obese (defined as BMI over 28.1): insulin did not improve control.

The fact that starting insulin in routine care usually fails to give good control in people with type 2 diabetes failing on oral agents is presumably one reason why the physicians in the DAWN study 27 showed considerable resistance to starting insulin therapy in type 2 diabetes; only about half of the physicians thought that insulin would be useful.

It also shows the benefits of increasing the therapeutic armamentarium by the introduction of new oral agents.

Has QOF changed practice?
Gallagher and colleagues (Diabetic Medicine 2014) used GPRD data from 1999 to 2008 to try to assess the impact of the QOF on diabetes management. They found an increase in the proportion of people with type 2 diabetes who had been started on drug therapy be 24 months after diagnosis. However the changes were not dramatic. In 2003 and 2004 (QOF started in 2004) the proportion on no pharmacological treatment was 41%; in 2007 and 2008 it was 37%. They comment that the reduction could not be said to be definitely due to the introduction of QOF, but might be due to uptake of clinical guidelines.

The draft update of the NICE guideline on type 2 diabetes (CG87) recommends

"1.6.1 In adults with type 2 diabetes, measure HbA1c levels at:
 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy

 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable."

And

"1.6.8 In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
 reinforce advice about diet, lifestyle and adherence to drug treatment **and**

 intensify drug treatment"

If these recommendations are adhered to, we would expect an end to clinical inertia. Patients would have their HbA1c closely monitored and their treatment promptly intensified once HbA1c rose above 7.5%.

This expectation created considerable problems in our economic modelling, because few drug trials recruit only patients whose Hba1c has only just exceeded 7.5%. In many trials, baseline HbA1c was at least 8.5, and sometimes over 9%. The higher the baseline, the larger would be the expected reduction in HbA1c. So if we are considering only patients managed according to the NICE guidelines, many of the effect sizes from trials would be too large. However if Professor Bain is correct that clinical inertia continues, we can have more confidence in the modelling inputs.

Professor Bain: *On page 29 of the AR, the authors state that sulfonylureas 'have been used for so long that all their adverse effects are known.' And yet there continue to be published metanalyses suggesting that they may increase both CV and total mortality, compared with other anti-diabetes therapies.*

Continued publication of meta-analyses does not always imply that there is any new information. There must have been about 40 reviews of the flozins published by now. The point we were trying to make is that sulfonylureas have been around for many years so any rare but serious adverse effects should be known. One of the reasons for our choice of gliclazide as sulfonylurea of choice was that it did not seem to have the same association with an increase in cardiovascular disease.

Professor Bain: *P36: the continued use of cana- and empagliflozin in patients with eGFR between 45-59 mL/min should be at the lower dose of each drug (a slightly bizarre recommendation, given that their efficacy falls as the GFR reduces).*

We agree that the recommendation is odd. Especially as in the case of empagliflozin, where the evidence of efficacy in patients with moderate renal impairment (GFR 30-59) comes only from the 25mg dose. In the Empagliflozin Renal Trial, the 10mg dose was not used in patients with moderate renal impairment. The 25mg dose was shown to be effective in reducing HbA1c.

Professor Bain: *P38: I believe that Metformin does increase lactate levels but is not associated with lactic acidosis. The comment stating that it does not increase lactate either needs to be referenced or removed.*

In two large trials in the USA, De Fronzo and colleagues randomised patients to metformin or placebo and measured plasma lactate. It did not increase on metformin. De Fronzo R, Goodman A, and the Multicenter Metformin Study group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med 1995;333:541-9)*

P80: The Saleem and Jibran manuscripts are identical and neither should be considered until the authors respond to queries regarding their independence. Similar considerations apply to the Shah manuscript, which includes authors from the other two publications.

We have not used the articles for the reasons given on page 80. However they were both included in the Boehringer NMA (see BI Submission figures 16 and 17).

P82: Most clinicians who have any understanding of network meta-analysis (a small minority) have significant doubts about their veracity.

This view is understandable. Perhaps with modern software packages, it is too easy to load in data from a batch of trials and produce impressive-looking network diagrams and forest plots, without paying sufficient attention to heterogeneity and quality of studies. However in the absence of head to head trials, NMAs are the best we can do, and NICE expects us to do them.

On page 115, table 14 of the Assessment Report, we compare the results of the Boehringer, Janssen and assessment group NMAs for the effect of the flozins, and find little difference between the Janssen one and our one. The Boehringer values were a little higher but the relativities were similar.

P101: Almost all diabetologists recognise weight gain as a common side-effect of sulphonylurea treatment – to suggest that it is not, based on a single reference, is questionable…

We did not say it did not occur, and we accept it is common, but it was not seen in the Olivarius study, which came from a primary care, and hence much more representative, population of people on sulfonylureas.

P212 (and elsewhere); I am perplexed as to why the AG would expect the SGLT-2 weight gain to disappear after a year or in cases whom continue to take it?

We don't – this was just one of a number of scenario analyses to inform the AC.

P70: The AACE/ACE Scientific and Clinical Review: Association of SGLT2 Inhibitors and DKA (October 24-25, 2015) felt it was still unclear as to whether there is any relationship between SGLT-2 inhibitor use and DKA.
This consensus document came out after our assessment report had been submitted.

P75: If blood pressure reduction was the major driver for the mortality benefit in EMPA-REG, one might have expected to see this impacting on non-fatal stroke, which was not the case.
Good point. Since the Empa-Outcome results were released, there has been much discussion about the mechanism (s) underlying the effect. To recap, there were small reductions in HbA1c (about 0.4%), SBP (about 4mmHg) and weight (about 3%). These might over time reduce CVD risk, but a striking feature of the Outcome trial was that benefits were rapid. Muskiet and colleagues (Lancet Diabetes 2015/3/928-9) have suggested that the effect might through empagliflozin acting as an osmotic diuretic and causing natriuresis.

Professor Collier

Professor Collier's comments in italics.

The BMIs in the SGLT2i studies are low and do not reflect areas such as the West of Scotland where the mean BMI is much higher (males 31 kg/m^2, females 32kg/m^2) so SGLT2i are much more likely to have a greater impact on weight loss than the studies suggest. "Real life" clinical practice reflects this.

This is a fair point. The BMIs were low in one canagliflozin trial (Inagaki BMI 25.8) but not the other CANTATA-M 31.6). BMIs were low in two dapagliflozin trials (Ji 25.8; Kaku 26.1) but not the third (Ferranini 33.1). Both the empagliflozin trials were in groups with BMIs similar to UK populations (Lewin 31.4; Roden 28.2).

Repaglinide, which is a weak SU, is likely to be associated with poor compliance/concordance particularly if it needs to be taken 2-3 times a day.

Agreed. There is evidence that adherence falls with complexity of regimens, including the number of diabetes medications and doses taken. Reference: Odegard P, Capoccia K. Medication Taking and Diabetes: A Systematic Review of the Literature. *The Diabetes Educator* 2007; 33; 1014

Pioglitazone is not a medication in common use following the problems with rosiglitazone. It may or may not be time for its "resurrection" but pioglitazone is associated with weight gain and fluid overload making it an unpopular choice amongst clinicians.

Pioglitazone is still widely used (Table 1, page 31, 1.4 million prescriptions 2103/14) and has the advantage of being useful in non-alcoholic fatty liver disease which is very common in people with type 2 diabetes. Targher et al (Diabetes Care 2007/30/1212-1218) reported that almost 70% of people with T2DM had NAFLD. An Edinburgh study in 939 people with type 2 diabetes found ultrasound-detected steatosis in 74%. (Williamson et al. *Diabetes* 2009;**58:**A271). Patients with T2DM and NAFLD may be at risk of progressing to cirrhosis. A systematic review published in 2011 identified four pioglitazone studies in NAFLD. Pioglitazone was found to improve all parameters of liver histology. (Shyangdan et al. Health Technology Assessment 2011/15/38).
We did mention this on page 31 but perhaps it deserved greater emphasis.

Dr Peter Winacour (endorsed by Royal College of Physicians of London).

Dr Winacour asks:
If there were patients in EMPA-REG study with empagliflozin monotherapy did numbers permit sub group analysis re safety outcomes etc ?

The answer is no, for two reasons. Firstly, very few patients in the Empagliflozin Outcomes study were on no drugs at baseline and only two third would start empagliflozin monotherapy. The numbers are as follow.

Glucose-lowering therapy at baseline, n (%)
None 128 (2)
Monotherapy 2055 (29)
Metformin (% of monotherapy) 745 (36)
Insulin (% of monotherapy) 954 (46)
Dual therapy 3188 (45)
Metformin + sulfonylurea (% of dual therapy) 1383 (43)
Metformin + insulin (% of dual therapy) 1420 (45)

Secondly, during the trial, 19.5% of those on empagliflozin had additional glucose lowering drugs added, so the number on empagliflozin monotherapy at the end would be less. (Details in assessment report page 72.)

Repaglinide dose schedule based on glycaemic response does not reflect likely use – initial recommended dose is 500 mg tds up to maximum titrated dose of 16 mg – potential 5-6 titration steps with costs of extra GP visits and blood glucose monitoring. Modelling needs to take account of extra costs of higher doses, extra visits and costs of blood glucose monitoring.

Noted. We may have under-estimated the costs of titration of repaglinide.

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Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. *Br J Gen Pract*2007; **57**:455–60.

Gallagher N, Cardwell C, Hughes C, O'Reilly D. Increase in the pharmacological management of Type 2 diabetes with pay-for-performance in primary care in the UK. *Diabetic Medicine 2015; 32:62-68*

Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness,complications, and resource utilization. *JAMA* 1997; **278**:1663–9.

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Shyangdan D, Clar C, Ghouri N, Henderson R, Gurung T, Preiss D, et al. Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review. Health Technol Assess 2011; 15(38).

Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, *et al.* Prevalence of Nonalcoholic Fatty Liver Disease and Its Association with Cardiovascular Disease Among Type 2 Diabetic Patients. *Diabetes Care* 2007; **30:**1212–18.

Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer drugs for blood glucose control in type 2 diabetes. *Health Technol Assess 2010;14:36*

Williamson RM, Price JF, Glancy S, Butcher I, Perry E, Nee LD, *et al.* Prevalence of and risk factors for hepatic steatosis and non-alcoholic fatty liver disease in type 2 Diabetes: The Edinburgh Type 2 Diabetes Study. *Diabetes* 2009; **58:**A271.

Yki-Järvinen H, Kauppinen-Makelin R, Tiikkainen M, Vahatalo M, Virtamo H, Nikkila K, *et al.* Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006; **49**:442–51.

AG responses to Astra Zeneca comments. November 18th.

The AG responses to the Astra comments are in two parts. Firstly we respond to some issues raised in the text. Secondly we add responses to points raised in the table by adding another column for AG responses.

1. **Sensitivity analysis excluding the Kaku trial.**

As noted on page 100 of the assessment report, the Kaku trial had a low baseline HbA1c of 7.5%. This met the AG criterion for inclusion so it was included in our NMA. It was also included in the Astra NMA. However because of the relatively low baseline HbA1c, in the NMAs it pulls down the mean effect of dapagliflozin. In their comments on the assessment report, Astra state that the median baseline HbA1c in the dapagliflozin arm was only [redacted]. In their original submission (appendix 8.7) the baseline HbA1c in the dapagliflozin arm was given as 7.46%.

Astra Zeneca have now helpfully provided an alternative NMA excluding the Kaku trial. This increases the effect size versus placebo from a reduction of 0.62 to a reduction of 0.75% (-1.08 to –0.43), and makes dapagliflozin more competitive with the other flozins. Unfortunately these figures are shaded as academic in confidence and cannot be used in the final version of our report.

The AG concurs and in retrospect we should have done the same, and we could then have mentioned the effect of exclusion of the Kaku trial.

Astra Zeneca ask for more discussion of the features of the dapagliflozin trials. We provided some discussion on page 100 of the assessment report, with brief details in the Summary, including the reduction in HbA1c in the placebo groups. However, in the Summary section on canagliflozin, we did not mention the rise in HbA1c in the placebo groups, so in the interests of balance we will provide more details and discussion in the final version.

2. **The Plain English Summary**

This will need to be revised anyway, being currently over the HTA editorial word limit. We will take the comments from all respondents into account in the revision.

3. **Sequences of treatment (AZ comments section 2.1)**

In the original manufacturer submission, dated 15th June, Astra Zeneca pooled all the flozins in the analysis. In their responses to the assessment report, table 3 provided a comparison of cost-effectiveness using dapagliflozin alone. They do not specify if this uses the NMA results after exclusion of the Kaku trial. The results of this analysis show that dapagliflozin has an ICER of £7.603 relative to the DPP4.

However it should be noted that this is based on a lifetime QALY difference of 0.0113 (equivalent to 4 days) and a lifetime cost difference of £85. An ICER based on such inconsequential differences cannot be regarded as convincing.

The AZ model assumes that if a flozin as monotherapy is insufficient, it is discontinued. We think this is contrary to the usual practice in type 2 diabetes treatment, where if one drug is not enough, a second is added. (We can see the merits of sometimes testing the effects of switching, for example from an insulin-secretagogue to an insulin-sensitiser.) The algorithm in the draft NICE (June 2015 version) clearly anticipates a move to dual therapy.

The Astra response to the assessment report notes that their view is that the place of SGLT2 inhibitors would be in people unable to take metformin or gliclazide, and so their intensification sequence will be different from the AG sequence. Given the difference in costs of flozins and gliclazide, the Astra position seems logical.

The Astra response draws our attention to the study by McGovern and colleagues (Br J Diabetes Vasc Disease 2014/14/138-143). This is a small case series of people in London starting dapagliflozin and followed up for up to 12 months. The value is that it provides results from use in routine care. The rate of discontinuation due to adverse effects was 22%, much higher than seen in the trials, with the commonest reason being genital candidiasis. McGovern and colleagues provide some interesting data on variations in response, noting that 29% of patients had no reduction in HbA1c on dapagliflozin, and 42% had reduction of 1% or more. The findings with weight were similar – a quarter lost no weight, most lost under 5kg, but a few had quite large weight reduction. The most interesting findings were in blood pressure, where there was a bimodal distribution, with 43% having no SBP response and 41% having reductions of 5mmHg or more. Similar findings were noted for diastolic BP. The larger responses reflect baseline blood pressure.

The McGovern study had only 96 patients, most followed for 6 months or less, but it does suggest that it might be worth analysing the trial data for responders and non-responders.

Table 1: AstraZeneca proposed alterations to the report

Page	AG comment in report	AstraZeneca comment/ description of proposed amendment	AG response
11	If drug treatment is required to control high blood glucose levels when metformin cannot be used, the other options suggested in the NICE guideline include; - Sulfonylureas - Pioglitazone - The DPP4 inhibitors - Repaglinide	Although repaglinide was included in the recent draft of the guideline update, there was large clinical criticism to this suggestion. In response to the recent draft guidelines O'Hare 2015 judged repaglinide to have significant limitations, including the dosing of three times daily, increased risk of hypoglycaemia and weight gain. In addition, there is very little use of repaglinide in clinical practice (Clinical Expert Opinion 2015). Data additionally indicates there have been no prescriptions for repaglinide in monotherapy over the last year (IMS, MAT Aug 2015).	No comment required.
11	DPP4s have the advantage of being weight neutral.	Although weight neutrality of DPP4s is an advantage over current treatments in monotherapy, it should be clarified that this is not a benefit versus SGLT2s, which are able to reduce weight.	The neutrality comment was in comparison to the other drugs mentioned above. No change required. The weight reduction benefits of the flozins are described later.
14	The reductions in HbA1c with pioglitazone and gliclazide were…	We suggest the AG also includes the reduction in HbA1c with sitagliptin	Agreed. We will do so in the final version of the report before publication as an HTA monograph.
17	Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin	This statement is unclear as to what this is referring to, particularly given the earlier comments on cost. It should be clarified that this is over a lifetime horizon, when used as monotherapy Additionally, it is not clear why there is a discrepancy between these treatment costs (page 62). Please clarify why this may be the case	Agreed. We will clarify in the monograph version.
20	Plain English summary: However they are much more expensive than older drugs such as	AstraZeneca propose the addition of 'and are a similar cost to DPP4s'; however we are surprised that the assessment group have chosen to	This is a plain English summary and the point made is a key one. No change required.

	gliclazide and pioglitazone	highlight cost in the opening paragraph when the focus of NICE is cost-effectiveness	
20	Plain English summary: If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin…	As described above, this is an implausible scenario, and should not be included in the summary	The weight changes are not implausible. No change.
20	Plain English summary: As a consequence, the flozins represent very poor value for patients as a whole compared pioglitazone, repaglinide and gliclazide	This text seems emotive and is unspecific. Suggested alteration: As a consequence, the flozins represent poor value for patients as a whole compared pioglitazone and gliclazide *in the monotherapy setting*	Accepted and we will revise for the monograph.
20	The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins. But if a patient's day to day living is affected …	As described above, this statement is misleading; we request that the text is redacted from the report, and the summaries should clarify that ICERs are based on limited available data with differences in study characteristics.	
Background			
22	Progression [of diabetes] may be slow.	Note: progression may also be rapid.	The use of the word "may" implies that progression may not be slow.
24	Pioglitazone is recognised as causing weight gain but does not cause hypoglycaemia. Metformin does not cause either weight gain or hypoglycaemia.	For completeness, we suggest that heart failure, fractures, oedema, and risk of bladder cancer associated with pioglitazone are also mentioned	The bladder cancer risk is unproven and is discussed later, as are the other AEs. But we will mention heart failure etc here in monograph version.
25	The first draft recommended that patients who cannot take or tolerate metformin should take repaglinide	Please note this was strongly criticised by commentators and the final version of the guideline is not yet released	No response required.
29	[SUs] But they are very cheap, and have been used for so long that all their adverse effects are known.	It is worth noting the additional blood glucose monitoring and costs associated when patients are on tablets with a risk of hypoglycaemia, including sulfonylureas. The DVLA guidance requires monitoring of blood glucose at least twice daily and at times relevant to driving [20]	
31	Despite its adverse effects, pioglitazone is still widely used,	More relevant data for this report may be the prescribing of treatments in a monotherapy	Interesting data but we don't have access to the IMS data and we note that they are given as confidential. So

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<td>though its use may be declining, with new initiations falling in recent years. The Health and Social Care Information Centre Report gives figures for items prescribed in 2013/143

<table>
<tr><td>Table 1 Prescriptions 2013/14
Metformin</td><td>18,100,000</td></tr>
<tr><td>Sulfonylureas</td><td>8,400,000</td></tr>
<tr><td>Sitagliptin</td><td>2,020,100</td></tr>
<tr><td>Pioglitazone</td><td>1,408,600</td></tr>
<tr><td>Linagliptin</td><td>329,400</td></tr>
<tr><td>Vildagliptin</td><td>173,200</td></tr>
<tr><td>Repaglinide</td><td>83,800</td></tr>
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(Source: Patient data, IMS Information Solutions UK Ltd, MAT Aug 2015)</td>
<td>we can’t include them in the final version of our report.</td>
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<tr>
<td>32</td>
<td>Box 1: CG87</td>
<td>Please clarify that in the most recent draft of the guidance (June 2015), the DPP4s had a more flexible positioning, alongside the generics</td>
<td>We should wait for the final version of the guideline.</td>
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<td>34</td>
<td>The amount blocked appears to vary amongst the different drugs, with dapagliflozin 10mg blocking only about a third of reabsorption.</td>
<td>This text may be misinterpreted to infer that the reabsorption of dapagliflozin is inferior to the other flozins: it should be clarified that the reference in fact states “none of these SGLT2 inhibitors are able to inhibit >30–50% of the filtered glucose load”.
Please note, one reference was in healthy volunteers</td>
<td>OK, will clarify in final version

We said so.</td>
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35	Box 2	It should be clarified that a partial update of TA288 is scheduled: due to additional available data NICE will review the triple therapy regimen. This indication has already been accepted by the SMC	Thanks, we had not been told about the planned update. We will amend in final version. If the NICE update is not ready, we will use the SMC guidance.
36	Renal impairment	Please clarify the following: - Canagliflozin or empagliflozin should not be initiated in patients with GFRs < 60 ml/min. For patients on canagliflozin 300 mg or empagliflozin 25 mg with GFRs below 60 ml/min, dose should be reduced for o 100 mg and 10 mg respectively. - Initiation of empagliflozin is not recommended in patients over 85 years - A 5 mg dose of dapagliflozin is also available; this dose is recommended as a starting dose for patients with severe hepatic impairment	Our omission – we should have mentioned the 5 mg starting dose and will do so.
36	Where should SGLT2 inhibitors fit into the therapeutic pathway? Factors to be considered include:	Hypoglycaemic events should also be included as a factor to be considered	We disagree, having taken the position that the SGLT2 inhibitors do not cause hypoglycaemia.
Chapter 2: clinical effectiveness		**Please clarify the following:**	
48	Kaku and colleagues 2014 did not define hypoglycaemia.	Kaku 2014 defined hypoglycaemic events as: symptoms with confirmed plasma glucose <3.5 mmol/L (<63 mg/dL). Major hypoglycaemic episodes were counted as plasma glucose value <3 mmol/L (<54 mg/dL)	Where was this reported?
54	Ferrannini 2010 did not report on lipid levels.	Total cholesterol changed by +1.10 **mg/dl** in the dapagliflozin 10 mg am and + 0.63 **mg/dl** in the dapagliflozin 10 mg pm dose (Page 378 of CSR)	We did not use the CSR.
55	The definition of hypoglycaemia varied amongst trials with most using 4.0 mmol/l as the threshold, which seems a little high, when the lower limit of normal is 3.5 mmol/l	Please note, all three dapagliflozin trials used the 3.5 mmol/l limit for a hypoglycaemic minor event	Thanks. We will add a comment to that effect.
58	We believe there are errors in the numbers reported for UTIs in Table	Please adjust **Ferrannini 2010/Bailey 2015** results to:	To be checked, but UTIs have little effect on ICERs.

	4. Please note this may also impact the text on page 66, and inputs into the AG model.	**Dapa 10 mg**: 24 weeks: 4/70 102 weeks: 6/70 102 weeks (men): 2/34 (*correct in report*) 102 weeks (women): 4/36 **Placebo**: 24 weeks: 3/75 102 weeks: 3/75 102 weeks (men): 0/31 (*correct in report*) 102 weeks (women): 3/44 <u>Please adjust **Kaku 2014** results to:</u> **Dapa 10 mg**: 24 weeks: 2/88 (*correct in report*) **Placebo**: 24 weeks: 2/87 <u>Please adjust **Ji 2014** results:</u> **Dapa 10 mg**: 24 weeks: 5/133 **Placebo**: 24 weeks: 4/132	
65	Dapagliflozin has been shown to have a dose-dependent effect on glycosuria in patients with T2DM.	Please clarify, this study was conducted in healthy subjects.	We will clarify in final report.

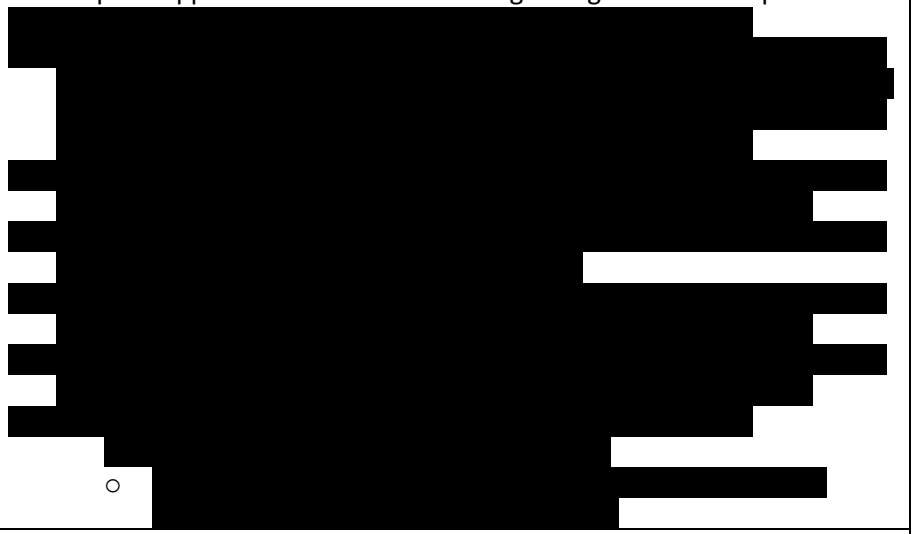
71-77	EMPA-REG	Considering that the section that includes the EMPA-REG ends in a sentence stating the 'results are not applicable to people starting monotherapy with empagliflozin' it is our position that these results should not be considered in the monotherapy indication. [redacted]	Position noted but the EMPA-Outcomes study has received so much publicity that we felt it could not be ignored. DECLARE was mentioned in the AZ submission but no data were provided. We can't add CiC data to our final report.
87 vs. 169	Table 9 on page 87 shows a mean difference in HbA1c from baseline of -0.59 (-0.70 to -0.48) for dapagliflozin This differs greatly from table 52 on pg 169, and in the model (μ = -0.704), while results for empa and cana are similar to pg 87.	Please could the AG clarify why there are such differences	This arises because in clinical effectiveness, the results are expressed as difference between drug and placebo, whereas in the modelling the effect size is based on the whole effect of the drug. So if drug reduced HbA1c by 1.25 % and placebo by0.25%, the clinical effectiveness difference is 1.0%. But in the modelling, the whole effect is used. The difference is greater for dapagliflozin because in all the dapagliflozin trials, the placebo group reduced HbA1c. See table 3 of assessment report.
102	The weight gain after adding gliclazide to a SGLT2 inhibitor may be different – it may only restore weight to the baseline before weight loss on the flozin.	Strojek *et al.,* demonstrated that when dapagliflozin is added to sulfonylurea monotherapy, there is a significant improvement in HbA1c (-0.13% vs -0.82%) and in weight reduction (-0.72 kg vs. -2.26kg). This suggests that an SGLT2 in combination with an SU is still likely to have a beneficial impact on the patient's	Noted. Though our comment was about adding gliclazide to a flozin, rather than the other way round.

		weight [21]	
103	So similar proportions in each group had to move to rescue therapy, implying no difference in durability	This is not correct. At week 208 the coefficient of failure was significantly lower in the dapagliflozin treatment group than glipizide (0.19 [95% CI 0.12, 0.25] vs. 0.61 [95% CI 0.49, 0.72]), indicating a lower rate of increasing HbA1c when treated with dapagliflozin	The figures in the assessment report are derived from the Del Prato study, figure 1A, and are correct.
103	For the effects of adding sitagliptin we have two useful trials with HbA1c baseline 7.7 and 7.8% which reported reductions in HbA1c of 0.67% and 0.79% (Scott 2007, Nauck 2007) giving a mean of 0.73%.	Please clarify: these are add on to metformin, active controlled trials.	Yes, these are add on to metformin with active controls, glipizide in Nauck, rosiglitazone in Scott.
Chapter 4: Clinical effectiveness from manufacturers			
104	Lilly now market a combination tablet with empagliflozin and linagliptin.	Please note that the empagliflozin and linagliptin combination is only currently marketed in the US	Noted.
106 + 109	AG disagrees with assumption that the classes of drugs can be grouped	As described in section **Error! Reference source not found.**, there are inherent differences between the SGLT2 trials, and limited evidence available in monotherapy. Appendix 2 presents updated forest plots, denoting the individual agents used in each trial, to allow for a more informed evaluation of the distribution of effects for each agent. The decision to lump treatments depends on the clinical assessment that treatments have similar effects (this has previously been considered in dual therapy: see Section 4.4 of the empagliflozin TA336 guidance). Indeed, page 109 states the 'lumping' of evidence into treatment classes may have overcome the issue of sparse evidence networks or zero values.	The updated forest plot shows the much smaller HbA1c effect of Kaku.
106 117	AG disagrees with assumption that when monotherapy fails NPH will be used.	See section 2.1 above	

	The AG sequence is Dapagliflozin 10mg > dapagliflozin + gliclazide > dapagliflozin + gliclazide + NPH		
Chapter 5: Cost effectiveness			
180	the AG calculate the baseline utility by implementing the -0.0061 quality of life decrement when the patient BMI rises above 25mg/m2. The mean BMI from UKPDS is 27.7 hence the calculation is 2.7*0.0061 which is added to the baseline utility of 0.785	This may be a typo: as it is a disutility we would assume that it would be 2.7*(-0.0061), then it will be added (as a negative value) to the baseline utility equalling 0.7685 and not 0.8015 as assumed in the report.	The adjustment is because the utility data within the reference will reflect the UKPDS BMI of 27.7 hence will already incorporate the 2.7*(-0.0061) disutility. This needs to be dialled out of the data before we apply the -0.0061 decrement for BMIs above 25 otherwise we would be double counting this impact. No revision required.
178	The AG mentioned that the baseline BMI from the NICE draft guideline is 31.6kg/m2	In this case should we use the formula above with the BMI from the actual baseline in the UK of 31.6kg/m2? This would be 6.6*(-0.0061)= 0.6763 Also in table 49 with the NICE CG baseline characteristics, the BMI presented is 31.9kg/m2	The model washes out the UKPDS BMI QoL impact as outlined above. Thereafter it applies the BMI disutility for whatever amount the patients is above 25kg/m2. No revision required.
AG Model	In the model, the utility input the Bagust effect of -0.0061 but we didn't find an input of +0.0061 associated with weight loss	Please confirm how the weight is modelled and if this works two ways, for weight gain and loss. It is unclear what assumptions are being applied in the AG model for extrapolation of weight effect (i.e. maintenance of weight effect and weight regain) over time. It would be helpful to see a plot on the average HbA1c and weight progression of the patients simulated in the model	The disutility is applied for every BMI point above 25kg/m2. So if a patient was at 30kg/m2 and a therapy brought it down to 25kg/m2 their disutility would be reduced from -0.0061*5 to zero. So there is a benefit from weight loss. If weight falls further to below 25kg/m2 the disutility is not applied to these reductions. This will only very rarely if at all have applied within the modelling. No revision required.
	The model uses a baseline HbA1c value of ~8.4.	A large standard error is applied as patients are simulated with baselines varying from HbA1c 6-12; please note this may not represent current practice	This is explicit in the report. No revision required.

Table 2: AstraZeneca response to AG questions in the report

Page	AG comment in report	AstraZeneca response
Chapter 4: Clinical effectiveness from manufacturers		
106 - 107	One problem with the AstraZeneca NMA is the data reported in the forest plot (Figure 4.6) for the pooled sulfonylureas, which include glibenclamide, glimepride, glipizide and one gliclazide trial. The net effect size in HbA1c lowering is 0.12%...	The error was only in the graphical presentation of the forest plots so there was no impact on the NMA. The forest plots were regenerated, correcting a previous error (please see Appendix 3).
	the primary analysis included the rescued patients and this is reflected in the one of the analyses, which reported a 0.09% reduction in HbA1c. (It is not clear where the rise of 0.03% in the AstraZeneca forest plot comes from.)	Please refer to updated forest plots in Appendix 3. The 0.09% reduction in HbA1c reported in the text was for change at 52 weeks. The data extracted for the AstraZeneca NMA looked at the primary endpoint at 26 weeks, and data was digitized from Figure 3a in Rosenstock *et al.,* (those patients who have a baseline and at least one post-baseline HbA1c assessment and no major protocol violations).
	It is not clear where the 0.1% figure used in the AstraZeneca meta-analysis comes from, though we note that the HbA1c difference between glimepiride and pioglitazone at 3 months as 0.1%.	The estimate of 0.1% represents the difference between glimepiride and pioglitazone arms at 6 months (not glimepiride and placebo); this was incorrectly labelled in the original forest plot. Please see updated plots in Appendix 3.
	The AstraZeneca forest plot reports a reduction in HbA1c of 0.14% compared to placebo. There was no placebo group in Erem 2014 which compared gliclazide with pioglitazone and metformin.	We confirm that there is no placebo group in Erem. Please refer to updated plots in Appendix 3.
106	N/A	Please note, in checking the NMA model, we have found an error in the results for hypoglycaemic events. Please see appendix 4 for updated results. We have therefore also re-run the base case analyses for DPP4, TZD and SU versus the grouped flozins to assess the impact on the ICER. There was very little impact on the results, with the main change being an increase in the ICER versus SUs from £52,047 to £59,013 (see appendix 4).
108	It specifies that vague priors were used for unknown parameters, however no details were provided as to the distributions or link functions used in the models.	For both continuous and binary endpoints, the NICE DSU code was used. Vague priors were: -Treatment effects had a vague prior of dnorm(0,.0001) -between-studies SD had a vague prior of dunif(0,5) (for RE models) Binary outcomes were modelled using the logit link.
108	Although it is not clear which treatment was the reference treatment in the network meta-analyses, results are presented for comparisons of the treatment classes with both placebo and SGLT2 only.	Placebo is the reference treatment throughout the analysis. In the tables, we realize that the term 'reference treatment' was used to label the treatment against which the relative effect measures were being compared to.

109	lacked details concerning the prior distributions and link functions used, its assessment of autocorrelation in MCMC models and sensitivity analyses concerning the elements of the models themselves (e.g. prior distributions, link functions and priors for parameters).	The analyses were run using a burn-in of 20,000, 100,000 iterations, and a thin parameter of 10 (i.e. retaining every tenth parameter in each of three Markov chains) to reduce the autocorrelation. Monte Carlo error was assessed (which reflects number of iterations and degree of autocorrelation) and was consistently less than 5% of the posterior standard deviation for all parameters of interest, in all models.
Cost effectiveness		
119	Only one paper was identified that addressed the cost effectiveness of flozin monotherapy in the patient group	A poster by Charokopu *et al.,* was also published last year on dapagliflozin monotherapy vs. DPP4 [22]
142	As far as the AG is aware the corollary of these has not been made available for the equations underlying the UKPDS OM2 model. As a consequence, it is not clear how the CDM of the AstraZeneca submission has implemented the probabilistic modelling.	Prior to UKPDS group making the bootstrapped regression coefficients available for the UKPDS OM1 equations the Cardiff model would sample risk probabilistically by using the published standard errors associated with each respective coefficient. This ignored information on covariance and the availability of the bootstrapped coefficients overcame this limitation. Bootstrapped coefficients for the UKPDS OM2 regression coefficients are currently available; consequently, only standard errors (ignoring covariance) are utilized.
142	During the STA of dapagliflozin the ERG noted various errors in the CDM implementation formulae for the evolution of the risk factors, which were subsequently corrected during the course of the STA. The AG assumption is that within the AstraZeneca submission these errors have been corrected.	This assumption appears correct. The following changes were incorporated: 
143	The submission did not present any analysis of model convergence over the number of patients modelled. The CDM	This is correct; the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion.

	only permits pair wise comparisons. As a consequence, the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion.	(See below in response to pg 216 for comment on convergence)
144	The submission does not appear to state what the baseline prevalence of the complications of diabetes was. The submitted electronic model sets these to zero.	That is correct. The complication history was assumed to be zero. Since the occurrence of complications is not a model driver, the effect is negligible.
145	The AG does not know how these figures for "intensified NPH" were obtained. Usually if NPH was insufficient, short-acting insulin would be added at meal-times	Source for HbA1c and weight effect NPH: 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. 81, 184–9 (2008) Source for HbA1c effect intensified NPH: Waugh, N. et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol. Assess. 14, 1–248 (2010). Source for weight effect intensified NPH: Montanana et al. 2008, chosen as most recent study reporting weight effect
146	A patient is modelled as intensifying treatment, first to NPH and then to intensified NPH, when their HbA1c breaches the 7.5% intensification threshold. The AG assumption is that the monotherapies are withdrawn at treatment intensification, but this is not explicit within the Astrazeneca submission	This is correct.
	Patients may also discontinue due to adverse events. The AG was unable to identify what was assumed for these patients: whether they switched to an alternative monotherapy and if so which, or whether they intensified to NPH insulin.	Patients switch to next treatment in case of discontinuation.
	The costs of the complications of diabetes in the first year and for subsequent years for blindness and amputation were based upon the UKPDS84. This is the same source as the AG though the AG arrives at somewhat lower values. … the source of the discrepancies is unclear.	Costs for blindness and amputation have been based on the UKPDS84 (cost year 2012). To inflate these costs to 2014, the hospital & Community health services (HCHS) index has been used. Index value in 2012: **282.5** Index value in 2014 **290.5**
148	AG calculations suggest that the UKPDS84 average inpatient costs and outpatient costs for those without any of the modelled complications have not been included within the AstraZeneca modelling. If this is the case it would be a quite serious omission, and would tend to bias the analysis in favour of the more effective treatment.	It seems that inpatient and outpatient costs have not been included for patients without complications. However, the difference in life years between the treatment arm and the control arm is minor (-0.010 for TZD to 0.004 for DPP4). This means that patients in the treatment arm live at most 0.004 years longer, resulting in an additional 0.004 times the annual inpatient/outpatient costs compared to the control arm. The impact seems negligible.
	Table 5.10 of the AstraZeneca submission also does not include a	The CDM does not support cost inputs for fatal IHD, only for non-fatal IHD. As

<table>
<tr><td></td><td>cost for fatal IHD events despite these being within the UKPDS84 and seeming to be associated with deaths in the UKPDS82 and the UKPDS OM2.</td><td>a consequence, costs for fatal IHD are automatically set to zero. However, the difference in fatal events between the treatment arm and control arm is minor (-0.00002 for SU to 0.00003 for DPP4), so the impact on results seems negligible.</td></tr>
<tr><td></td><td>For reasons that are unclear, AstraZeneca chose to revert to the costs of the UKPDS65 for the ongoing costs among those with a history of IHD, CHF and stroke, and probably MI as well.</td><td>It is unclear what this means. The history of IHD, CHF and stroke are set on zero.</td></tr>
<tr><td></td><td>ESRD was costed using the estimate of Baboolal et al. for continuous ambulatory peritoneal dialysis. Previous NICE assessments have also used this reference, though have also tended to use the higher cost estimates within Baboolal et al for hospital haemodialysis. Astrazeneca argued that the use of the peritoneal dialysis cost was conservative</td><td>ESRD events are more frequent in the treatment arm than the control arm for TZD and SU, so the lower ESRD price is <u>not</u> a conservative approach here. However, the difference is minor, so the impact is not expected to be considerable.</td></tr>
<tr><td>152</td><td>The scenario analyses around adverse events and discontinuations for the comparison with pioglitazone were reported as having the same values as the corresponding analyses for sitagliptin, so appear to be typos.</td><td>This is a typo in the report (p 79, table 5.14) the model results for pioglitazone should read:
<table>
<tr><td>No discontinuation</td><td>£ 1,901</td><td>0.1000</td><td>£ 19,001</td></tr>
<tr><td>No disutilities for AE</td><td>£ 1,912</td><td>0.0958</td><td>£ 19,961</td></tr>
</table></td></tr>
<tr><td>216</td><td>A concern with the Janssen and the Astrazeneca model is that there has been little presented on model convergence. The AG has relied upon the work of the draft NICE CG for diabetes, which resulted in deterministic model runs having 50,000 patients simulated with 1,000 inner loops for each patient to reduce the Monte-Carlo error. The draft NICE CG for diabetes could be read as suggesting that only 100 inner loops are necessary for convergence, but even this seems to be somewhat more model runs that any of the company submissions. As a consequence, the AG is uncertain whether the company models have reliably converged</td><td>Please find below results for 500 and 1000 runs (using the new probabilities for hypoglycaemic events). Although more than 100 runs may have been appropriate, the ICER is improved whether 500 or 1000 runs are used:
<table>
<tr><td></td><td>Previous ICER (100 runs)</td><td>ICER (500 runs)</td><td>ICER (1000 runs)</td></tr>
<tr><td>DPP4</td><td>6,125</td><td>3,995</td><td>4,333</td></tr>
<tr><td>TZD</td><td>20,639</td><td>19,513</td><td>19,965</td></tr>
<tr><td>SU</td><td>59,013</td><td>51,609</td><td>53,554</td></tr>
</table></td></tr>
<tr><td>218</td><td>Note that the baseline HbA1c of 7.5% of Astrazeneca is based upon the treatment intensification threshold rather than the Astrazeneca NMA, which had a mean of 8.2%. The Astrazeneca proportion who smoke has been taken from the electronic model, where it is ambiguous whether this is the proportion at diagnosis, the proportion at baseline, or both.</td><td>The proportion who smoke represent the proportion at diagnosis and has been derived from a 52-week NMA of RCTs of anti-diabetic agents added to metformin:

Oxford Outcomes. Network Meta-Analysis of Anti-Diabetic Agents in Type 2 Diabetes Mellitus: Metformin add-on therapy. 139 (2011).</td></tr>
</table>

219	Given the recentness of the diagnosis of diabetes, the companies and the AG all suggest low prevalences of complications at baseline. But Astrazeneca assumes these to be zero.	No scenario was performed on history of complications. In the Metformin + Dapagliflozin STA, this analysis has been done. However the prevalence of complications is not an important driver of the model, so the impact is expected to be minor.
223	All the analyses have used the CODE-2 quality of life decrement for BMI above 25kgm-2. Astrazeneca may not have restricted this to when the patient BMI is above 25kgm-2, but given baseline BMIs the impact of this will not have been large. All analyses also rely upon the estimates of Currie et al (2005) for the quality of life impacts of hypoglycaemic events, though again it appears that Astrazeneca may have applied the coefficient for non-severe hypoglycaemia to the event rate rather than to its logarithm.	From section 5.7.3 of the original submission for TA288 is states that "The resultant disutility is calculated as follows: - Severe event (binary variable: if ≥1 event then [1], else [0]) * 0.047 + number of symptomatic events * 0.0142 + number of nocturnal events * 0.0084" If this is how hypo related disutility was calculated in the submission (rather than the model's in-built function) then no log transformation is required- the AG have not read all the Currie 2006 manuscript. The values of 0.0142, 0.0084 and 0.047 are taken directly from the text: - "Regarding the association between fear of hypoglycaemia (HFS) and the EQ5Dindex, a difference of one unit on the HFS would result in a change in the EQ5Dindex of 0.008 units, whereas a difference of 5.881 units on the HFS would result in a change of 0.047 units on the EQ5Dindex. Similarly, each symptomatic hypoglycaemic episode yields a 0.0142 (1.42%) decrement in utility, while each nocturnal episode is associated with a 0.0084 (0.84%) utility reduction." As the log transformation referred to in the Currie manuscript refers to the regression equations only (used to derive the above numbers) the AG's concern is unwarranted. If the submission used the Cardiff Model's in built equations from the Currie paper, then the log transformation is undertaken anyway (and applied to number of symptomatic events)

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Boehringer Ingelheim

Comments on Multiple Technology Appraisals (MTA)

Canagliflozin, dapagliflozin, empagliflozin monotherapy for treating type 2 diabetes [ID756]

Order number	Section Number	Page Number	Comments	
1.	Summary	11	"Their [sulfonylureas'] safety record is well established." The most recent meta-analysis of CV outcomes (Monami et al, 2013) showed an increased risk of mortality (Mantel-Haenzel-OR: 1.22 [1.01–1.49], p=0.047). The authors concluded that CV safety cannot be considered unless it is evaluated in long-term cardiovascular outcomes trials. Therefore, while sulfonylureas are a well-established treatment for treating type 2 diabetes, there continue to be concerns about their long-term safety, particularly the potential increased risk of mortality.	We should perhaps have said "well-known", because the sulfonylureas have been used for decades.
2.	Summary	13	It is stated that *"Compared to placebo, empagliflozin*	Thanks for this. We will clarify in the final

			10 mg reduced HbA1c by 0.74% and empagliflozin 25 mg by 0.86%. Weight loss was about 2 kg, and SBP was reduced by 2.6 and 3.4 mm Hg." However, in the previous sentence it is stated that *"One empagliflozin trial was carried out in 197 centres in 22 countries, and the other in 124 centres in 9 countries, mainly western countries but including China, India and Japan."*: The manner in which this is currently written implies that the numbers presented refer to both trials. Please either include information for both trials, or describe the trial to which you are referring. For reference, in the EMPA-REG-MONO study, compared to placebo, empagliflozin 10mg reduced HbA1c by -0.74% (95% CI: -0.88, -0.59) and empagliflozin 25mg reduced HbA1c by -0.85% (95% CI: -0.99, -0.71). Weight loss was about 2kg	monograph version, though only one of the empagliflozin trials (Roden) had a placebo arm.

			and SBP was reduced by 2.6 and 3.4 mmHg.	
3.	Summary	13	*"The only significant adverse effects reported in the trials were increases in urinary and genital tract infections, mainly in women. Both UTIs and GTIs occurred in about 4% to 9% in women."* It is not clear if this is referring to the empagliflozin trial data or all SGLT2i data included in the monotherapy assessment report. Please make it clear which trial(s) this data has been reported from.	All flozins. We will clarify in final version.
4.	Summary	13	*"The proportions of MIs reported as fatal were surprisingly low at 4.0% and 4.4% for placebo and empagliflozin respectively."* It is unclear where these values have come from. Figures for adjudicated fatal or non-fatal MI are 5.4% and 4.8% for placebo and empagliflozin (NEJM, table 1) respectively, and 0.5% and 0.3% for fatal MI (supplementary appendix	These values are derived from Table 1 of the NEJM paper. PBO Emp Fatal or non-fatal MI 126 223 Non-fatal MI 121 213 So fatal 5

			table S5). Please correct these values to reflect the NEJM publication.	10 % 4% 4.48% The only correction that is required is that rounding up would give 4.5% in the empagliflozin group.
5.	Summary	13	*"Subgroup analyses showed that the primary outcome only reached statistical significance in Asians."* This statement is misleading as it indicated that there is only an effect in Asian patients. However, the trial has not been powered to demonstrate superiority in subgroups. The treatment-by-race interaction test (p=0.0872) is not significant, and the 95% CIs of the race subgroups include the overall effect. This p-value for interaction was not significant for ethnicity and multiple testing was not accounted for. In addition, due to the nature of tests for heterogeneity not being accounted for in the statistical analysis plan, these results would only ever be hypothesis generating and not confirmatory in nature. The HR for Whites (0.88) is	The statement does not say that there is only an effect in Asian patients. No correction required. See forest plot on page 5.

			almost identical to the overall HR (0.86). Please note that for CV death the effect is significant even in the separate subgroups of Whites and Asians.	
6.	Summary and EMPA-REG OUTCOME	13 and 72	"The mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group." "Despite the addition of other glucose-lowering drugs, the mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group, a difference of 0.35%." These numbers are not in the NEJM publication.	Yes they are. See foot page 10, top page 11. "…..many patients did not reach their glycemic targets, with an adjusted mean glycated hemoglobin level at week 206 of 7.81% in the pooled empagliflozin group and 8.16% in the placebo group."
7.	Summary	14	"However in some trials the untreated controls might also have had an increased risk of UTIs due to poor control and hence	Accepted – this sentence would be better elsewhere.

			glycosuria." It should be clarified that this statement does not relate to the EMPA-REG-OUTCOME study because the design of the study did not include an untreated group. All patients were treated at the discretion of the investigator, including background glucose lowering medications.	
8.	Summary	14	*"Only one dose of dapagliflozin is used, despite larger effects being reported with larger doses such as 20mg daily."* Only one dose of dapagliflozin is used. Larger effects have been reported with larger doses but this is outside the summary of product characteristics and is unlicensed. Please make it clear that 20mg is an unlicensed dose.	OK, will revise accordingly for final version of report.
9.	Summary	19	"Only empagliflozin has long-term cardiovascular outcomes reported yet, showing a reduction in mortality. " Please consider including	Accepted and we will add. [redacted]

			the reduction in hospitalisation for heart failure as well.	
10.	Summary	20	*"If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin over the more traditional treatments of pioglitazone, repaglinide and gliclazide. The traditional treatments may even provide more patient benefits. The flozins and sitagliptin cost around £400 more each year than the traditional treatments. As a consequence, the flozins represent very poor value for patients as a whole."* Weight loss is intrinsic to reducing insulin resistance (a key driver of the type 2 diabetes process) and compared to treatments such as pioglitazone and gliclazide is a significant benefit to patients. It is unclear what additional benefits pioglitazone, repaglinide and gliclazide offer to patients over the DPP-4is and SGLT-2is.	The Plain English summary will need considerable revision for the final version because it is currently well over the permitted word count. This section will be revised.

			Please detail which additional benefits traditional treatments may provide patients over and above the gliptins and flozins? Please also amend the final sentence to included sitagliptin. We also question the conclusion given the potential benefits of lower hypoglycaemia, no weight gain and also potential CV benefits the flozins offer significant benefits to patients.	
11.	1	33	"Due to their insulin-independent mode of action, they do this without weight gain or hypoglycaemia". The lack of weight gain may also relate to the loss of calories in the urine.	This sentence is about the effect of insulin. Loss of calories is the urine is not relevant to that and is covered elsewhere.
12.	1	34	*"There is also an SGLT1 transport mechanism, which is present both in the kidney and the gut. In the kidney, it is much less important than SGLT2. Inhibition of gut SGLT1 reduces absorption of glucose there, and it has been suggested that canagliflozin may have a dual action. This was reported first in healthy volunteers but has since been reported in a study of*	

			people with type 2 diabetes." This was reported first in healthy volunteers but has since been reported in a study of people with type 2 diabetes. However, additional SGLT1 inhibition has not been shown to have a clinically meaningful effect. There are no head-to-head comparisons between the current licensed SGLT2 inhibitors. Please make this more complete by stating the additional inhibition of SGLT1 and relevance to HbA1c reduction remains uncertain and there are no head-to-head studies comparing SGLT2 inhibitors.	We gave the answer on page 98; "One question was whether canagliflozin is more potent than other SGLT-2 inhibitors, due to its dual effect on SGLT-2 and SGLT-1 receptors. In monotherapy, both doses of canagliflozin lowered HbA1c slightly more than both doses of empagliflozin, which does not have a significant effect on SGLT-1 receptors. Nor does canagliflozin 100mg". The Introduction poses questions. Answers come later after analysis so it would be inappropriate to have answers in the Introduction.
13.	1	34	"In addition to improving glycaemic control, the SGLT2 inhibitors also reduce blood pressure." Please note that weight loss is also seen with SGLT2 inhibitors.	Yes, but this paragraph is about blood pressure.

14.	Study design	47	The studies were all double blind multicentre trials and only the two empagliflozin trials had active comparators (Roden 2013/4 and Lewin 2015)." It should be noted that the two studies were not primarily powered for the active comparison between the active monotherapies.	
15.	2	General	Patients with Asian race (ethnicity) and patients from Asian countries (region) are used interchangeably. Please clarify which patient group (i.e. of Asian ethnicity or from Asian region) is being referred to enhance clarity.	
16.	2	52	*"Empagliflozin at 10 mg/day reduced HbA1c by between 0.66 (Roden) and 0.83% (Lewin) from baseline, which amounted to 0.16% more than with linagliptin, no difference to sitagliptin, and 0.58% more than with placebo."* Can this commentary be amended to describe each	Is this necessary when the trials are named? However we are happy to amend as suggested.

			trial i.e. the Monotherapy (Roden) and the Fixed Dose Combination (FDC) empagliflozin/linagliptin initial combination (Lewin). It could be confusing as the reader may think that this is referring to 1 study. This is difficult when comparisons are made between both sitagliptin and linagliptin.	
17.	2	55	*"Empagliflozin at 10 or 25 mg/day reduced systolic blood pressure by between 2.1 and 3.7 mmHg from baseline, which amounted to between 1.7 and 3.4 mmHg more than in the control group. None of these differences were significant."* Can this be clarified that this is referring to the empagliflozin/linagliptin (Lewin et al) trial which involved an active comparator (linagliptin), as opposed to comparing against placebo. The statement "none of these differences were significant" is misleading as the monotherapy results are as follows: • 10mg: -2.6 (95% CI: -4.9, -0.4), p = 0.0231 • 25mg: -3.4 (95% CI: -5.7, -1.2), p =	Yes, we will clarify.

			0.0028	
18.	2	70	Cardiovascular safety. "All three of the SGLT2 inhibitors reviewed in this report are in large, long-term cardiovascular studies" It should be clarified here that the CV trial for Empagliflozin has been completed and reported	Accepted. The Empa-Reg-Outcome study was released only a week before our report was due in. A commentary was added but we omitted to update this sentence.
19.	2	71, general	The official name of the study is EMPA-REG OUTCOME®	
20.	2	71	*"72% were white, 21% Asian and 5% Black including African-Americans. The Asians were from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea."* Asian patients by race were 21%, patients from Asian region were 19%, so the sentence is technically not factually correct. Please clarify in the document either that "19% were Asian from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea" or	Minor point but we are happy to clarify. Note that the details provided in this comment were not provided in any of the published papers from the study. It would be useful if the Asian group could be divided into south Asian and east Asian – this information has not yet been provided.

			that “21% were Asian” but remove the statement around which countries they were from. The two statements together are not referring to the same patient population and could result in confusion.	
21.	2	71	When stating *“About 30% were on monotherapy, and 48% were on dual therapy implying **26%** were on more complex regiments with three drugs or more”;* “More complex regimens” is being used here to refer to patients treated with three drugs or more. It is implied that 26% here is calculated by subtracting 30% and 48% from 100 (i.e. the total population) to give 26%. This is incorrect. The correct calculated value if subtracting both 30% and 48% from 100% would be 22%. In addition, given that 2% of patients included were drug naïve patients (the baseline paper: Cardiovascular Diabetology 2014, 13:102), this also needs to be subtracted from the total population to give 20% as the proportion of patients on “more complex regimens” (i.e. three drugs	Our error. The details given in the protocol paper for baseline therapies are; Drug-naïve 2% Monotherapy 29% Dual therapy 45% suggesting that 24% were on complex regimens, rather than 26%.

			or more). Please correct this to state that 20%, rather than 26%, of patients were on three drugs or more.	
22.	2	71	EMPA-REG-OUTCOME. The results demonstrating the reduction in the hospitalisation for heart failure should also be included.	
23.	2	72	*"ACEIs or ARBs in 23.6%, which does not seem compatible with the 81% on these drugs at baseline"* At baseline, 81% of patients were on either ACEIs **and/or** ARBs, with a very small proportion on both ACEIs **and** ARBs. As the patients on both ACEIs and ARBs at baseline were very few, either ACEIs or ARBs could be added to the existing treatment if patients were not treated with either of those medications at baseline. In addition, "medication introduced post-baseline" is defined as new initiation or re-initiation of the medication. Therefore, this cannot be interpreted based on simple addition.	Noted. "Re-initiation" does not seem the same as "introduced post-baseline". But the clarification is useful and we will revise.

			Please remove statement "…which does not seem compatible with the 81% on these drugs at baseline".	
24.	2	72	*"Similarly Table S12 reports statins being introduced in 22% of the empagliflozin group, which implies that at study end, 99% were on statins, with 14% also on fibrates"* "Medication introduced post-baseline" is defined as new initiation or re-initiation of the medication. Therefore, this cannot be interpreted based on simple addition. At baseline, 77% of patients were already being treated with statins, whereas 22% of patients had statins introduced post-baseline. Some of these patients may have stopped and resumed statin regimes during the trial, whilst others were newly initiated patients on statin treatment. A similar case exists for patients treated with fibrates at baseline and throughout the study duration. Please remove statement "…which implies that at study end, 99% where on	As above.

			statins, with 14% also on fibrates".	
25.	2	72	*"The results were analysed by staff from Boehringer Ingelheim who co-funded it with Eli Lilly"* Please note, the outcome events were adjudicated by an independent blinded adjudication committee. The data was also analysed and validated by a group of independent external statisticians from the University of Freiburg in Germany.	
26.	2	72	*"The two empagliflozin groups were pooled for the analysis, because event rates were almost identical…"* The EMPA-REG OUTCOME study is powered to show the superiority of pooled empagliflozin vs. placebo with 2:1 randomization. Therefore two doses were pooled according to the predefined statistical analysis plan in the protocol. This is because the study was designed on the assumption that the CV benefit of both doses of empagliflozin would be the	Accepted.

			same. It is incorrect to state that the groups were pooled because the event rates were the same. In addition, the HRs versus placebo was almost identical for both doses when analysed separately (0.85 for 10mg and 0.86 for 25mg). Please note that for CV death and all-cause mortality a significant superiority has been shown even for the individual dose comparisons vs. placebo. Please also remove statement "…because the event rates were almost identical".	
27.	2	72	*"When the main outcomes were assessed for the 10mg and 25mg empagliflozin groups separately, the differences were not significantly different from the placebo group"* The EMPA-REG OUTCOME study is powered to show the superiority with pooled empagliflozin vs. placebo with 2:1 randomization. The pre-planned analyses of individual subgroup vs. placebo were conducted to assess whether the	One implication being that if there is a good response to 10mg for glycaemic control, there is no cardiovascular reason to use 25mg.

			benefit size was consistent between two doses.	
28.	2	73	*"Supplementary table S5 reports 11 deaths from acute MI in the placebo group and 15 in the pooled empagliflozin group, but these figures do not match those in table 1 in the main paper. The figures for fatal stroke also differ between main text and supplement 11 versus 9 for placebo, 16 versus 14 for empagliflozin"* It is unclear where these figures (i.e. 9 for placebo and 14 for empagliflozin) come from. Table 1 in the main NEJM publication does not report the number of deaths from acute MI. In addition, fatal stroke is also not presented in the main text. These numbers (i.e. 11 for placebo and 15 for empagliflozin) are correct as "fatal MI or stroke" were defined as death occurring ≤ 30 days after a MI or stroke event. Any death caused by MI or stroke occurring >30days after previous MI or stroke was defined as "CV death; caused by stroke"; this is standard way of capturing CV death, and fatal	Deaths from MI and stroke can be calculated from Table 1.

			MI/stroke event.	
29.	2	73 (table 6)	In Table 6 results of EMPA-REG OUTCOME trial – there are the following inconsistencies compared with table S5 of the supplementary appendix: • Fatal MI is 0.5% for placebo (as reported in Table S5), not 0.2%. Fatal stroke is 0.5% for placebo (as reported in Table S5), not 0.4%. Please also note that the true value for Non-cardiovascular mortality is 2.1% for empagliflozin, not 2.0%. This is because the values reported in the paper were rounded Please correct these values to reflect the supplementary appendix of the EMPA-REG OUTCOME study publication (DOI: 10.1056/NEJMoa1504720).	
30.	2	73	*"The proportion of fatal to non-fatal MIs looks odd – 5 deaths out of 126 MIs. Similarly of 69 strokes, only*	If there were 11 deaths from MI, why is the difference between all MI and non-fatal MI only 5 in

			9 were fatal. This raises the question of where the 137 cardiovascular deaths come from." In the placebo group, 126 patients had an adjudicated MI, 11 were adjudicated as resulting in CV death (main publication Table 1, and Supplementary appendix Table S5). Figures for both empagliflozin groups are 223 patients including 15 resulting in death. For strokes the figures are 69 including 11 resulting in death (placebo) and 164 including 16 resulting in death (both empagliflozin groups). Please correct these values to reflect the main EMPA-REG OUTCOME publication and accompanying supplementary appendix.	the placebo group in Table 1? If there were 11 deaths from MI and 11 from stroke in the placebo group, that only accounts for 22 of the 137 cardiovascular deaths.
31.	2	73	*"The DKA rate in the empagliflozin was double that in the placebo group but the excess risk was only about 1 in 1500 per year, and numbers were very small."* With 1, 3, and 1 DKA events in the three arms	I case in 2333 patients on placebo = 0.43 per 1000 4 cases in 4687 on empagliflozin = 0.85 per 1000 Close enough to be called doubling.

			(placebo, empagliflozin 10mg and empagliflozin 25mg), respectively, this does not support a statement of doubling the DKA rate. The summary by the safety committee and the NEJM authors was that there was no increase of DKA cases with empagliflozin in this study.	
32.	2	74	*"The ill-defined "other cardiovascular deaths"* All fatal events were adjudicated by an independent adjudication committee. If the cause of death was definite non-cardiac origin such as trauma, end stage of cancer etc. it was classified as "non-CV death". If there was well documented definite cause of CV death then that event was captured as CV death with specific cause. If the cause of CV death was not clearly documented, then the event was classified as "other CV death", which is the standard adjudication procedure of a CV outcome trial.	

33.	2	74	*"…with curious accelerations in the placebo group curves after 42 months"* The mean observation time was 3.1 years. After 42 months only a few participants were reflected in the Kaplan-Meier curves. Therefore, any change in the curves needs to be interpreted with caution.	No explanation given.
34.	2	74	*Referring to the section "How were these cardiovascular benefits achieved?* ": Please note that this study was not designed to answer how the benefits could be achieved; this study was designed to be a "CV risk factors equipoise" trial. Patients in the placebo arm received more CV and glucose lowering medications.	
35.	2	75	*"Discontinuation rates from study drugs due to adverse events are reported as 19.4% for placebo and 17.3% for empagliflozin in the paper but as 13.0% and 11.5% in appendix H."*	Noted.

			Adverse event leading to discontinuation of a study drug" includes temporary discontinuation; whereas "prematurely discontinued from trial medication due to adverse event" in the patient's disposition only included permanent discontinuation.	
36.	2	75	*"Of the 282 primary events in the placebo group 49% were cardiovascular deaths. Of 490 primary outcomes events in the empagliflozin group, 35% were cardiovascular deaths."* This is not correct; the contribution of CV deaths for the 3-point MACE is 107 patients (38%) for placebo and 143 patients (29%) for empagliflozin. Reason is that for 3-point MACE the first event counts.	Table 1 reports that there were 137 deaths in the placebo group, not 107. The 282 is reported as primary outcomes. Does this mean that if a patient had a non-fatal MI, followed by a fatal one, only the non-fatal first event is counted under primary outcomes?
37.	2	75, 77 Regarding subgroup analyses	One of the major objectives of subgroup analyses for the key CV endpoint is to investigate consistency of the result across the subgroups and whether the data suggests an interaction related to patient characteristics. Some heterogeneity was observed in primary outcome event but none in	

			CV death. The subgroup analyses were not adjusted for multiple testing which increases type 1 error dramatically. Therefore we cannot conclude statistical significance using the results of subgroup analyses. For primary outcome subgroup analyses; - Ethnicity, BMI, Background antihypertensive therapy: there was no interaction between subgroups. - Age, HbA1c : Some heterogeneity was observed however multiple testing was not adjusted. The results would be hypothesis generating and not confirmatory.	
38.	2	77	*"There was no evidence of overall mortality reduction in white people…"* This is incorrect. The HR for Whites for CV mortality is 0.64 and highly significant. The HR for Whites for all-cause mortality is not yet published.	Accepted and we will correct. This should have referred to the primary outcome.

39.	2	77	*"The subgroup analyses in EMPA-REG Outcome are interesting. Younger, lighter, better controlled patients did better, as did the Asian group. There could be overlapping features here in that the East Asians tend to be lighter. There was no evidence of overall mortality reduction in white people but some reduction in CVD mortality, which suggests that there were more non-cardiovascular deaths in white people on empagliflozin. Further details will no doubt be released but with such a very large study, further analysis is bound to take time."* As mentioned above this is seriously misleading and scientifically wrong. We cannot make conclusions such as the above based on the results of the subgroup analyses as there was no evidence of any significant interaction in CV death and multiple testing was not adjusted for.	Accepted as above.
40.	2	77	*"The differences observed do not seem sufficient to justify the very optimistic media coverage, such as*	The patients in the Outcome study were very high risk, and the results cannot be assumed to

			reports that 'Lilly's Jardiance diabetes pill could be a $6 billion-a-year blockbuster'." While we cannot speculate on future sales, the results from EMPA-REG OUTCOME study are clearly a breakthrough. The hardest possible endpoint in a clinical trial is all-cause mortality as there is no room for misinterpretation. A 32% relative and 2.6% absolute risk reduction is highly clinically relevant. The magnitude of the effect on CV death and all-cause mortality is fully in line with that seen in other landmark trials with statins and ACE inhibitors / ARBs. This was achieved despite the fact that the patients in EMPA-REG OUTCOME were very well treated as evident by their blood pressure and LDL cholesterol levels, as demonstrated by the use of co-comintant medication. The Number Needed to Treat to prevent one death over 3 years was 39 (calculated to be 25 over 5 years) and is therefore, again, in the same range as the aforementioned landmark trials.	apply to low risk groups in which the NNT would be much higher. The results in the Outcome study cannot be assumed to apply to the patient group in this appraisal.

			In addition, The Alliance would like to highlight that results such as these have never been demonstrated by diabetes treatments and, as such, warrant specific reference to empagliflozin within the document in this regard. Empagliflozin is the only glucose lowering agent in a completed dedicated cardiovascular trial to have demonstrated superiority in the primary composite cardiovascular endpoint. Studies involving metformin have demonstrated some cardiovascular benefit in historical studies, however, it should be noted that this was not in a prospective dedicated cardiovascular outcome trial of the design, size and robustness of EMPA-REG OUTCOME. It should be noted that these results cannot be extrapolated across the SGLT2i class until the other class members' cardiovascular outcome trials report in the coming years and that it is empagliflozin alone that has thus far demonstrated	

			this important effect for patients with type 2 diabetes.	
41.	2	77	*"It is worth noting that the Empa Outcome trial involved patients at high cardiovascular risk who had had diabetes for many years and who were on complex regimens for their diabetes. The results are not applicable to people starting monotherapy with empagliflozin*." Although few drug naïve patients were included in the EMPA-REG OUTCOME study, potential benefits of empagliflozin as monotherapy cannot be excluded. In a previous meta-analysis of 11314 patients on placebo and 2,395 patients on all empagliflozin (1,098 patients on empagliflozin 10 mg, and 1,297 patients on empagliflozin 25 mg) including a monotherapy study (published EPAR), the HR of 4P MACE was 0.48. Therefore the potential benefit of empagliflozin in the earlier T2DM patients might be even larger than what we observed in the EMPA-REG OUTCOME trial.	Strictly speaking, this is correct. However since the mechanism by which the benefits were achieved in the high-risk patients in the Outcome study is uncertain, we do not know if the same effect would be seen in low risk patients.

42.	5	116, general	It has to be noted that the cost-effectiveness model did not include any data from the EMPA-REG OUTCOME study. While the EMPA-REG OUTCOME study only included a small proportion of patients on monotherapy, it cannot be definitively concluded that empagliflozin has no positive effects on CV outcomes. Therefore, it would make sense to explore the potential impact of empagliflozin in monotherapy in patients at high CV risk. If only in sensitivity analysis to explore what potential impact this benefit could have on the cost-effectiveness results.	Correct – the data were not available in time. But in addition, event rates in the high-risk patients in the Outcome study could not be applied to the patients being treated with monotherapy. Nor could the savings from the reduction in hospital admissions. The data would be more applicable to empagliflozin used in combination therapy as appraised in the recent STA. This merits consideration. It could not be done before the Appraisal Committee meets. We would expect a favourable impact on cost-effectiveness, admittedly only for the high risk group. However an exploratory sensitivity analysis could be done applying the same relative reduction to lower risk groups. For discussion with NICE.

Comments from Janssen and AG responses

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes [ID756]

9th November, 2015

Issue 1 **Incorrect clinical information presented**

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 53, when discussing weight for canagliflozin, while the reductions from baseline are correct, the reductions compared to placebo are incorrect.	For 100 mg, the reductions vs placebo should be 1.9 kg and 2.1 kg, instead of 3.0 and 3.1 kg. For the 300 mg dose, the reduction vs placebo should be 2.9 kg instead of 3.9 kg.	Janssen advocate that that these errors in the data are corrected. Janssen is unsure whether this error appears only in the text or has been pulled through into the modelling. Janssen has attempted to replicate the network meta-analysis (NMA) conducted by the Assessment Group (AG, further detail provided in a separate document by Janssen, titled "Additional Information") and from this do not believe that this error features in any further analyses conducted by the AG.	Error accepted. The correct figures were used in NMA and hence modelling.

Issue 2 **Incorrect clinical information**

prese nted

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 54, when discussing systolic blood pressure reductions with canagliflozin 300 mg, the Assessment Report (AR) states that a 0.5 mmHg was seen from baseline, which is 0.9 mmHg more than placebo.	For 300 mg, the reduction from baseline was 5.0 mmHg rather than 0.5 mmHg. And when compared to placebo this should be 5.4 mmHg.	Janssen attempted to replicate the network meta-analysis (NMA) conducted by the AG. While exact replication was not achieved as too few details were reported in the AR reported about how missing data were handled, near replication was achieved, which suggests a high likelihood that this error is not only a typographical error in the text, but an error that has been pulled through to the NMA and subsequent economic modelling (disadvantaging CANA 300 mg). For a summary of the replication analysis conducted, please consult the separate file, titled “additional information”. Janssen advocate that on page 54 this error is corrected.	Error accepted, and unfortunately this error was carried into the NMA. We will assess the effect.

Issue 3 **Incorrect clinical information presented**

Description of problem	Description of proposed amendment	Justification for amendment	AG response
In table 4, on page 57, of the AR the AG has presented inaccurate data for urinary tract infection (UTI) rates associated with the use of canagliflozin. It appears that GMI rates from Stenlof, et al (2013) were incorrectly extracted as UTI rates.	Note that values for UTIs need correction (genital mycotic infection (GMI) rates were mistakenly provided for UTI rates). The correct UTI rates at 26 weeks are: 14/195 (7.2%) for 100 mg, 10/197 (5.1%) for 300 mg and 8/192 (4.2%) for placebo. The correct UTI rates for the high HbA1c sub-study at 26 weeks are: 3/47 (6.4%) for 100 mg and 2/44 (4.5%) for 300 mg. The correct UTI rates at 52 weeks are: 16/195 (8.2%) for 100 mg, 14/197 (7.1%) for 300 mg and 12/192 (6.3%) for placebo/sitagliptin. These data are also summarised in Table 3, on page 19 of the submission made by Janssen.	It appears that the AG has presented figures for genital mycotic infections (GMIs) instead of UTIs. Janssen has provided the correct values for UTIs, and is unsure if this will have an impact on the modelling. Janssen advocate that Table 4 be corrected.	Accepted, but differences are slight (7.2 vs 6.2; 6.6 vs 5.1) and won't affect modelling. Table 4 will be corrected.

Issue 4 **Misinterpretation of the**

SUCRA

Description of problem	Description of proposed amendment	Justification for amendment
On page 112, the AG have incorrectly summarised how the SUCRA was used by Janssen in the interpretation of the NMA results.	The AG correctly summarise that Janssen reported both the point estimates (and credible intervals) of the mean difference and odds ratios and the probability of the different treatments as being the most effective based on the Surface Under the Cumulative Ranking (SUCRA). Although the summary of the interpretation of SUCRA was correctly presented in the report, the way in which the SUCRA was described to be used by Janssen to interpret the results is incorrect. The treatments were ranked based on the SUCRA, where treatments with the highest values have the highest probability of being most effective. The SUCRA is expressed as a percentage and ranges between 0% and 100%, with a SUCRA of up to 100% indicating treatments to be ranked first with the high certainty, while low SUCRA values indicate the opposite. Separately to treatments being ranked, the probability for canagliflozin to perform better than each comparator considering specific end point was calculated. This probability is a separate concept to the interpretation using SUCRA. There is no threshold reported in the guidelines to show the superiority of a treatment versus its comparators; therefore, these probabilities were interpreted as follows: - if the probability of performing better for treatment A compared to treatment B was >70%, then A was assessed as better than B - if this probability was between 30% and 70%, then A and B were reported as similar, and - if the probability was <30%, then B was described as better than A.	Janssen has clarified the use of SUCRA in the interpretation of their NMA.

Issue 5 **Differences in inclusion of sulfonylureas in AG versus Janssen NMAs**

Description of problem	Description of proposed amendment	Justification for amendment
On page 113, the report describes that all sulfonylureas were pooled in the Janssen NMA.	The Janssen analysis did not pool all sulfonylureas. All sulfonylureas (i.e. gliclazide, glipizide, glibenclamide and glimepiride) were considered separately and pooling was performed for the different doses of a same treatment. This was necessary as most identified trials allowed for the titration of SU doses; as such, not enough data is available to investigate separate doses. In addition, the AG found no suitable trial of gliclazide vs. placebo, so they used 2 trials of gliclazide vs. pioglitazone (Lawrence, t al 2004 and Erem, et al 2014) and 1 trial of gliclazide vs. vildagliptin (Foley, et al 2009). The additional level of indirectness poses an additional source of uncertainty in the efficacy estimates of gliclazide in the NMA conducted by the AG. The Janssen analysis included one of these trials (Lawrence, et al 2004). Erem, et al 2014 was not included as it compared gliclazide to a titration of pioglitazone (and we	Janssen has clarified the pooling of sulfonylureas and provided an explanation for the approach that was used. Differences by inclusion of additional SU trials do not significantly change the treatment effect of gliclazide. Please consult Section 5 in a separate document provided by Janssen, titled “additional information” for further detail.

	considered different doses of pioglitazone separately) and Foley, et al 2009 (versus vildagliptin) was excluded from the Janssen NMA as numeric results were available at 104weeks only (data at 26 weeks could be estimated from a graph but exact numbers were not reported). Including sulfonylureas other than gliclazide could have the following effects on the Janssen NMA. Glimepiride and glipizide were not involved in loops in the network therefore deleting them would have no consequence on other estimates. Glibenclamide was linked to placebo, gliclazide, pioglitazone 30 mg, and pioglitazone 15 mg. Deleting it would predominantly impact the assessment versus gliclazide and would have a small impact on pioglitazone 30 mg and pioglitazone 15 mg estimates. DPP-4 estimates could potentially be affected through the loops via pioglitazone; however, effects are small because there are a number of other studies that inform these values, as well.	

Issue 6

Inclusion of dapagliflozin 5 mg as a comparator in the Janssen NMA

Description of problem	Description of proposed amendment	Justification for amendment
On page 112, it was noted that Janssen NMA included comparators that the AG considered irrelevant (such as dapagliflozin 5 mg).	Janssen identified 4 trials assessing dapagliflozin, only one of which (Bailey, et al 2012) assessed only dapagliflozin 5 mg. Its size was comparable, if smaller to the other studies. Therefore, it would be expected to have a minor impact only on the comparison versus dapagliflozin 10 mg and no impact versus other comparators.	Janssen has provided an explanation of the anticipated impact for the inclusion of dapagliflozin 5 mg as a comparator included in the NMA.

Issue 7

Differences in studies included

Description of problem	Description of proposed amendment	Justification for amendment in Janssen NMA
On pages 112, the AG notes that the Janssen NMA includes some studies that it does not find relevant.	The Janssen NMA planned to include more comparators than the AG NMA, and in this sense it is broader and has found more studies that matched its inclusion criteria (details of which may be found in Table 3 of the study report). In some cases, the inclusion of comparators on this occasion not considered relevant by the AG can benefit the network of evidence by providing studies that link 2 relevant comparators indirectly.	Janssen has provided justification for including a greater number of studies in the NMA supporting Janssen's submission.

Issue 8

Differences in inclusion criteria between AG and Janssen NMAs

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 79, the report notes that studies included in the AG NMA were restricted to those of 24 or 26 weeks in duration but Janssen included studies of 26 +/- 4 weeks [page 113].	Note that only one study included in the Janssen NMA did not report results at 24 or 26 weeks. This study, NCT01183013, assessed linagliptin vs. pioglitazone with data at 30 weeks.	Janssen has identified only 1 the study which was included due to the differences in inclusion criteria related to the time of trial reporting and do not believe that the inclusion of this study impacts the results of the Janssen NMA in a significant manner.	Agreed.

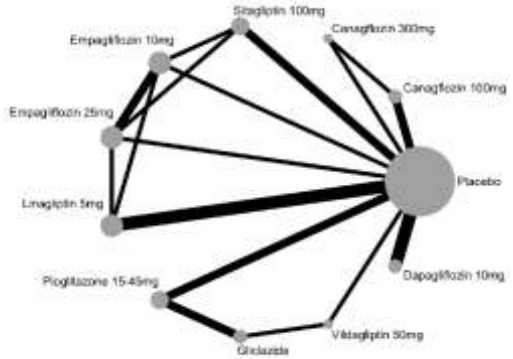
Issue 9

Differences in AG and

Janssen NMA results

Description of problem	Description of proposed amendment	Justification for amendment
Tables 106, 107, and 108 illustrate differences in the results from the AG and Janssen NMAs, specifically related to comparisons to pioglitazone and sulfonylureas.	Note that there are some examples where the results were similar between the 2 analyses: • HbA1c change of -1.20 with canagliflozin 300 mg in the Janssen submission and -1.153 in the AG; Table 106 • HbA1c change of -0.64 with dapagliflozin 10 mg in the Janssen submission and -0.704 in the AG; Table 106 • SBP change of -3.40 with empagliflozin 25 mg in the Janssen submission and -3.743 in the AG; Table 107 • Weight change of -3.42 with canagliflozin 300 mg in the Janssen submission and -3.577 in the AG: Table 108. However, there are some marked differences for some efficacy results. In particular: • In a recently updated analysis by Janssen, HbA1c change with sulfonylurea is reported as -1.04, however the AG report this change as -1.301 (Table 106). Janssen are unsure how this input parameter was generated. In Table 9 of the assessment report, the change in HbA1c reported more closely matches that found in the Janssen analysis, at -0.95. • AG also had much more favourable HbA1c lowering for pioglitazone. HbA1c change with pioglitazone in the updated analysis conducted by Janssen is reported as -0.76 and the AG report this value to be -1.200 in	Janssen has clarified the potential differences in the NMAs that may have resulted in the observed differences in the results, some of which may be reflected also later in the economic outcomes.

	Table 106. Again, Janssen are unsure as to how the AG determined this value as the input parameter for the economic modelling as in Table 9 of the Assessment Report the AG report the change in HbA1c with pioglitazone to be -1.13. • SBP change of -5.41 with canagliflozin 300 in the Janssen submission and -1.338 in the AG; Table 107. AG had worse SBP lowering for canagliflozin than that from Janssen NMA; this may be as a result of the AG wrongly extracting SBP data from the CANTATA-M study. Please consult Section 2.4.3. in the separate document supplied by Janssen, titled "additional information" for further clarification. • SBP change of +0.88 with pioglitazone in the Janssen submission and -1.400 in the AG; Table 107. Janssen understand that this is an assumed effect by the AG, as no SBP value was determined by the NMA conducted by the AG for pioglitazone; however, Janssen are unsure as to how this assumed effect has been determined. • Weight change of +0.62 with sulfonylurea in the Janssen submission and +1.397 in the AG: Table 108 Differences in the results for pioglitazone can be explained by the choice of dose specific nodes. The AG NMA pooled pioglitazone doses together, whereas the Janssen NMA considered separately pioglitazone 15, 30, and 45 mg. Moreover, the studies assessing pioglitazone included in the AG NMA and Janssen NMA differed to an extent. The Janssen NMA excluded the study with pioglitazone titration (Erem 2014) that was included in the AG analysis. Some pioglitazone trials with high drop-out rates were excluded from the AG NMA but included in the Janssen NMA (e.g. Aronoff 2000, Chou 2012 and Scherbaum 2002). A trial that assessed pioglitazone versus glibenclamide (Watanabe 2005) was excluded from the AG NMA and included in the Janssen NMA. As described above, the NMAs differed in how sulfonylureas	

	were included. Janssen considered multiple sulfonylureas, but the AG considered that the only sulfonylurea of relevance was gliclazide. Accordingly, the evidence base on sulfonylurea differed between the two NMAs. The AG evidence on the relative efficacy of canagliflozin vs. sulfonylurea was obtained from a double-indirect link (canagliflozin <-> placebo <-> (pioglitazone or vildagliptin) <-> gliclazide; see figure below). Regardless, within the updated NMA conducted by Janssen, the reduction HbA1c for sulfonylureas closely matched that determined by the AG.  Figure 4 Network plot – glycated haemoglobin (HbA1c) Differences in hypoglycaemia event rates were also seen between the 2 NMAs that likely resulted from the differences in inclusion of sulfonylurea studies. The gliclazide studies included in the AG NMA reported low hypoglycaemia rates, which may have driven the low rates seen in the AG NMA: • Lawrence 2004: did not report the hypoglycaemic events • Erem 2004: 0 patient in both arms (gliclazide and pioglitazone) had an hypoglycaemic event • Foley 2009: did not report hypoglycaemia data at 24-26 weeks but at the end of the study (104 weeks), the rates of patients with at least one grade 1 hypoglycaemic event were: vildagliptin = 0.7% and gliclazide = 1.7% (0 patient had a grade 2	

	hypoglycaemic event in both arms) The high amount of uncertainty associated with the HbA1c effect estimates for pioglitazone, vildagliptin and gliclazide in the AG NMA (see for example Figure 5 within the AR) indicate a possible heterogeneity or lower information content in this part of the evidence network. This is confirmed in the results on weight gain (Figure 7 of the AR) that also show a large uncertainty for the estimates associated with vildagliptin and gliclazide. In light of differences in the efficacy estimates for sulfonylurea and pioglitazone between the Janssen submission and the AG NMA, it would be interesting to see how the AG NMA efficacy estimates would change with their removal. Janssen have conducted such an analysis, please see separate document, titles “Additional Information”. Moreover, the AG assumed some efficacy estimates that were unavailable from the NMA. In particular, the values for SBP change with pioglitazone and sulfonylurea were based on assumptions. Janssen was able to source these estimates from the NMA used to inform the submission, which was conducted in line with NICE Guidelines 2008 and DSU 2011.	

Issue 10

Lack of statistical details for the Janssen NMA

Description of problem	Description of proposed amendment	Justification for amendment
On pages 112-115, the report noted a lack of statistical details for the Janssen NMA.	As stated by the AG, the Janssen NMA was conducted appropriately and thoroughly. Janssen summarised only the fundamental elements of the NMA within the submission as to allow for space for the full reporting of results within this size restricted document. Thus, in places for contributing analyses such as the NMA, Janssen refer the reader to consult the study report for more technically specific information and within which on this occasion the required information can be found on page17. In brief, the AG is correct in finding that both random- and fixed-effects analyses were carried out. In a sparse network of evidence, the inclusion of treatments that are informed by only one study should pose no problem in terms of estimating the rest of the evidence network unless convergence in the variance estimator becomes a problem. The efficacy estimate for that treatment with sparse evidence will, however, be subject to more uncertainty than the treatments informed by multiple studies. The Gelman-Rubin plots were examined in case of doubts on the convergence. The convergence was good for all analyses, except for the analysis of hypoglycaemic events. Due to this non-convergence, the number of iterations was increased only for	Janssen has provided a brief summary of key statistical information related to the NMA, which may be found in the original study report, as signposted within the Janssen submission.

	the analysis hypoglycaemic events where we have used 100,000 burn-in and 100,000 iterations for the estimate for the fixed effect model. More information on the convergence of the modelling may be found in the NMA report from Janssen, on page 16 and in Appendix 8. Results for treatment efficacy were presented as the efficacy relative to canagliflozin, because this was the treatment of interest in the Janssen submission. As the purpose of the NMA is to establish a network of evidence, it is also possible to present the results relative to any other comparator, the way the AG did in Figures 5, 7, etc.	

Issue 11 **Question regarding differences between 2 Janssen NMAs**

Description of problem	Description of proposed amendment	Justification for amendment	AG comments
On pages 124, the AG questions the differences in the rates of severe and non-severe hypoglycaemic events for	The Janssen base case did not include comparison vs. repaglinide; therefore the NMA without repaglinide was used in the base case.	Janssen has provided an explanation of the differences observed in the NMAs with and	

pioglitazone and sitagliptin observed in the NMAs with and without repaglinide.	The AG is correct that for pioglitazone and for sitagliptin, the hypoglycaemia rates are lower when the two Jovanovic studies assessing repaglinide were included: (Jovanovic et al. 2000)(repaglinide vs. placebo) and (Jovanovic et al. 2004) (repaglinide vs. pioglitazone 30 mg). The inclusion of these 2 trials added an indirect link to pioglitazone 30 mg via placebo – repaglinide – pioglitazone 30 mg. Moreover, pioglitazone 30 mg is linked to sitagliptin via the (Henry et al. 2014). This explains why the inclusion of repaglinide in the network had an impact on the results of pioglitazone and sitagliptin. This difference is further explained in the analysis of the hypoglycaemic events as there were fewer studies in the analysis for this endpoint. Therefore, the estimates are less robust as they are based on less evidence (for example, for HbA1c there were 4 studies on linking placebo and sitagliptin while there are only 2 studies for the analysis of hypoglycaemia). Moreover the analysis of hypoglycaemic events is less stable in a more general point of view as the model experiences some convergence issues due to low number of events in most trials included in the NMA and standard approach adjustments were necessary to reach convergence (this limitation has been explain in detail in the NMA report on page 30 and Table 34 in Appendix 8). The trial by Jovanovic 2000 was excluded by the AG due to a high drop-out rate, but Janssen could not	without repaglinide.	Jovanovic 2004 was an RCT with three arms: pioglitazone, repaglinide or both. HbA1c on pioglitazone alone was reported to <u>rise</u> by 0.32%. This is highly unusual.

	identify the rational for the exclusion of Jovanovic 2004. In scenario analyses 1 through 4, repaglinide was used as a comparator and the full set of treatment effects (for all comparators) were sourced from the NMA that included the 2 repaglinide studies, including rates of hypoglycaemic events. The alternative parameter inputs did not demonstrably alter the results for pioglitazone and for sitagliptin, for example reducing the ICER for canagliflozin 100 mg vs. sitagliptin from £1,407 in the base case to £1,254 in scenario 1 and increasing the ICER for canagliflozin 100 mg vs. pioglitazone from £78,518 in the base case to £84,048 in scenario 1 (though remember that scenario 1 includes differences, albeit much smaller, in the other NMA treatment effects as well).		

Issue 12 **Inconsistencies in the AG efficacy estimates**

Description of problem	Description of proposed amendment	Justification for amendment	AG response
Janssen has identified	The AG explains in considerable detail in the	Janssen has highlighted	Table 9 shows differences

inconsistencies between the reporting of treatment effects between Table 9 and Tables 51-53, in the AR.	Section 3 (“Network meta-analysis”) of the AR how the NMA was conducted. Janssen believe that the methods used by the AG are adequate and were in most part able to replicate the analysis (as explained in a separate document provided by Janssen, titled “Additional Information”). Janssen were able to achieve very similar results to those presented in Table 9 of the AR. However, in the cost-effectiveness modelling section, different estimates are presented in Tables 51 and 52. It is unclear how the estimates in Tables 51 and 52 have been derived. The AG states on Page 166 that "Clinical effectiveness was sampled within the NMA" and that a check was made that the subsample of 1000 draws for the HE modelling had the same means. From comparing across the above mentioned tables it is apparent, though, that the means do not match. One possible reason may be the sentence on Page 118 stating that “we need to be selective in the trials from which we extract data, rather than using the effect sizes from broad-spectrum meta-analysis”. This sentence suggests to Janssen that the AG did not use the network meta-analysis presented in this AR to inform the efficacy parameters of economic assessment. However, Janssen are unable to identify another source for the efficacy estimates that were used in the economic evaluation conducted by the AG.	inconsistencies in the reporting of treatment effects that are a crucial element of the economic analysis. Janssen is unclear as to how these inconsistencies may have arisen and would advocate that the AR includes further information to allow for the full understanding of the AG analysis.	between drug and placebo. In the modelling, the whole effect of drugs is used. So, for example, if drug reduced HbA1c by 1.2% and placebo by 0.2%, the differences as reported in clinical effectiveness would be 1.0% but the effect size used in modelling is 1.2%. However some slight differences were also unexpectedly caused by two runs of the NMA, one in WinBugs for the clinical effectiveness, one in R for the modelling.

	Additionally, on Page 169, the AG writes that "For the intensifications, due to a lack of data the addition of a treatment is assumed to have the same clinical effectiveness regardless of what it is being added to". These efficacy estimates are shown in Table 53. It is unclear which studies informed these estimates as they match neither the AG's meta-analysis nor the earlier Table 51 (gliclazide HbA1c, PIO and gliclazide weight, etc.).		

Issue 13 **AG Misunderstanding**

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 122, there appears to be a misunderstanding that only pairwise comparisons are permitted in the ECHO-T2DM model. Consequently, the AG is unclear whether the characterisation of uncertainty within the probabilistic sensitivity analyses (PSAs) across all the comparators is correct (i.e., whether each treatment arm used the same sampled parameter values across the various pairwise comparisons).	Details about the way in which the ECHO-T2DM model runs comparisons can be found on page 48 in the Janssen submission and in its accompanying Appendices, Appendix 4. In brief, the results submitted were based on multiple comparison methods, in which the same hypothetical patients and the same PSA parameters were applied for each of the treatment alternatives. This means that for each simulation run, canagliflozin and comparator were simulated with identical patients and PSA parameter values, so agents cannot be stochastically favoured or disfavoured relative to the others.	The approach used was consistent with NICE expectations and appropriate for addressing the study question.	Accepted. The text "Note also the it appears that only pairwise …uncertainty around it would be affected" will be deleted.

	However, although the patients and PSA parameter values are identical for all agents within each simulation run, they did vary across simulation runs (e.g., the base case versus scenario analysis 1 and scenario analysis 2, etc.).		

Issue 14 **AG Misunderstanding**

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On pages 125-127, there appear to be misunderstandings with regard to the treatment effect rebound assumptions.	The AG is correct in finding that the Janssen economic modelling includes a rebound of treatment effects whenever a treatment is discontinued. This rebound is applied regardless of the reason for discontinuation (e.g., adverse events, failure to meet HbA1c targets, and eGFR-related stopping rules). While the ECHO-T2DM model supports different assumptions, the magnitude of the rebound always equalled the magnitude of the initial treatment effect itself in the simulations supporting the current submission. That is, the initial treatment effect is reversed (rebounding to "natural history" and not to "baseline"). This rebound mechanism is applied equally to all covariates (HbA1c, BMI, SBP, LDL, HDL, triglycerides, and total cholesterol). Rebound is applied regardless of the position in the treatment sequence of the treatment being withdrawn, and regardless of the treatment that	As noted on page 40 in the submission, Table 12 specifies rebound as immediate reversal of the treatment effect; further clarification appears in the in the neighbouring text.	The AG found the original text ambiguous. No revision required.

	follows the discontinued treatment. The AG is correct that the additional "effect" of having applied a differential annual drift during the treatment is not reversed (although this would not apply once patients have altered treatment) and thus becomes permanent (even when an agent is discontinued). For the simulations submitted, this advantages pioglitazone and disadvantages sulfonylurea. Discussion at a clinical advisory board suggested that the ADOPT study would be the most suitable source for HbA1c drift parameters. This same panel of experts that recommended the SBP and weight drift approaches as well. Rebound effects are strictly related to the discontinuation of agents. Whenever an agent is discontinued, the ECHO-T2DM model will assign the next indicated agent in the treatment sequence as needed to reach glycaemic control. Thus, the AG is incorrect in the following statement "It is not obviously reasonable to assume that there will be rebound when patients start insulin", where the AG is trying to associate the "rebound" to the agent being started, not to the agent being discontinued. It is true, that the net effect of the rebound and treatment effect associated with rescue medication (insulin in the above case) would logically not be associated with an increase in HbA1c (i.e., worse control), since ECHO-T2DM would intensify the rescue medication by increasing the dose or add additional agents as needed to achieve glycaemic control.		

Issue 15

AG Misunderstanding

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 218 (Table 104), there is an incorrect value reported for patient characteristics	In Table 104 of the AR, the duration of diabetes for Janssen canagliflozin trials is listed as 0.0. This is not correct. The ECHO-T2DM model uses a uniform distribution for this parameter where the min/max ranges are set. Specifically, we applied a range of 0 to 9.358, which is presented in the Appendix, Table 13, page 36. This range is based on the pooled monotherapy RCTs for canagliflozin. The mean value is 4.679.	Janssen advocate that Table 104 be corrected.	This is based upon the Table reference of the Janssen submission: Table 12 of appendix 5 which states this as being zero. The text of the AR report on page 123 goes into more detail discussing the apparent Janssen contradictions. This was a Janssen error but we are happy to amend.

Issue 16 Incorrect description of modelling of uncertainty and convergence

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 122, when describing the Janssen economic model, Janssen are unsure of the definition used to describe	Janssen is unsure about the terminology regarding “deterministic” (which the AG define as including no second order sampling, but presumably allowing for 1st order stochastic	While we did not perform deterministic analyses, we posit that these types of analyses are inappropriate given the inherent	No AG error and no revision required.

deterministic analyses and calls into question whether characterisation of uncertainty within the PSAs across all the comparators is correct and robust.	uncertainty). ECHO-T2DM does have the capability to inactivate second order sampling of parameter values, and thus does qualify as "deterministic" modelling; however, it includes only Monte Carlo based micro-simulation sampling of patient cohorts and ultimate outcomes (i.e., a cohort-level deterministic analysis is not supported). As for inactivating second order uncertainty, we did not present such simulation results because Janssen believe they would be fundamentally flawed for analysis of complex, multi-factorial diseases like T2DM with complex, inherently non-linear models. The clinical trial results provide a distribution, but the sample mean is only a point estimate of the true value. To the degree that T2DM models are constructed with many interdependent, highly non-linear equations, assuming a true parameter value rather than using the distribution of possible values generated by the trials (and other data sources) themselves will lead to biased estimates of the outcomes (Claxton 2008) (Claxton, 2008). With regard to the AG's characterization of simulation results as having a high degree of Monte Carlo error, we disagree. The number of patient cohorts is directly related to the parameter uncertainty, and the large number of patients per cohort ensures that uncertainty due to patient heterogeneity can be captured adequately. The choice is, essentially, one of simulating a given number of heterogeneous patients once each or simulating a smaller number of heterogeneous patients multiple times. While it is always desirable to reduce Monte Carlo error, in the face of this trade-off,	nonlinearity arising from the complex pathophysiology of T2DM	

	capturing as much of the between-patient variation as possible by simulating a larger number of different individual patients per cohort was preferred. This captures more patient heterogeneity and thus eliminates more uncertainty in the cohort means than if a Monte-Carlo loop had been added.		

Issue 17 Incorrect description of treatment algorithm

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 122, of the AR, the AG question the credibility of the ECHO-T2DM model on the basis that no convergence analysis was presented as part of the Janssen submission.	It is correct that we did not present an analysis of model convergence across patients modelled due to space constraints. Such data were presented to NICE during the course of a previous single technology appraisal (STA) submission for the use of canagliflozin in combination therapy, however, and the results were deemed stable at lower sample sizes than those used during this multiple technology appraisal (MTA) (1,000 x 1,000 for the base case). The doubling of patients for this submission (1,000 x 2,000) was done intentionally to give confidence in the stability of the results. A convergence analysis similar to the convergence analysis run for the STA od canagliflozin has retrospectively been conducted. Scenario 1 (identical key assumptions as the base case with the inclusion of repaglinide as a comparator) was simulated ten times, with a 1,000 x 1,000 sample size, and with different seed values. The variation of the following outputs was assessed:	Janssen has justified why no model of convergence for ECHO-T2DM was presented as part of the original submission made by Janssen.	No error. Presumably not the same model as was submitted for previous assessments. No revision required.

	• Absolute costs • Absolute QALYs • Incremental Costs • Incremental QALYs • ICERs • Net Monetary Benefit Please note that the variability in the ICER cannot be assessed here because there are no comparators for which at least two quadrants of the cost-effectiveness place were not covered. Therefore, we present the variability in the NMB, which is invariant to those problems, and the variation is relatively stable across comparators and relatively modest (between about £70 and £100). Perhaps more interesting, however, is the variability surrounding the Δcost and ΔQALY. Again, the sample size here seems sufficiently robust, the variation of Δcost and ΔQALY (between about £20 to £35 for Δcost and around 0.005 for ΔQALY). Remember that the base cases were simulated with 2,000 x 1,000 sample size and will have even less variation.		

Issue 18 Incorrect description of treatment algorithm

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On pages 123, 126, and 133, the report indicates that there is ambiguity regarding the modelling of oral	On page 48 of the submission made by Janssen, it is explained that three arms of canagliflozin use are modelled, where canagliflozin 100mg is defined as the base case and canagliflozin 300 mg, and canagliflozin 100 mg dose increase as two further comparator arms.	Janssen has provided clarification of the treatment algorithms used. Janssen believe that this information has been provided in the	No error, no revision required. Note that since the license

rescue medication upon treatment discontinuation.	Thus far, canagliflozin is investigated in clinical trials only as 100 mg and 300 mg separately. However, a recently completed trial, DIA4004, investigates the efficacy, safety, and tolerability of canagliflozin (100 mg, up-titrated to 300 mg, if applicable) in the treatment of patients with T2DM with inadequate glycaemic control on metformin and sitagliptin therapy. No results are as yet available. The AG correctly noted that canagliflozin 100mg is followed by gliclazide rescue medication in the intervention arm but by canagliflozin 300 mg prior to gliclazide rescue medication in the canagliflozin dose titration comparator arm. The intervention arm of canagliflozin represents the clinically plausible scenario in which patients are treated initially with canagliflozin 100 mg are tolerating canagliflozin 100 mg once daily and have an eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, as a result the dose can be increased to 300 mg once daily orally. On page 38 of the Janssen submission the structure of the titration scenario is explained in full. Furthermore, all treatment pathways are clearly described in Appendix 4.2.4 of the submission made by Janssen. The three different arms are: ○ Intervention Arm: Just canagliflozin 100mg, which was naturally followed by the addition of gliclazide as rescue therapy (like most of the other comparators) ○ Intervention Arm: Just canagliflozin 300mg, which was naturally followed by the addition of gliclazide as rescue therapy (like most of the other comparators) ○ Canagliflozin Dose Titration Arm: Begins with canagliflozin 100mg and increases to canagliflozin 300mg as needed to maintain control, which is followed by the addition of gliclazide rescue therapy as needed. The treatment algorithm is correctly reflected in AG Table 16, but needs to be corrected in Table 103. The correct treatment algorithm is reproduced in the Table below to correct this misunderstanding. To clarify, unlike when patients simply lose HbA1c control, if patients	submission materials.	for canagliflozin states that the 300mg dose should only be used after trying the 100mg dose, it could be argued that Janssen ned n have submitted the direct to 300mg scenario.

	discontinue their monotherapy treatment due to adverse events or contraindications, they switch to the next agent in the treatment sequence (as the details are presented in Appendix 4.2.4. The rescue therapy profile (i.e., treatment effects and adverse events) is the same regardless of whether the patient discontinued the monotherapy treatment or not (i.e., the effect is "incremental"). The AG is correct that repaglinide was included as a comparator only in scenario analyses 1 through 4 (as mentioned in Table 13 on page 47 of the submission). Further details about repaglinide as a comparator can be found in Appendix 8.1.1. Repaglinide was not included in the base case for a number of reasons: current market share of repaglinide stands at <0.16% by volume; there is limited clinical experience with the drug within U.K.; and there are few relevant clinical studies on which to build a robust analysis. **Actual Janssen Modelling of Treatment Sequence** See table below		

Initial Therapy (Start of Mono)	First Rescue	Second Rescue	Third Rescue	Fourth Rescue
Cana, Empa, Dapa DPP-4i (Sitagliptin) Pioglitazone 30mg	+SU (Gliclazide)	+NPH - Cana, Empa, Dapa, DPP-4i, Gliclazide	+Aspart	n/A
Sulfonylurea (Gliclazide)	+DPP-4i (Sitagliptin)			
Repaglinide	+Pioglitazone 30mg - Repaglinide	+ Gliclazide	+ NPH - Pio 30mg, Gliclazide	+Aspart

Issue 19 Clarification needed for source estimates

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 125, there is	Because of its flexible delivery schedule (and many	Janssen has provided clarification	The suggested revision is

confusion regarding the source of the clinical effectiveness estimates used for insulin rescue medication in Table 18.	possibilities for titrating dose), insulin therapy is more complicated to model than conventional oral (or other injectable) agents. While the ECHO-T2DM model can simulate insulin as a fixed-dose conventional agent like oral medications (with a one-time treatment effect), ECHO-T2DM also supports the more realistic scenario, in which insulin doses can be titrated upwards on an annual basis in order to maintain glycaemic control. This was the approach used in the simulations underlying this submission. The relevant details of this approach are provided in Table 12, on page 33 in the Appendix supporting the submission made by Janssen. Additionally, details of the parameterization are discussed in Appendix 4.2.4; below is a brief summary.	on the sources for insulin rescue medication.	accepted and the cited references will be noted: • Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2008;31(1):20-5. • Riddle M, Vlajnic A, Zhou R, Rosenstock J. Baseline HbA1c predicts attainment of 7.0% HbA1c target with structured titration of insulin glargine in type 2 diabetes: A patient-level analysis of 12 studies. Diabetes, Obesity and Metabolism 2013;15:819-825. • Fonseca V, Staels B, Morgan Ii J, Shentu Y, Golm G, Johnson-Levonas A, et al. The

			addition of sitagliptin to metformin and pioglitazone therapy enhances glycemic control in patients with type 2 diabetes. Diabetes Conference: 71st Scientific Sessions of the American Diabetes Association San Diego, CA United States. 2011 A308 Conference Publication:

Issue 20 Incorrect assumption that needs to be clarified

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 124, the report states that based on the electronic input sheets submitted by Janssen and the model having an annual cycle, the 26-week estimates were assumed to apply at the end of the first cycle.	There is concern over the application of 26-week data over the 52-week 1st cycle. As the ECHO-T2DM model operates with a Markov cycle length of one year, the ERG is correct in noting that 26-week treatment effects are not applied at 26 weeks. They are instead applied in the first year, which is the level of detail in time resolution available in ECHO, though it should be noted that patients experience ½ cycle of upward drift in HbA1c and the other bio-markers to counter the omission of data for weeks 26 to 52 in the NMA.	Janssen has provided clarification on the incorrect assumption regarding treatment effects.	No error – the AR report also explains the ½ cycle addition of the assumed annual drift in some detail on page 128. This cannot be sensibly introduced prior to this as the annual rate of drift has not been discussed prior to this. No revision required.

Issue 21 Clarification needed on hypoglycaemia event rates

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 133 regarding the hypoglycaemia event rates, clarification is needed on whether these rates were adjusted to be annual rates, to align with the annual model cycle.	To clarify, the ECHO-T2DM model simulates hypoglycaemic event rates (per year) and so rates are annualised. The 26 week data represents the time horizon of the trials underlying the NMA, the event rate endpoints in the trial were however calculated as rates per patient-year (i.e., on an annualised basis). For example, 100 events in trial with 400 patients over 26 weeks would imply 100 events over 200 patient-years (and an annual rate of 0.5 events per patient-year). In ECHO-T2DM, the hazard of hypoglycaemic events is modelled to match the mean rates of events observed in the clinical studies of each AHA. These hazards are modified to take into account the increased risk of hypoglycaemic events at lower values of HbA1c. The AG correctly notes that the relationship between HbA1c and the hypoglycaemic event rate (a hazard ratio of 1.43) comes from the large and long-term DCCT (DCCT 1991)study of Type 1 diabetes mellitus (T1DM). This is currently believed to be the most appropriate available data on this relationship (77), where multivariate adjustment for confounding factors and a large sample size engender relatively high confidence in the results. As explained in Appendix Section 4.2.3, results specific to insulin-treated T2DM patients based on a	Janssen has provided clarification on hypoglycaemia event rates and their incorporation into the ECHO-T2DM model.	No error. Original submission ambiguous. No revision required

	meta-analysis of 82 studies (155 trial arms) were presented at the ISPOR European Congress in 2013 (McEwan et al. 2013). While the methods used differed somewhat from those used in the DCCT analysis, for example the DCCT analysis was estimated from long-term patient-level data and the recent analysis was estimated using (presumably much shorter) aggregated trial data, exponentiation of the reported coefficients from the new meta-analysis generated hazard ratios that are similar, if not slightly larger (1.53 for non-severe and 1.89 for severe hypoglycaemic events) than the DCCT figure of 1.43. Differences in the choice of covariates and timing of the HbA1c measurement may explain the difference in part (the new analysis included both baseline HbA1c and achieved reduction, whereas DCCT used the current HbA1c value only). . Because rescue medication leads generally to convergence of HbA1c curves, the exact value of this hazard ratio is unlikely to be a major driver of the results and Janssen has interpreted the new evidence as confirmatory of the DCCT estimate used in the model. Additional supporting evidence on the relationship for T2DM comes from (Pontiroli, Miele, and Morabito 2012). The authors analysed clinical correlates of HbA1c, and of overall, nocturnal and severe hypoglycaemia in T2DM patients receiving insulin, and confirmed that lower HbA1c values are associated with a higher incidence of hypoglycaemia.		

Issue 22 Clarification needed on adverse event rates

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 134 regarding adverse events, clarification is needed on whether the UTI and GTI event rates were adjusted to be annual rates and so to be in line with the annual model cycle.	The UTI and GTI event rates are indeed defined as events per patient-year. The average length of time for which an event is experienced was estimated, using online resources such as NHS Direct, and the appropriate annual rate derived. The 26- week duration refers to the time horizon of the clinical trial, and not to the time period over which the rate applies. Thus, they are in line with the annual model cycle.	Janssen has provided clarification on adverse event rates.	No error. Original submission ambiguous. No revision required

Issue 23 Factual inaccuracies that need to be corrected

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On pages 129-131, there are factual inaccuracies in the report regarding estimates for the evolutions of HbA1c and convergence between treatments.	In the ECHO-T2DM model, the evolution of HbA1c is determined by treatment effects, reversals associated with treatment withdrawal, and annual drift. Because treatments are intensified when a patient's HbA1c value exceeds the specified target value, which results in an application of treatment effects, convergence occurs in the simulations. This convergence was noted by the AG and is depicted in the plot showing mean HbA1c over time (Figure 11 on page 130 of the Janssen submission), which shows a convergence to values near the target value for all treatments during a large part of the simulation time horizon. While ECHO-T2DM does model events on an	Janssen has provided clarification on the evolutions of HbA1c and convergence between treatments.	No error. Original submission ambiguous and AR report is clear on the lack of clarity and ambiguity. No revision required.

	annual Markov cycle, treatment intensification of more than one escalation in a given cycle can occur if required to reach glycaemic control. The portion of patients escalating from the starting canagliflozin dose to the next treatment in the first year explains why the observed average drop in HbA1c in the first year for patients started on canagliflozin can exceed the treatment effect of canagliflozin obtained from the NMA, a question raised by the AG. Whilst the convergence in HbA1c is probably more pronounced for patients modelled to be receiving insulin, because their doses can be increased, this convergence is already evident earlier in the simulation, due to patients' escalation from the first treatment to the next treatment at different time points according to requirements to meet HbA1c; i.e. Patients with higher HbA1c (overrepresented in the control arm) reach the intensification threshold sooner, so they get the additional HbA1c lowering sooner, so on average the two HbA1c curves are pushed closer together (convergence). Heterogeneity in the timing of treatment escalation is modelled in ECHO-T2DM. As evident from Figure 10 within the AR, there is large-scale convergence in HbA1c evolution in the Janssen simulations. The AG question whether the linear rates of annual drift derived from Kahn et al. reflect reality adequately is, therefore, secondary. Of note, the plot on HbA1c evolution (Figure XX, in the AR) shows the population means averaged over many patient cohorts, i.e., individual steps such as clear saw tooth patterns, would be masked by heterogeneity		

	in the timing of intensification due to patient heterogeneity and second-order uncertainty in treatment effects.		

Issue 24 Factual inaccuracies that need to be corrected

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 132, the AR incorrectly states that using the ECHO-T2DM model, the absolute difference in SBP will be maintained even after insulin therapy is started.	Just as with HbA1c, antihypertensive rescue medication forces convergence over time in SBP values. Treated patients that worsen or do not improve SBP values will over time be prescribed more antihypertensive medicines than patients who had lower SBP values. Thus, patients with higher SBP will receive treatment (and experience SBP reductions) sooner than those with lower SBP values.	Janssen has provided clarification of the misunderstanding of convergence with the model.	No error. Original submission ambiguous and AR report is clear on the lack of clarity and only states “As far as the AG can ascertain, it also appears that unlike HbA1c this absolute difference for SBP will be maintained even after insulin therapy has started”. No revision required.

Issue 25 Missing sources for QALY decrements

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 134 (including Table 21), the AG was unable to identify the proper sources for QALY decrements.	The QALY decrements for GMI and UTI complications were sourced from Fordham et al (2013a) and Fordham et al (2013b) which correspond to reference 99, and 124, respectively, in the submission (please see page 43 of the Janssen submission and Table 30 in Appendix 6.2). Furthermore, these figures have also been published in (Shingler et al. 2015).	Janssen has provided the appropriate references for the QALY decrements.	The Fordham et al references do not appear to have been supplied as part of the Janssen reference pack, or Shingler et al. It also appears that the published study by Shingler et al is not referenced within the submission or its

			appendices. No error. No revision required.

Issue 26 Question on rate of neuropathy adverse events (AEs)

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 137, the AG questions the reported rate of neuropathy with gliclazide and pioglitazone, indicating that it is not clear how this was handled in the ECHO-T2DM model.	The AG did a commendable job in trying to analyse the source of differences in QALY disutility. However, when a comparator has some categories with QALY gains and others with QALY losses, the AG appears to have summed the absolute values, thus giving a denominator that has no relationship to the total difference in QALYs between canagliflozin 100 mg and the comparator. Given that this unnatural summing was pronounced only for pioglitazone, Janssen do not find it odd that there were differences between pioglitazone and many of the other comparators (in particular gliclazide, which the AG pointed out specifically). In addition to this mathematical feature, it is important to note that the proportion of QALY differences between the comparators and the intervention (canagliflozin 100 mg) depend on individual treatments relative strengths and weaknesses. Because neuropathy rates are primarily steered by the degree of HbA1c control, treatment arms with relatively poor HbA1c control will experience greater differences in neuropathy	Janssen has provided clarification of how neuropathy AE rates were handled in the model.	Accepted. We will remove the sentence "The AG considers it odd…"

	when compared with canagliflozin 100 mg than agents with HbA1c control much more similar to canagliflozin 100 mg. Not surprisingly, the QALY disutility associated with neuropathy is almost identical for pioglitazone and canagliflozin and the QALY differences between pioglitazone and canagliflozin are primarily associated with other factors. It is important to consider that just as RCT's are typically powered primarily for specific outcomes and not for secondary outcomes and AE's, small stochastic differences in these particular outcomes in the modelling may occur, as such small absolute differences for individual items are of lesser importance.		

Issue 27 No eGFR stopping rule <<*Placeholder to be completed by Pierre*>>

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 165, the AG expressed an interest in understanding the impact that turning off eGFR-influenced discontinuation would have upon the cost effectiveness estimates of the Janssen modelling.	Janssen have provided a full description of this analysis in a separate document provided by Janssen, titles "Additional Information". In brief, Janssen agree with the AG that evaluating the impact of the flozin-specific modifications supported in ECHO-T2DM provides useful information. An exploratory analysis was conducted utilising the assumptions and inputs of the base case simulation submitted by Janssen with the eGFR stopping rule and the eGFR treatment effect multipliers deactivated. The sample size was 1,000 cohorts of 1,000 patients.	Janssen have conducted an analysis whereby the functioning of the eGFR modules has been removed.	The AG suggested that it would have been good if the submission had included some such analysis, and Janssen provided additional material, subsequent to its original submission. Based upon the Cana300 vs PIO ICER as far as the AG can see the eGFR stopping rule module has little impact upon the ICER. So the use of the ECHO-T2DM to the extent that it is driven by a desire to implement the eGFR stopping rule may not be necessary. No

	The direct consequences of this scenario are that time on flozins will increase in proportion to the number of patients with eGFR drifting below the discontinuation thresholds and that initial treatment effects will be maintained for the time for which a patient's HbA1c remains controlled with the flozins. Please be aware that the simulations here are based on the current price of canagliflozin 300mg. The results show: • Only small stochastic differences for the non-flozins (which were unaffected by the stopping rule) • Drug acquisition costs for canagliflozin 100mg increased from £3,184 in the base case to £3,279 in this scenario (since patients take them on average longer), but insulin medication costs decreased from £5,553 to £5,528. ○ Note: the relatively small differences between the two scenarios for canagliflozin 100mg are due to the low proportion discontinuing due to low eGFR • Drug acquisition costs for canagliflozin 300mg increased from £3,407 in the base case to £3,681 in this scenario (since patients take them on average longer), but insulin rescue medication costs decreased from £5,296 to £5,095. • The same pattern was true for the other flozins as well • LYs and QALYs for all of the flozins		revision required.

	increased in general from the base case to this scenario, with the exception of empagliflozin 25 in the canagliflozin 300 BC. Again this is due to the fact that it is a small proportion that discontinues due to low eGFR and the influence of stochastic differences. The relative difference to the non-flozin comparators for canagliflozin 100mg and canagliflozin 300mg increased in general as well, with the exception of pioglitazone vs. canagliflozin 100mg and gliclazide vs. canagliflozin 300mg. • Summary of the cost-effectiveness results are presented for canagliflozin 100mg and canagliflozin 300mg in the Tables of the additional Information document provided separately by Janssen. As can be seen, while the mean costs and mean utilities varied slightly, the HE verdict is qualitatively (and indeed almost numerically) identical.		

Issue 28 Disagreement with progression rates used for sulfonylureas

Description of problem	Description of proposed amendment	Justification for amendment
On page 128, the report suggests that applying the glibenclamide progression rate to gliclazide may not be appropriate, citing (Satoh et al. 2005).	The Satoh et al. study referred to by the AG was a non-randomised chart review of Japanese patients on sulfonylureas: • 65 patients on gliclazide only • 168 patients on glibenclamide only • 41 patients who crossed-over The authors found that start of insulin was delayed in the gliclazide group. Grouping together the patients who used glibenclamide or	Janssen has provided justification for the progression rates which were used.

	crossed over, they found a mean duration from start of sulfonylurea until start of insulin of 8.0 years, compared with 14.5 years in the gliclazide-only group (P <0.0001). While this is an interesting finding, there are a number of reasons why it may not with certainty support the claim that gliclazide has a better coefficient of durability than glibenclamide in actual practice. First, the study was non-randomised and the sample sizes in each study arm are relatively small. Non-measured confounding factors, such as selection biases in which patients are given gliclazide or glibenclamide, may partly explain the results. Also, the authors present no calculation of required sample size and do not state what methods have been used to adjust for multiple testing. It is, thus, possible that some statistically significant results were observed purely due to chance. The study researchers noted imbalances between the two patient groups at baseline. Gliclazide patients also had on average lower n patients' fasting plasma glucose (FPG) at the start of the first oral anti-hyperglycaemic agent; lower HbA1c at the start of both the first oral AHA and at the start of sulfonylurea; and their average HbA1c during all treatment periods was lower than in the glibenclamide patients. The authors attempted to correct these biases by combining the patients receiving glibenclamide only and those that switch between the sulfonylureas into one group, but this did not resolve the differences in the patient baseline characteristics. In defence, the advantage of insulin-delay for gliclazide vs. glibenclamide did persist even when correcting for these baseline imbalances (see the Cox proportional hazard model in Table 3 of this publication) but it is still unclear whether any other unmeasured confounding factors could explain this observed difference. Moreover, the study fails to state whether this attempted adjustment using the Cox proportional hazard model was applied to the time from diabetes diagnosis to start of insulin, time from start of first oral	

	agent to insulin, or time from start of sulfonylurea to insulin, all of which have been studied. Perhaps even more importantly, Janssen is unclear how the results from the Satoh et al. study can be used to support the modelling of upward HbA1c drift in this kind of health-economic model because time to insulin is not exclusively determined by the annual drift. Indeed, other factors influence time to insulin initiation as well, including the magnitude of the initial treatment effect, compliance, and early discontinuation (e.g., due to AEs). All of these are handled explicitly in ECHO-T2DM (and presumably the UKPDS OM1); annual drift has to be parameterised separately from these. A scenario analysis (#2) was conducted within the Janssen submission, in which gliclazide was given an identical glycaemic drift to the other AHAs (described in Table 13, p. 47 and results presented in Table 19, p. 58). The ICER of canagliflozin 100 mg vs. gliclazide increased from £2,377 in the base case to £29,186 in scenario analysis 2, a value that remains below an acceptable threshold of £30,000 and one that is likely quite conservative given the low likelihood that gliclazide has the same drift. It should also be noted that the price used for the gliclazide comparator in the Janssen submission is about 2.5 times lower than the price used by the AG, which would artificially inflate the ICER.	

Issue 29 Dismissal of relevance of Mt. Hood assumptions

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On pages 121-122 and 215, the report states that modelling assumptions used in the Janssen submission	The AG is correct that the simulations conducted for Mt. Hood challenges and the simulations conducted for external validity testing differ (e.g. model inputs and treatment pathway assumptions) from the	Janssen has provided an explanation of why the modelling assumptions would be expected to be different in part but also how	The Mt Hood is not dismissed, and as Janssen notes the evolution of biomarkers in the

were likely different than those used for the Mt. Hood challenges.	simulations conducted for this submission (monotherapy treatment with the flozins and key comparators). However, that is the nature of simulations to address different study questions. The purpose of Mt. Hood challenges and external validation is to test the ability of the models to replicate the results of long-term trials and observational data in settings where the true results are known and we can evaluate how well the models perform, so each of the individual validation exercises is customised to model the patients and intervention in the study being considered. If during the validation the models can reproduce results of a large number of quite different studies reasonably well, then it increases the chances (and our confidence) that it will perform well even in a new setting for which long-term data are not available. The references to the Mt. Hood Challenges and to external validation were to inform the AG of previous validity testing so that the AG can interpret the results with an appropriate degree of confidence. The AG is correct, however, in assuming that bio-marker evolution has been modelled differently in some of these validation settings than in the Janssen submission, however, the approach is the same, matching drift to the best available data. For some studies, the long-term biomarker progressions are publically available and can be use directly from the study. For many others, the evolution has not been available, as such the best available matches are sources, often resulting in the use of the results of the ADOPT study in the same manner as in this submission.	a number of the modelling approaches have been used in validation setting previously.	submission differ from those assumed in Mt Hood. This is the only real point that the AG makes here. No revision required.

Issue 30 Mistake in eGFR discontinuation rules

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 133, the report notes some issues with the eGFR discontinuation rules used for empagliflozin	The discontinuation of empagliflozin 25 mg if eGFR drops below 60ml/min/1.73m^2 was correct; however there was a mistake in the modelling for empaglifozin 10 mg, which should have been continued until eGFR dropped below 45 ml/min/1.73m^2.	Janssen has provided updated base case results to correct this mistake. Greater detail of these results have been presented in in a separate document provided by Janssen, titled "Additional Information",	This appears to identify an error by Janssen rather than the AG. No revision required.

Issue 31 Canagliflozin 300 mg results were omitted from scenario analysis 2

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 140, the report notes that canagliflozin 300 mg results were omitted from scenario analysis 2.	We apologise that canagliflozin 300mg was inadvertently omitted from Table 51 in the Janssen submission appendices. We have reproduced this Table below and included the correct estimates from the original submission for canagliflozin 300 mg from scenario analysis 2. The correct ICER for canagliflozin 300 mg is slightly lower.	Janssen has provided an updated table to correct this inadvertent mistake.	This is an error by Janssen rather than the AG. No revision required.

	<table><tr><th>Therapy</th><th>Mean Costs</th><th>Mean QALYs</th><th>Cost per QALY (ICER)</th></tr><tr><td>Repaglinide</td><td>£20,982</td><td>10.03</td><td>-</td></tr><tr><td>Pioglitazone</td><td>£21,485</td><td>9.95</td><td>Dom</td></tr><tr><td>Gliclazide</td><td>£22,589</td><td>10.01</td><td>Dom</td></tr><tr><td>Sitagliptin</td><td>£23,615</td><td>9.99</td><td>Dom</td></tr><tr><td>Cana. 100</td><td>£23,732</td><td>10.05</td><td>£137,500</td></tr><tr><td>Empa. 25</td><td>£23,732</td><td>10.03</td><td>Dom</td></tr><tr><td>Empa. 10</td><td>£23,739</td><td>10.02</td><td>Dom</td></tr><tr><td>Dapagliflozin</td><td>£23,786</td><td>10.02</td><td>Dom</td></tr><tr><td>Cana. 100/300</td><td>£23,853</td><td>10.06</td><td>£95,700</td></tr><tr><td>Cana. 300</td><td>£24,460</td><td>10.09</td><td>£57,967</td></tr></table> Recall, however, that the price of canagliflozin 300 mg has changed and the following Table below reflects this new price change. Canagliflozin 300 mg (and canagliflozin dose titration) naturally become cheaper, rendering a new ICER of £42,517. \		

Issue 32 Differences in AG versus Janssen modelling

Description of problem	Description of proposed amendment	Justification for amendment	AG response
On page 121, the report describes differences in the Janssen modelling compared with that of the AG and other companies. Janssen has recognised that some differences identified by the AG may have arisen due to misunderstandings of the ECHO-T2DM model and are in fact similar between the two modelling	In a separate document, titled “additional Information”, Janssen has provided a summary to demonstrate the potential misunderstanding of the ECHO-T2DM model, which led the AG to believe that the model differs considerably from OM1. This summary aims to highlight the number of similarities between the models and also highlights the steps Janssen took to align the assumptions and modelling approaches as closely to those proposed by the AG in the original protocol document.	Janssen has provided a separate detailed explanation of the ECHO-T2DM model to illustrate similarities to the AG modelling approach.	No error and no revision required.

approaches.			

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

A Multiple Technology Appraisal (MTA) of Dapagliflozin, Canagliflozin and Empagliflozin

Submission by AstraZeneca

15th June 2015

Contents

List of abbreviations

ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of covariance
AZ	AstraZeneca
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
CUA	Cost-utility analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DPP4	Dipeptidyl peptidase-4 inhibitor
EASD	European Association for the Study of Diabetes
eGFR	Estimated Glomerular Filtration Rate
ESRD	End stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effect
FPG	Fasting plasma glucose
GI	Genital infection
GLP-1	Glucagon-like peptide-1 analogues
HbA1c	Glycated haemoglobin
HRQoL	Health related quality of life
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
LOCF	Last observation carried forward
LRM	Longitudinal Repeated Measures
LYG	Life years gained
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MTA	Multiple technology assessment
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis

NYHA	New York Heart Association
OAD	Oral antidiabetic
OD	Once daily
OR	Odds ratio
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised, controlled trial
RE	Random effects
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose cotransporter 2
SPC	Summary of Product Characteristics
ST	Short term
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
UKPDS	UK Prospective Diabetes Study
ULN	Upper limit of normal
UTI	Urinary tract infection

Executive summary

Dapagliflozin monotherapy is an effective and well tolerated treatment for T2DM patients who have failed on diet and exercise, when metformin is contraindicated or not tolerated, as supported by a large evidence base. The SGLT2 class as monotherapy offers patient benefits over other classes of therapies expected to be displaced in clinical practice, being associated with greater weight reduction compared to DPP4s, TZDs, and SUs, and less risk of hypoglycaemic events than SUs (demonstrated in a NMA). Cost-effectiveness analyses demonstrate that the SGLT2s provide cost-effective treatment alternatives to DPP4s and pioglitazone. According to the evidence presented in this submission, the optimal positioning for the SGLT2s in monotherapy is as an alternative to DPP4s and to pioglitazone, in patients who are unsuitable for metformin and SUs.

Over 2.5 million people are estimated to be living with T2DM in England and Wales, and this is expected to rise steadily over the coming years (Section 0). With the prevalence of T2DM rising, fuelled by increasing levels of obesity and unhealthy lifestyles, T2DM represents a substantial health and economic burden.

T2DM treatment aims to improve glycaemic control to reduce symptoms and minimise microvascular and macrovascular complications. Weight gain is also an important consideration in treatment choice due to the reduced patient quality of life, and link to long term cardiovascular complications. The majority of patients require medication, with metformin monotherapy being the preferred and NICE recommended initial agent; however, in around 15% of patients metformin is contraindicated or not tolerated. Treatment for these patients can be challenging due to the risk of hypoglycaemia and/or weight gain associated with alternatives such as SUs, which are most commonly used, repaglinide or a TZD. DPP4s, which are rarely used in clinical practice as monotherapy, are weight neutral and as such do not address the importance of reducing weight for T2DM patients.

Dapagliflozin (Forxiga®) is a selective SGLT2, and was the first in this novel class of insulin independent, glucose-lowering medications (SGLT2s also include canagliflozin and empagliflozin). SGLT2s are associated with a low risk of hypoglycaemia and have demonstrated weight reduction. As SGLT2s act independently of insulin they can be used at varying stages of the T2DM 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. The specific license of all the SGLT2s in monotherapy is in adult patients with T2DM when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin is considered inappropriate due to intolerance.

The use of dapagliflozin 10 mg once daily monotherapy is supported by four Phase 3 studies in monotherapy. Data from the pivotal Phase 3 randomised controlled trial, included in the NMA, demonstrated dapagliflozin as an effective and well tolerated agent with:

- Clinically meaningful and durable reductions in HbA1c (pivotal study at 102 weeks: mean difference = -0.44%, P=0.048)
- Sustained reduction in patient weight compared with placebo (pivotal study at 102 weeks: mean difference = -2.6 kg, P=0.016)
- Associated with a moderate decrease in systolic blood pressure (SBP) relative to placebo
- Not associated with an elevated risk of hypoglycaemia compared to placebo
- Generally well-tolerated. The adverse events associated with dapagliflozin (e.g. urinary tract and genital infections) are consistent with its mechanism of action, which causes glucosuria (glucose in the urine).

The NMA and the economic model compared the clinical and cost-effectiveness of SGLT2s to DPP4s, TZD (i.e. pioglitazone), and SUs as per the NICE scope: no eligible studies for repaglinide were identified for inclusion in the NMA. The SGLT2s were grouped due to limitations in the monotherapy evidence base, and NMA, to enable meaningful comparisons between the individual treatments (see Section 4.4 of the submission), as anticipated by the Warwick Technology Assessment Team (see Section 6 of the TAR protocol). Additionally SGLT2s have been considered in previous NICE technology appraisals (in indications with more substantial data) to have similar efficacy and safety (e.g. Section 4.4 of the empagliflozin TA336 guidance).

The NMA demonstrated that SGLT2s have comparable HbA1c control efficacy to DPP4, TZD (pioglitazone) and SU classes of drugs in monotherapy, but are superior to all these classes in terms of weight reduction, and are associated with less risk of hypoglycaemic events than SUs. The base case cost-effectiveness results were estimated to be ICERs of £5,904 per QALY gained for SGLT2s vs. DPP4s, £20,089 per QALY gained vs. pioglitazone, and £52,047 per QALY gained vs. SUs. The incremental QALYs estimated for the SGLT2s are primarily driven by the weight reduction advantages of these drugs (which are similar between the SGLT2s). Although the ICER compared with SUs is high, it is likely to be an overestimate as it was only possible to perform the NMA on study follow-up at 24 (±6) weeks, due to limited 50 week data. The SUs tend to have a large initial impact on HbA1c in the first 6 months which then drops off (the 'J effect'); such treatment effect will not have been captured in the NMA and economic evaluation. SUs are currently the most frequently prescribed monotherapy treatment for metformin intolerant patients; DPP4s have a larger monotherapy market share than pioglitazone (~13% vs. ~4% market share, see section 5.2) and, combined with the good cost-effectiveness of the SGLT2s vs. DPP4s, are therefore considered to be the most likely therapies to be displaced by SGLT2s.

Overall, dapagliflozin monotherapy, and SGLT2s as a class are a cost-effective therapy when metformin is contraindicated or not tolerated, with clinical benefits over alternative T2DM classes, in particular in weight reduction and with regards to hypoglycaemic events. The clinical and cost-effectiveness results in this submission indicate that when metformin is contraindicated or not tolerated NICE should consider recommending SGLT2s as an effective alternative monotherapy to DPP4s, and to pioglitazone, in patients who are unsuitable for SUs due to risk of hypos or weight gain.

1. Context

1.1 NICE multiple technology appraisal of dapagliflozin, canagliflozin, and empagliflozin monotherapy

1.1.1 Scope of the MTA

As part of a multiple technology appraisal (MTA), NICE has invited AstraZeneca (AZ) to submit the clinical and cost-effectiveness of dapagliflozin within the licensed indication for treating type 2 diabetes (T2DM) as monotherapy i.e. in adults aged 18 years and older with T2DM 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.[1] Table 1.1 shows the details of the final scope for the appraisal issued by NICE.

Table 1.1: Scope for the NICE MTA of dapagliflozin, canagliflozin and empagliflozin monotherapy

Interventions	• **Dapagliflozin monotherapy** • Canagliflozin monotherapy • Empagliflozin monotherapy
Population	People with type 2 diabetes for whom metformin is not tolerated or is contraindicated
Comparators	The following interventions as monotherapy: • Repaglinide • Sulfonylureas • Pioglitazone • DPP4 inhibitors • The SGLT2 inhibitors will be compared with each other
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.

This submission consists of a presentation of the clinical evidence for dapagliflozin at the recommended dose of 10 mg daily for the treatment of T2DM as monotherapy. The dapagliflozin clinical trial evidence for monotherapy used in this submission is from treatment naïve patients,

which is considered to be a relevant proxy for the specific population in the scope due to insufficient available evidence in patients contraindicated or intolerant to metformin. Due to limitations in the indirect comparison for comparing dapagliflozin with other SGLT2s and the expectation that the individual SGLT2s have comparable efficacy and safety, an assessment is made of the cost-effectiveness of the SGLT2 class vs. the comparator classes of dipeptidyl peptidase-4 inhibitors (DPP4s), thiazolidinedione (TZDs) and sulfonylureas (SUs) (see Section 5).

1.1.2 NICE guidance for T2DM monotherapy: current and draft updated guidance

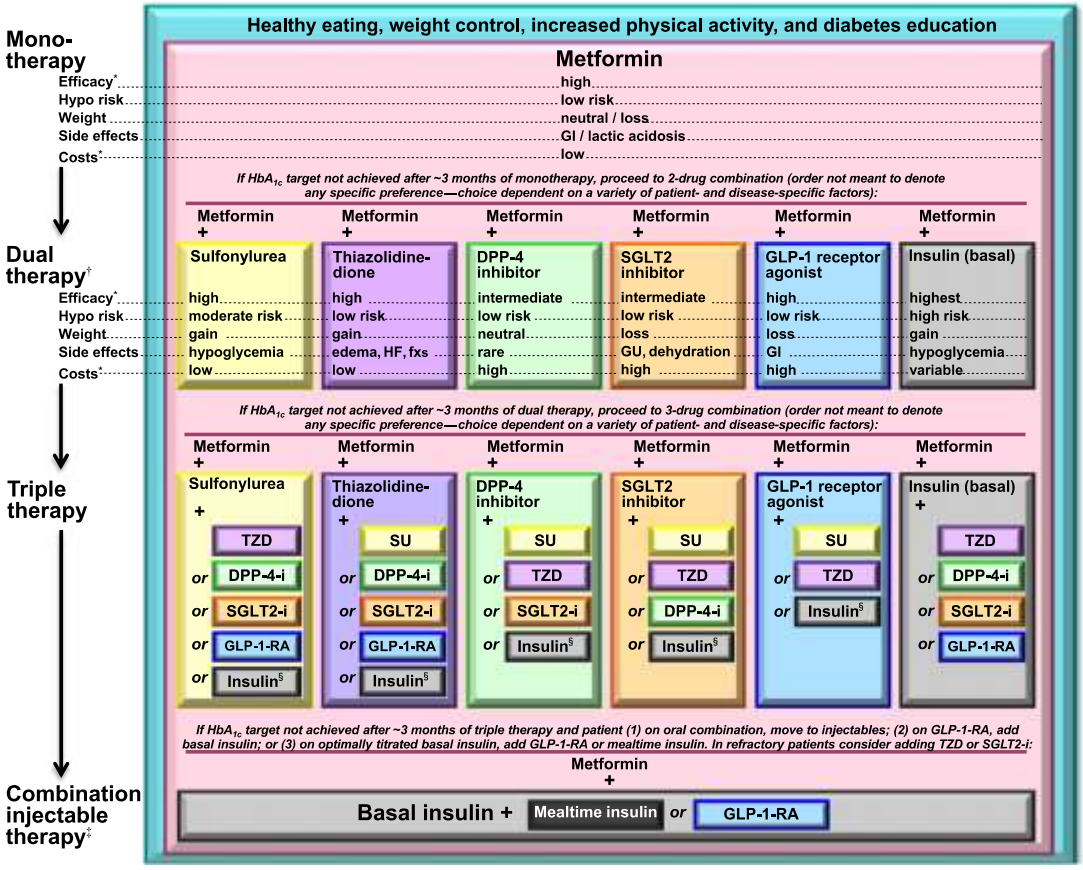
In the current NICE guidelines (published in 2009) on the management of T2DM metformin is recommended as first-line pharmacotherapy if lifestyle interventions (diet and exercise) fail to control blood glucose in patients with T2DM.[2] A SU can be considered for the first-line therapy if the patient is not considered overweight; or if metformin is not tolerated or is contraindicated; or if a rapid response to therapy is required because of hyperglycaemic symptoms.

An update of the 2009 guideline has been drafted and released for consultation.[3] In the draft, while metformin is still recommended as the initial drug treatment, repaglinide is recommended if metformin is contraindicated or not tolerated. However, concern has been voiced about this recommendation[4,5] as repaglinide is associated with increased risks of hypoglycaemia and weight gain.[4,6] In addition, the three-times daily dosing of repaglinide may have a negative impact on adherence;[5] and as repaglinide is only authorised for use as monotherapy or in combination with metformin, if optimal results are not achieved as initial therapy, no licensed options to intensify with another agent are available. NICE therefore suggest that patients would need to switch to pioglitazone, a TZD, a SU or a DPP4 before adding another treatment.[4]

The 2009 NICE guideline preceded the availability of the SGLT2s dapagliflozin, canagliflozin and empagliflozin, which received their UK marketing authorisations in 2012 [1] 2013 [7] and 2014,[8] respectively. The new draft guideline does not include the SGLT2s as an option for monotherapy. Rather, the SGLT2s may be considered for add-on therapy for the first and second intensification of treatment in some patients,[3] according to the individual NICE guidance following single technology assessments (STA).[9-11] NICE recommends dapagliflozin in a dual therapy regimen in combination with metformin, only if it is used as described for DPP4s in the NICE clinical guideline 87;[2] and in combination with insulin with or without other antidiabetic drugs.[9]

In contrast to NICE guidance, the recently updated position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[12] recommends monotherapy treatment with one of the recommended second-line agents where metformin is contraindicated or not tolerated (Figure 1.1), including the SGLT2s. The ADA/EASD statement promotes the need to individualise treatment strategies to the patient taking into account, for example, the benefits as well as adverse effects of various glucose-lowering medications (particularly hypoglycaemia), the patient's age and health status, costs, and other practical aspects of care, such as dosing schedule and requirements for glucose monitoring.[12]

Figure 1.1: ADA/EASD treatment algorithm for the pharmacotherapy of glucose lowering in patients with T2DM



The ADA/EASD states that for monotherapy "In patients intolerant of, or with contraindications for, metformin, consider initial drug from other classes depicted under "Dual therapy" and proceed accordingly. Drug choice is based on patient preferences as well as various patient, disease, and drug characteristics, with the goal being to reduce glucose concentrations while minimising side effects, especially hypoglycaemia."

Source: Inzucchi et al., 2015 [12]

1.2 Dapagliflozin

- Metformin monotherapy is the preferred NICE recommended first line pharmacotherapy for patients with T2DM. When metformin is contraindicated or not tolerated (in approximately 15% of patients) patients may receive an SU (most commonly used), a TZD (pioglitazone) or a DPP4

- Reducing body weight in T2DM patients is an important medical need, however the current NICE recommended monotherapies in patients for whom metformin is not tolerated or is contraindicated i.e. SUs and TZDs, are associated with weight gain and the DPP4s are weight neutral. Replaglinade, as recommended in the draft updated guidelines, is also associated with weight gain. In addition, SUs and replaglinade are associated with increased risks of hypoglycaemia.

- SGLT2s, including dapagliflozin, are associated with reductions in weight and blood pressure and a low risk of hypoglycaemia, due to the novel mechanism of action.

- These advantages are likely to be particularly apparent when SGLT2s are used in monotherapy and not combined with other therapies that bring with them higher risks of weight gain and hypoglycaemia.

- In line with the EASD/ADA position statement and the evidence presented in this appraisal, dapagliflozin should be recommended in monotherapy when metformin is contraindicated or not tolerated as an effective alternative therapy to DPP4s and to pioglitazone, in patients who are unsuitable for SUs due to the risk of hypoglycaemia or weight gain

1.2.1 Overview of dapagliflozin

Dapagliflozin (Forxiga®), a selective SGLT2, was the first in this novel class of insulin independent, glucose-lowering medications. In contrast to existing therapies, SGLT2s (dapagliflozin, canagliflozin and empagliflozin) actively 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 SGLT2s can lead to weight loss. Dapagliflozin may also cause a mild diuretic effect, with potential for modest blood pressure lowering in hypertensive patients through the inhibition of sodium and glucose transport in the proximal tubule. Furthermore, dapagliflozin can be used at varying stages of the T2DM treatment pathway[1] providing renal function is adequate, as it acts independently of insulin secretion and insulin action.

The dapagliflozin trial programme is one of the largest diabetes trial programmes to date, comprised of 24 Phase 2b and 3 studies, including 9 completed studies for monotherapy (see Appendix 8.1.1 Table 8.1). 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 advance disease. Treatment with dapagliflozin is associated with prompt and sustained improvements in HbA1c, weight reduction, lowered blood pressure, and a low intrinsic propensity to cause hypoglycaemia. In addition, a real-world, observational, non-randomised study of patients initiated on dapagliflozin in a diabetes specialist outpatient centre of a London teaching hospital reported improvements in HbA1c, weight, and blood pressure that were consistent with those reported in clinical trials.[14] In addition, real-world evidence from the UK (n=96 from an observational, non-randomised study of patients initiated on dapagliflozin in a diabetes specialist outpatient centre of a London teaching hospital[14] and n=1732 from a retrospective observational study was conducted using the Clinical Practice Research Datalink, which contains records from 684 primary care practices in the UK)[15] have reported improvements in HbA1c and weight that are consistent with those reported in clinical trials.

1.2.2 Rationale for treatment with dapagliflozin monotherapy

Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia). T2DM is caused by a shortage of the hormone insulin (insulin deficiency) and a fault in the way the body uses the insulin it produces (insulin resistance). Over 2.5 million people are estimated to be living with T2DM in England and Wales, and this is expected to rise steadily over the coming years (Section 0: budget impact). With the prevalence rising rapidly, fuelled by increasing levels of obesity and unhealthy lifestyles, T2DM represents a substantial burden on the National Health Service (NHS); the considerable morbidity and mortality associated with diabetes is currently costing the NHS an estimated £10 billion (10% of the NHS budget).[16] The total cost

[1] Dapagliflozin is licecnsed for use in monotherapy, and as an add-on therapy to other oral glucose-lowering medicinal products and to insulin

(direct care and indirect costs) associated with diabetes in the UK currently stands at £23.7 billion and is predicted to rise to £39.8 billion by 2035/6.[16,17]

People with T2DM in the UK continue to be at a significantly increased risk of microvascular and macrovascular complications such as heart disease, stroke, kidney disease, blindness, limb amputations, and premature death, leading to substantial impacts on health, wellbeing and health care service use and costs.[18] Many of these complications are also compounded by modifiable factors such as obesity, high blood pressure, high cholesterol, inactivity, and smoking.[19] Reducing body weight in T2DM patients is an important medical need, and modest reductions in weight of 5-10% are likely to be associated with health benefits.[20] Approximately 90% of adults with T2DM are overweight or obese[21] additional weight gain augments insulin resistance, which, in turn, exacerbates the progression of diabetes. Furthermore, obesity is associated with increased risks of diabetic complications, for example, people with diabetes with a high body mass index (BMI) (35+ kg/m^2) are over twice as likely as those with a lower BMI to suffer from heart failure.[21]

T2DM treatment aims to improve glycaemic control (bring elevated blood glucose down to target ranges) to improve symptoms and minimise complications. There is limited long-term success of lifestyle programmes to maintain glycaemic goals and therefore the majority of patients require medication with an oral antidiabetic medication (OAD), usually starting with metformin monotherapy. However, in about 15% of patients metformin is contraindicated or not tolerated.[4] In contrast to currently recommended treatments for these patients (SUs, DPP4s and TZDs), dapagliflozin as with the class of SGLT2s, are associated with clinically meaningful reductions in weight, and a low risk of hypoglycaemia, while improving glycaemic control (see also the network meta-analysis (NMA) in Section 4). Blood pressure reductions have also been noted with dapagliflozin, consistent with modest drug-induced diuresis and weight loss. In a meta-analysis of clinical trials on dapagliflozin (monotherapy or as add-on therapy) a lower rate of cardiac events was seen in patients taking dapagliflozin compared with those taking comparators (pooled placebo, metformin and the SU glipizide) and this suggestion of cardiovascular (CV) benefit is consistent with dapagliflozin associated reductions in weight and blood pressure.[22] The effect of dapagliflozin on CV outcomes will be definitively evaluated post-approval in DECLARE (TIMI-58, Study D1693C00001).[23]

Significantly, across the clinical trial programme, dapagliflozin has demonstrated durable efficacy; over a 2-year period as monotherapy[13] (Section 3.3) and over a 4-year period as add-on to metformin[24] (see Appendix 8.1.6), the longest follow-up period for an SGLT2 inhibitor to date. In addition, dapagliflozin monotherapy has been associated with less use of rescue therapy over a 2-year period compared to placebo + low dose metformin[13] (Section 3.3.4) and compared to metformin over a 24 week period[25] (Appendix 8.1.3.1).

In summary, as monotherapy, dapagliflozin offers an alternative once daily therapy when metformin is contraindicated or not tolerated with benefits over other classes of T2DM therapies (SUs, DPP4s and TZDs), in particular with weight reduction and a low intrinsic risk for hypoglycaemia.

1.2.3 Dapagliflozin use in the UK

1.2.3.1 UK marketing authorisation

Dapagliflozin has a UK marketing authorisation in adults aged 18 years and older with T2DM to improve glycaemic control as:[1]

- 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 with other glucose-lowering agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

1.2.3.2 UK recommended dose and administration

Dapagliflozin can be taken orally once daily at any time of day with or without food and tablets are to be swallowed whole.[1] The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.[1] Dapagliflozin is also available as a 5 mg tablet, but a dose of 5 mg daily is expected to be rarely used in monotherapy: a starting dose of 5 mg is recommended in patients with severe hepatic impairment, and if well tolerated, the dose may be increased.[1]

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) because the efficacy of dapagliflozin is dependent on renal function, and is reduced in patients who have renal impairment. In addition, initiation of dapagliflozin therapy is not recommended in patients 75 years and older due to the limited therapeutic experience in these patients.

1.2.3.3 Comparative price of dapagliflozin

Dapagliflozin 10 mg has the same drug price as canagliflozin 100 mg and empagliflozin (£1.31 per day); canagliflozin 300 mg has a higher acquisition cost (£1.67 per day)[26]. All of the SGLT2s have a slightly higher price than the DPP4s (£0.95-£1.19 per day)[26], which can be considered the most likely class of drugs, along with TZDs, used as monotherapy to be displaced by dapagliflozin and the SGLT2s (see Section 5.2). 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 Table 5.9).

1.2.4 Evidence presented in this submission

The evidence presented in this submission includes:

- Clinical efficacy and safety of dapagliflozin 10 mg as monotherapy (Section 3): Three randomised, placebo-controlled, double-blind, phase 3 trials that were identified from a systematic review and included in the NMA are the focus of this submission. Due to a lack of evidence for metformin intolerant patients, the dapagliflozin clinical trial evidence for monotherapy presented is for treatment naïve patients in a trial design considered generalisable to the defined population in the scope

- Systematic review and NMA (Section 4): As there are no direct head-to-head trials of dapagliflozin vs. the comparators in the NICE scope (Table 1.1) an indirect comparison and NMA has been performed

- Cost-effectiveness (Section 5): A cost-utility analysis has been conducted for the comparison of monotherapy with dapagliflozin 10 mg vs. the comparators listed in the NICE scope (Table 1.1)

- Budget impact assessment for dapagliflozin monotherapy (Section 0).

2. Innovation

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Reducing body weight in T2DM patients is an important medical need, however the current NICE recommended monotherapies in patients for whom metformin is not tolerated or is contraindicated i.e. SUs and TZDs, are associated with weight gain and the DPP4s are weight neutral. Replaglinade, as recommended in the draft updated guidelines is also associated with weight gain. In addition, SUs and replaglinade are associated with increased risks of hypoglycaemia. SGLT2s, including dapagliflozin, may represent an innovative approach to monotherapy in these patients because, due to the novel mechanism of action, they are associated with reductions in weight and a low risk of hypoglycaemia.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?

Dapagliflozin and SGLT2s represent a new approach for managing T2DM, and have the added advantage of being oral and associated with greater weight reduction properties than other OADs used in monotherapy. However, there are no substantial additional health-related benefits that are not likely to be captured within a QALY calculation.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Not applicable.

3. Clinical evidence

3.1 Summary of clinical evidence

- **Dapagliflozin as monotherapy is an effective and well tolerated treatment in T2DM patients inadequately controlled with diet and exercise, reducing HbA1c, weight and seated systolic (SBP) and diastolic blood pressure (DBP), whilst hypoglycaemic events remain uncommon**
- The key dapagliflozin monotherapy RCTs were in treatment naïve patients; these are considered to be a relevant proxy for the specific population in the scope due to insufficient available evidence in patients contraindicated or intolerant to metformin

Key monotherapy RCT (Section 3.3)

- Study MB102-013 compared dapagliflozin monotherapy vs. placebo over 24 weeks[27] and thereafter vs. placebo + low dose metformin for 78 weeks (102 weeks total)[13] introduction of low-dose metformin for the placebo group at the beginning of the extension period was approved by regulatory authorities as representative of good practice and ethical conduct to reduce protracted poor control in the placebo group and enable double-blinding to be continued
- This study was conducted in the USA, Canada, Mexico and Russia and included a predominantly Caucasian population
- **Glycaemic control**
  - Dapagliflozin 10 mg significantly reduced HbA1c compared with placebo at 24 weeks: adjusted mean change from baseline: -0.89% vs. -0.23%; P<0.0001 vs. placebo
  - At 102 weeks, there were significantly greater and sustained improvements in glycaemic control with dapagliflozin 10 mg compared to placebo+low dose metformin: -0.61% vs. -0.17%; P=0.048
- **Weight loss**
  - Dapagliflozin showed reductions in body weight compared to placebo at 24 weeks: -3.2 kg vs. -2.2 kg), although this was not statistically significant at this time point due to an unusually high placebo effect, likely due to the provision of relatively intensive diet/exercise counselling given to motivated patients with newly diagnosed diabetes in a clinical trial setting
  - At 102 weeks the difference in body weight with dapagliflozin was significantly different compared to placebo + low dose metformin (-3.94 kg vs. -1.34 kg; P=0.016) demonstrating a sustained clinically meaningful reduction in weight with dapagliflozin
  - Dapagliflozin showed reductions in BMI compared to placebo at 24 weeks (-1.15 kg/m^2 vs. -0.8 kg/m^2) (NB P-value not evaluated, and data not reported at 102 weeks)
- **Blood pressure**
  - Dapagliflozin patients showed a decrease in mean SBP and DBP compared to placebo at 24 weeks: SBP**:** -3.6 mmHg vs. -0.9 mmHg: DBP -2.0 mmHg with dapagliflozin vs. -0.7 mmHg with placebo (P value not evaluated)
- **Safety and tolerability**
  - Dapagliflozin as monotherapy is generally well tolerated, with 80% of patients on dapagliflozin and 77.3% of patients on placebo (+low dose metformin) experiencing any AE over 102 weeks
  - The incidence of hypoglycaemia was low across treatment groups (4.3% with dapagliflozin and 5.3% with placebo (+low dose metformin) over 102 weeks) and there were no major

episodes
  - More subjects in the dapagliflozin arm reported genital infections (15.7% with dapagliflozin and 1.3% with placebo (+low dose metformin) over 102 weeks) and UTIs (8.6% with dapagliflozin and 4% with placebo (+low dose metformin) over 102 weeks) (P values not evaluated); however, they were generally of mild to moderate intensity and responded to standard treatment

- **The efficacy and safety of dapagliflozin is supported by a large evidence base, including three additional trials in monotherapy further demonstrating it as an effective and well tolerated treatment**

Supportive monotherapy studies (Section 0)

- Supportive evidence from two 24-week Phase 3 studies of dapagliflozin as monotherapy in Asian populations **confirmed the acceptable safety profile and the efficacy of dapagliflozin monotherapy with regards to reductions in HbA1c, weight and SBP/DBP[28]**

Additional studies of interest (not eligible for inclusion in the NMA)

- Study MB102-034 compared dapagliflozin monotherapy to metformin XR monotherapy over 24 weeks (Appendix 8.1.3.1)[25]
  - Dapagliflozin 10 mg demonstrated non-inferiority for HbA1c reduction and superiority for FPG reduction compared with metformin monotherapy, with significant reductions in weight and greater mean reductions in seated SBP/DBP compared to metformin

- Pooled analyses of dapagliflozin clinical trials showed that the benefits of dapagliflozin as monotherapy are consistent with findings from other phase 3 RCTs for dapagliflozin as add-on therapy (Appendix 8.1.4)[29,30]

- Long-term studies over 2 years (monotherapy and add-on therapy)[29] and over 4- years as add-on therapy to metformin vs. the SU glipizide (Appendix 8.1.6)[24] have demonstrated the maintenance of the benefits of dapagliflozin over time
  - The 4 year follow-up is the longest follow-up period for an SGLT2 to date
  - Over 4-years dapagliflozin was well tolerated and associated with sustained glycaemic efficacy and greater reductions in body weight and SBP versus glipizide

3.2 Dapagliflozin monotherapy studies identified from the systematic search

A systematic review (SR) identified eligible RCTs for the clinical evidence and the NMA, as described in Section 4. The full list of dapagliflozin monotherapy trials and the reasons for the exclusion of studies other than the three selected for the NMA are shown in the Appendix 8.1.1 in Table 8.1.

Three studies were identified for dapagliflozin monotherapy (Table 3.1). These were all randomised, placebo-controlled, double-blind, phase 3 trials. The pivotal study (MB102-013) compared dapagliflozin vs. placebo over 24 weeks[27] and thereafter vs. placebo + low dose metformin (500 mg) for 78 weeks, thereby evaluating double-blind treatment with dapagliflozin over 102 weeks in total;[13] this study was conducted in a predominantly Caucasian population. In addition, two 24-week Phase 3 studies of dapagliflozin as monotherapy in Asian populations were identified[31] and are presented briefly as supportive evidence.

Using a set of criteria to assess bias in RCTs study quality can be considered to be high quality (see Appendix 8.4). The data presented are predominantly from the publications for the dapagliflozin studies, supplemented with data from the clinical study reports (CSR) as necessary.

In the Appendix additional evidence of interest for this appraisal has been presented (see Table 3.2 for an overview and Appendix 8.1 for further details). In an additional study the benefits of dapagliflozin monotherapy compared to metformin XR monotherapy over 24 weeks has been demonstrated (Study MB102-034).[25] This study was excluded from the SR/NMA because one of the SR criteria was to exclude studies with metformin monotherapy, as the indication for dapagliflozin is for individuals intolerant to metformin (see inclusion/exclusion criteria in Section 4.1). In addition, we show that the short-term and long-term (2-year) benefits of dapagliflozin as monotherapy are consistent with findings from other Phase 3 RCTs for dapagliflozin as add-on therapy (pooled efficacy analyses by Parikh et al., 2015 [29] and safety analyses from the dapagliflozin submission to the FDA Endocrinologic and Metabolic Drug Advisory Committee (EMDAC).[30] We have also presented 4-year data of dapagliflozin vs. the SU glipizide as add-on to metformin. Although not in monotherapy, this evidence demonstrates the durability of the efficacy of dapagliflozin.[24]

Table 3.1: Overview of dapagliflozin RCTs identified in the systematic review and included in the NMA

Study	Study design	Patient population	Interventions and patient numbers	Study length	Primary endpoint	Secondary endpoints	Primary references/ publications
Pivotal study							
MB102-013 (Phase 3; vs. placebo)	Randomised, parallel-group, double-blind, placebo controlled phase 3 trial	Treatment-naïve adults with T2DM and inadequate glycaemic control on diet and exercise	Patients with HbA1c 7.0-10%: Placebo (n=75) Dapagliflozin 10 mg OD in morning (n=70; main cohort)[a] Dapagliflozin 10 mg OD in evening (n=76; exploratory cohort) Patients with HbA1c 10.1-12%: 10 mg OD dapagliflozin (high-HbA1c exploratory cohort)[a]	24 weeks (plus 78 week long term extension to 102 weeks)	Change from baseline in HbA1c at week 24 in main cohort	Change from baseline at week 24 in FPG in main cohort Change from baseline at week 24 in body weight in main cohort	Ferrannini et al., 2010 [27] Bailey et al., 2014 [13]
Supportive studies							
D1692C00006 (Japanese population; Phase 3)	Randomised, parallel-group, double-blind, placebo controlled phase 3 trial	Japanese adults with T2DM and inadequate glycaemic control on diet and exercise; treatment-naïve or patients who underwent a washout period before study treatments	Dapagliflozin 10 mg OD (n=88)[a] Placebo (n=87)	24 weeks	Change in mean HbA1c from baseline to week 24	Change from baseline to week 24 in FPG and body weight	Kaku et al., 2014 [28]
MB102-054 (Asian populations; phase 3)	Randomised, double-blind, placebo-controlled, parallel-group, Phase 3 study	Drug naïve adults with inadequately controlled T2DM; Asian population	Dapagliflozin 10 mg OD (n=133)[a] Placebo (n=132)	24 weeks	Change in mean HbA1c from baseline to week 24	Change from baseline at week 24 in FPG, total body weight and 2-hour PPG Proportion of patients achieving a therapeutic glycaemic response (HbA1c <7%) HbA1c for patients with baseline HbA1c ≥9%	Ji et al., 2014 [31]

FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; NMA, network meta-analysis; OD, once daily; PPG, postprandial glucose; RCT, randomised controlled trial; T2DM, type 2 diabetes

[a] The study also included other doses of dapagliflozin, which are not included in this submission because the recommended dose used in normal clinical practice is 10 mg OD.[1]

Table 3.2: Overview of additional dapagliflozin evidence of interest for the appraisal not included in the NMA

Study	Study design	Patient population	Interventions and patient numbers	Study length	Primary endpoint	Secondary endpoints	Primary references
MB102-034 (Phase 3; vs metformin XR)	Randomised, double-blind, active controlled, parallel group, phase 3 trial	Treatment-naïve adults with T2DM and inadequate glycaemic control on diet and exercise	Dapagliflozin 10 mg OD + metformin XR (n=211) Dapagliflozin 10 mg OD + placebo (n=219) Placebo + metformin XR (n=208)	24 weeks	Change from baseline in HbA1c at week 24	Change from baseline in FPG % patients achieving HbA1c < 7% HbA1c for patients with baseline HbA1c ≥ 9% Total body weight Proportion of subjects discontinued/rescued for failing to achieve glycaemic targets Non-inferiority of dapagliflozin to metformin XR for FPG & HbA1c Difference in weight reduction	Henry et al., 2012 [25]
Pooled efficacy analyses	Dapagliflozin 10 mg data from (i) two short-term, comparator studies (vs. metformin-XR over 24 weeks and vs. glipizide over 52 weeks), (ii) pooled 24-week analyses of five placebo-controlled trials (as mono- or add-on therapy), and (iii) long-term studies over 2 years	T2DM patients with inadequate glycaemic control on (i) diet and exercise alone; (ii) metformin alone; (iii) SU alone; (iv) pioglitazone alone; (v) on insulin ± OADs	Pooled analyses Dapagliflozin 10 mg OD (n=690) Placebo (n=689)	24 weeks (+ 2 year long term data)	Change in mean HbA1c from baseline to week 24	Other endpoints: FPG, weight and SBP	Parikh et al., 2015 [29]
Pooled safety analyses	Dapagliflozin 10 mg safety data from (i) All phase 2b and 3 pool (21 studies); (ii) placebo controlled pool (short-term; 13 studies); and (iii) placebo controlled pool (short-term+long term; 9 studies)	T2DM patients with inadequate glycaemic control on diet and exercise alone; metformin alone; SU alone; pioglitazone alone; on insulin ± OADs	(i) Dapagliflozin all doses (n=5936), comparator (n=3403); (ii): Dapagliflozin 10 mg (n=2360), placebo (n=2295); (iii) Dapagliflozin 10 mg (n=2026), placebo (n=1956)	(i) 24 weeks (+ 4 year long term data); (ii) 12-24 weeks; (iii) 24-104 weeks	AEs, SAEs, AES of special interest including hypoglycaemia, UTIs, genital infections; malignancies, CV risk	-	Dapagliflozin submission to the FDA EMDAC [30]
D1690C00004 (Long-term (4-year) efficacy and safety: add-on to metformin; head to head vs. SU)	Randomised, double-blind, parallel-group, active-controlled trial (non-inferiority study design)	Adults with T2DM inadequately controlled on metformin alone	Dapagliflozin (n=406, starting 2.5mg OD up-titrated to ≤10mg OD); Glipizide (n=408, starting 5mg OD up-titrated to ≤20mg OD), both in addition to open-label metformin at 1500-2000mg daily.	52 weeks with extension periods to 104 and 208 weeks	Change from baseline in HbA1c % at 52 weeks	Change in total body weight at 52 weeks Proportion of patients reporting at least one episode of hypoglycaemia at 52 weeks Proportion of patients with total body weight decrease of ≥5% at 52 weeks	Del Prato et al., 2015 [24]

FDA EMDAC, Food and Drug Administration Endocrinologic and Metabolic Drug Advisory Committee; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; NMA, network meta-analysis; OAD, oral antidiabetic medication; OD, once daily; RCT, randomised controlled trial; PPG, postprandial glucose; SBP, systolic blood pressure; SU, sulphonylurea; T2DM, type 2 diabetes; XR, extended release

[a] The study also included other doses of dapagliflozin, which are not included in this submission because the recommended dose used in normal clinical practice is 10 mg OD.[1]

3.3 Study MB102-013: Dapagliflozin as monotherapy vs. placebo

Summary of Study MB102-013

Study design (Section 3.3.1)

- Study MB102-013 was a 24-week phase 3 placebo-controlled RCT to evaluate the safety and efficacy of dapagliflozin as monotherapy in treatment naïve subjects[27] with a 78-week double-blind extension[13]

Dapagliflozin demonstrated significant reductions in HbA1c and weight over 102 weeks while maintaining an acceptable safety profile with low risk of hypoglycaemia

Efficacy (Section 3.3.3 and 3.3.4)

- Dapagliflozin significantly reduced HbA1c compared with placebo (-0.89% vs. 0.23%; P<0.0001 vs. placebo) at 24 weeks
  - A higher proportion of dapagliflozin patients achieved an HbA1c target of <7% at 24 weeks (50.8% vs. 31.6%) and at 102 weeks (27.9% vs. 19.4%)
  - At 102 weeks, the change from baseline HbA1c in the dapagliflozin arm was maintained at **-**0.61%, significantly reduced compared to placebo + low dose metformin (-0.17%; P value for difference = 0.048), demonstrating significantly greater and sustained improvements in glycaemic control with dapagliflozin compared to placebo+low dose metformin
- Dapagliflozin reduced body weight
  - Dapagliflozin showed reductions in body weight compared to placebo (-3.2 kg vs. -2.2 kg) at 24 weeks, although this was not statistically significant at this time point due to an unusually high placebo effect likely due to the provision of relatively intensive diet/exercise counselling given to motivated patients with newly diagnosed diabetes in a clinical trial setting
  - At 2 years the difference in body weight with dapagliflozin was significantly different compared to placebo+low dose metformin (-3.94 kg vs. -1.34; P = 0.016) demonstrating a sustained clinically meaningful reduction in weight with dapagliflozin
  - Dapagliflozin showed reductions in BMI compared to placebo at 24 weeks (-1.15 kg/m^2 vs. -0.8 kg/m^2) (NB P-value not evaluated, and data not reported at 102 weeks)
- Dapagliflozin patients showed a decrease in mean seated systolic and diastolic blood pressure at 24 weeks
  - SBP**: -**3.6 mmHg with dapagliflozin 10 mg vs. -0.9 mmHg with placebo at 24 weeks
  - DBP: **-**2.0 mmHg with dapagliflozin 10 mg vs. -0.7 mmHg with placebo at 24 weeks

Safety (Section 3.3.5)

- Overall, dapagliflozin used as monotherapy was well tolerated over 24 weeks and 102 weeks in subjects with T2DM.
  - The proportion of participants who experienced an AE and SAE over 24 weeks and 102 weeks was similar in the dapagliflozin and placebo (+low dose metformin after 24 weeks) groups
  - No SAEs were considered to be related to study medication
- Hypoglycaemic events were uncommon
  - Rates over the 102 week period were 5.3% for placebo(+low-dose metformin) group

and 4.3% for the 10 mg dapagliflozin group, and there were no major episodes of hypoglycaemia

- More subjects in the dapagliflozin arm reported genital infections and UTIs
  - All AEs suggestive of genital infection and the majority of AEs suggestive of a UTI were mild or moderate in intensity and responded to standard treatment
- No malignancies were reported in the dapagliflozin 10 mg arm over 102 weeks

3.3.1 Overview of study design and patient population

This was a multicentre, randomised, double-blind, placebo-controlled, parallel group, Phase 3 trial to evaluate the safety and efficacy of dapagliflozin as monotherapy in treatment naïve subjects with T2DM who have inadequate glycaemic control with diet and exercise. The study had a 2-week diet/exercise placebo lead-in (1 week for patients with enrolment HbA1C 10.1–12.0%), and a 24-week double-blind treatment period.[27] In addition, eligible subjects who completed the 24-week short-term treatment period could continue in a long-term treatment period for 78 weeks on blinded study medication (102 weeks overall), with patients randomised to the placebo group receiving low-dose metformin 500 mg/day plus dapagliflozin-matching placebo (placebo+low-dose metformin), and participants randomised to the dapagliflozin groups continuing on the same active treatments but with the addition of metformin-matching placebo.[13] Introduction of low-dose metformin for the placebo group at the beginning of the extension period was approved by regulatory authorities as representative of good practice and ethical conduct to reduce protracted poor control in the placebo group and enable double-blinding to be continued introduction of low-dose metformin for the placebo group at the beginning of the extension period was approved by regulatory authorities as representative of good practice and ethical conduct to reduce protracted poor control in the placebo group and enable double-blinding to be continued. The study design is summarised in Table 3.3. Further details of the methodology i.e. key inclusion/exclusion criteria and the statistical analysis are in Appendix 8.1.2.

The 24-week and 102 week data are predominantly from the publications by Ferrannini 2010 [27] Bailey 2014,[13] respectively, except where indicated that the data is from the CSRs.[32,33] Patients with HbA1c 7.0–10% were randomly assigned equally to one of seven arms to receive; in Group 1, once-daily placebo or 2.5, 5, or 10 mg dapagliflozin, administered once daily either in the morning (main cohort) or evening (exploratory cohort) for 24 weeks. In Group 2, patients with HbA1c 10.1–12% (high-HbA1c exploratory cohort) were assigned randomly in a 1:1 ratio to receive blinded treatment with a morning dose of 5 or 10 mg/day dapagliflozin (a placebo group was not included because of the high HbA1c levels). Data for the 2.5 and 5 mg doses are not reported in this submission because the recommended dose used in normal clinical practice is 10 mg dapagliflozin once daily.[1]

Patients with fasting plasma glucose (FPG) >270 mg/dl at week 4, >240 mg/dl at week 8, or >200 mg/dl at weeks 12–24 were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2,000 mg). Patients with HbA1c >8.0% for 12 weeks despite a maximum tolerated metformin dose were discontinued. Throughout the study, patients received diet/exercise counselling per ADA recommendations. Subjects who received rescue medication during the short-term double-blind period continued to receive the same open-label rescue medication in addition to their randomly assigned study medication.[33] Subjects exhibiting a lack of glycaemic control during the long-term period and who had not previously received rescue medication in the short-term double-blind period were eligible to receive open-label rescue medication in addition to their blinded study treatment.[33]

The majority of participants in the main cohort completed both the 24-week treatment period (84.7%) and the full 102-week study (60.9%) (see Appendix 8.1.2 for more details). In general, the treatment groups were balanced with respect to demographic characteristics (see Appendix 8.1.2.3 for more details).

Table 3.3: Study design characteristics

Study MB102-013 (NCT00528372)	
Location[34]	• 85 sites in the U.S., Canada, Mexico, and Russia
Design	• Randomised, parallel-group, double-blind, placebo controlled phase 3 trial
Patient population	• Treatment-naïve adults[a] aged 18–77 years with T2DM and inadequate glycaemic control on diet and exercise[b]
Duration	• 24 weeks + 78 week extension (week 102) (double-blind treatment throughout)
Randomisation	• Eligible participants were randomly assigned to one of 7 treatment groups using computer-generated randomisation by an IVRS and were stratified by site in blocks of 7
Blinding	• Investigators, other clinic staff and participants were blinded to treatment allocation during the 24-week double-blind and 78-week extension periods
Intervention(s) (n) and comparator(s) (n) [35]	• Patients (n=513; Group 1) with HbA1c 7.0–10% were randomly assigned equally to one of seven arms[c] which included: o Placebo OD[d] (n= 75) o Dapagliflozin 10 mg (n=70) administered OD in the morning (main cohort) o Dapagliflozin 10 mg (n=76) administered OD in the evening (exploratory cohort) • Patients (n=78; group 2) with HbA1c 10.1– 12% (high- HbA1c exploratory cohort) were assigned randomly in a 1:1 ratio to receive blinded treatment with a morning dose of 10 (n=39) or 5[e] mg dapagliflozin OD
Primary endpoint	• Change from baseline in HbA1c at week 24 in main cohort
Secondary endpoints of relevance	• Change from baseline at week 24 in FPG in main cohort • Change from baseline at week 24 in body weight in main cohort • To compare the proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c < 7.0%, after 24 weeks
Other endpoints of relevance	• Change from baseline in HbA1c, FPG and body weight at week 24 in exploratory evening dose and high-HbA1c cohorts
Safety	• Vital signs, laboratory measurements, and AEs • Clinical signs and symptoms suggestive of UTIs and genital infections • Unusually high or low blood glucose event or any symptoms suggestive of hypoglycaemia
Pre-specified 78 week extension outcomes	• Change from baseline over 102 weeks in HbA1c level, FPG and total body weight • The proportion of participants who achieved glycaemic • control [defined as an HbA1c of < 53 mmol/mol (< 7%)] • The long-term safety and tolerability of dapagliflozin treatment over 102 weeks: general AEs and AEs of special interest, which included hypoglycaemia and events suggestive of genital or of UTI
Analyses	• Analyses were conducted in all randomised participants who took at least one dose of study medication during the 24-week, short-term, double-blind period[f] • Analyses of change from baseline in HbA1c, FPG, and body weight were performed using an ANCOVA with treatment group as effect and baseline value as covariate, with last observation carried forward (LOCF) • The proportion of patients achieving a therapeutic glycaemic response was analysed using logistic regression based on established methodology[36] • For the analysis of continuous efficacy variables over 102 weeks (HbA1c, fasting plasma glucose and total body weight), longitudinal repeated-measures mixed models were performed • Safety was evaluated in all subjects who received at least 1 dose of double-blind study medication during the 24 week treatment period[f,g]
Publications	• Ferrannini, E., S. J. Ramos, A. Salsali, W. Tang and J. F. List. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010; 33(10): 2217-2224.[27] • Bailey, C. J., E. C. Morales Villegas, V. Woo, W. Tang, A. Ptaszynska and J. F. List. Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabet Med 2014.[13]

Study MB102-013 (NCT00528372)
AEs, adverse events; ANCOVA, analysis of covariance; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; IVRS; Interactive Voice Response System; OD, once daily; T2DM, type 2 diabetes; U.S, United States; UTI, urinary tract infection [a] defined as subjects who have never received prescription medications for diabetes or have received prescription medications for diabetes for <24 weeks since the original diagnosis [b] defined as a central laboratory HbA1c ≥ 7.0 and ≤ 10.0% at the enrolment visit for the main cohort; and central laboratory HbA1c ≥ 10.1 and ≤ 12.0% at the enrolment visit for the high HbA1c cohort [c] The arms also included 2.5 mg and 5 mg dapagliflozin administered once daily in the morning (main cohort) and in the evening (exploratory cohort) which are not included in this submission because the recommended dose used in normal clinical practice is 10 mg dapagliflozin OD [1] [d] After 24 weeks, participants randomised to the placebo group received low-dose metformin 500 mg/day plus dapagliflozin-matching placebo (placebo+low-dose metformin), and participants randomised to the dapagliflozin groups continued on the same active treatments but with the addition of metformin-matching placebo [e]Data for the 5 mg dose are not reported in the submission because the recommended dose is 10 mg dapagliflozin once daily[1] [f] From the CSR[32] [g]Including any subject who accidentally received double-blind study medication, but was not randomised into the study

3.3.2 Study outcomes of relevance to NICE appraisal

Table 3.4 shows which outcomes listed in the NICE scope for the appraisal were reported in study MB102-013 and which were not reported. In addition, other endpoints of interest with regards to appraising the efficacy of dapagliflozin are shown, including the assessment of blood pressure and total body weight and other glycaemic parameters (FPG and the proportion of patients achieving a therapeutic glycaemic response [HbA1c < 7%]). Changes in weight and systolic blood pressure (SBP), in addition to HbA1c, are modifiable risk factors used in the economic model (Section 5).

The efficacy outcomes for the main cohort at 24 weeks and 102 weeks are presented below. For the exploratory cohorts, no P values were generated for the endpoints as per the study design and the outcomes of relevance for the exploratory cohorts i.e. HbA1c, FPG and weight are shown in Appendix 8.1.2.4. The safety outcomes at 24 weeks and 102 weeks, including hypoglycaemia and urinary tract infections (UTIs), genital infections and malignancies, are presented within the overall safety results (Section 3.3.5).

Table 3.4: Outcomes of relevance to the NICE appraisal

Outcome	Endpoint for NICE outcome	Other endpoints of interest for short-term period (24 weeks)	Other endpoints of interest for long-term period (102 weeks)
Outcomes included in the NICE scope			
HbA1c/glycaemia control	Primary endpoint: Change from baseline in HbA1c at week 24 in main cohort	Secondary endpoints: Change from baseline at week 24 in FPG in main cohort Change from baseline in HbA1c, FPG at week 24 in exploratory evening dose and high-HbA1c cohorts The proportion of participants who achieved glycaemic control [defined as an HbA1c of < 53 mmol/mol (< 7%)]	Change from baseline over 102 weeks in HbA1c level & FPG The proportion of participants who achieved glycaemic control [defined as an HbA1c of < 53 mmol/mol (< 7%)]
BMI	Exploratory endpoint: Change from baseline at week 24 in BMI	Secondary endpoints: Change from baseline at week 24 in body weight	Change from baseline over 102 weeks in total body weight

Outcome	Endpoint for NICE outcome	Other endpoints of interest for short-term period (24 weeks)	Other endpoints of interest for long-term period (102 weeks)
		in main cohort and in the exploratory cohorts	
Mortality	NR	-	-
Complications of diabetes, including CV, renal and eye	Safety endpoints[a, b]	-	-
Frequency and severity of hypoglycaemia	Safety endpoint[c]	-	-
Changes in cardiovascular risk factors	[a] Primary endpoint: Change from baseline in HbA1c at week 24 in main cohort Secondary endpoints: Change from baseline at week 24 and 102 in body weight Safety endpoint: seated systolic and diastolic blood pressure Exploratory endpoint: change from baseline in lipid: TC, HDL-C, LDL-C[d]	-	-
Adverse effects of treatment, including urinary tract infections, genital infections and malignancies	Safety endpoint[e]	-	Safety endpoint[a]
Health-related quality of life	NR	-	-
Other outcomes of interest for the appraisal but not in the scope			
Blood pressure	-	Safety endpoint: seated systolic and diastolic blood pressure	Safety endpoint: seated systolic and diastolic blood pressure
The proportions of participants discontinued or rescued for failing to meet prespecified glycaemic targets	-	-	The proportions of participants discontinued or rescued for failing to meet prespecified glycaemic targets by 102 weeks

BMI, body mass index; CV, cardiovascular; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NR, not reported: TC, total cholesterol

[a] In the economic evaluation the outcome has been modelled based on trial data

[b] Events of special interest including renal impairment/failure and hypotension/dehydration/hypovolemia were identified from a pre-specified list of Preferred Terms (PT) [redacted]

[d] Data not reported in the clinical Section

[e] Separate summaries were provided for specific AEs of interest, including: signs and symptoms and other reports suggestive of "genital infection", signs and symptoms and other reports (including positive culture in some cases) suggestive of "urinary tract infection", hypoglycaemia (major, minor, and other episodes); AEs and SAEs by SOC/PT were reported including malignancies[27,32]

3.3.3 Efficacy outcomes of relevance in the main cohort at 24 weeks

Dapagliflozin as monotherapy in treatment-naive patients with T2DM resulted in clinically meaningful decreases in HbA1c and FPG, along with favourable effects on weight, BMI and seated

blood pressure (SBP and DBP), as described in Table 3.5 and more detail below for HbA1c, FPG and total body weight.

Dapagliflozin was associated with statistically significant reductions in mean HbA1c from baseline compared with placebo at week 24 (-0.89% vs. -0.23% respectively; P < 0.0001 vs. placebo) (Figure 3.1A). Reductions in FPG were apparent as early as week 1 and were statistically significant at week 24 (-28.8 mg/dl with dapagliflozin 10 mg vs. -4.1 mg/dl with placebo; P<0.0001) (Figure 3.1B). Additionally 51% of patients reached the ADA/EASD target HbA1c of <7% at 24 weeks when treated with 10 mg dapagliflozin compared with 32% treated with placebo.

Mean body weight decreases were greater with dapagliflozin than with placebo (-3.2 kg vs. -2.2 kg respectively) (Figure 3.1C). Lack of statistical significance versus placebo is considered associated with a large study placebo effect, possibly due to the provision of relatively intensive diet/exercise counselling which, when given to motivated patients with newly diagnosed diabetes in a clinical trial setting, could inflate placebo outcomes, such as weight and HbA1c reduction.[27] Of note the progressive decrease in weight had not reached a plateau by the end of 24 weeks and the difference between the dapagliflozin and the placebo+low-dose metformin group was significant at week 102 (-2.60 kg; P=0.016) (Section 3.3.4).

Furthermore, dapagliflozin treatment was associated with increased renal glucose excretion. This glucose excretion persisted for the full 24-week study period and was consistent with the urinary loss of approximately 200–300 calories/day as reported in other studies.[37] In pooled data from the morning and evening cohorts, changes from baseline in fractional renal glucose excretion at week 24 were significantly related (r=0.13, P=0.008) with the corresponding changes in body weight, such that across all study arms greater renal glucose losses were associated with larger decrements in body weight.

Table 3.5: Summary of the key outcome variables in the main cohort at 24 weeks

		Placebo (n=75)	Dapa 10mg morning dose (main cohort) (n=70)
Glycaemic parameters			
HbA1c (%): Primary endpoint			
Week 24 (LOCF)[a]	Adjusted mean change from baseline (± SEM)	-0.23 ± 0.10	-0.89 ± 0.11
	Difference vs. placebo (± SEM)[b]		-0.66 ± 0.15
	P-value for difference vs. placebo		P < 0.0001*
FPG (mg/dL): Secondary endpoint			
Week 24 (LOCF)[a]	Adjusted mean change from baseline (± SEM)	-4.1 ± 3.9	-28.8 ± 4.0
	Difference vs. placebo (± SEM)[b]		-24.7 ± 5.63
	P-value for difference vs. placebo		P < 0.0001*
Subjects with HbA1c <7%: Secondary endpoint			
Week 24 (LOCF)	Percent adjusted	31.6%	50.8%
	Difference vs. placebo		19.2%
Weight: total body weight and BMI			
Total body weight (kg): Secondary endpoint			
Week 24 (LOCF)[a]	Adjusted mean change from baseline (± SEM)	-2.2 ± 0.4	-3.2 ± 0.5
	Difference vs. placebo (± SEM)[b]		-0.97 ± 0.62
	[redacted]		[redacted]

		Placebo (n=75)	Dapa 10mg morning dose (main cohort) (n=70)
BMI (kg/m^2): Exploratory endpoint			
Week 24 (LOCF)[a]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
Other outcomes of interest for the appraisal			
Seated blood pressure (mmHg): Safety endpoint			
Week 24 SBP[c]	Mean change from baseline (± SEM)	-0.9 ± 1.8	-3.6 ± 1.9
Week 24 DBP[c]	Mean change from baseline (± SEM)	-0.7 ± 1.0	-2.0 ± 1.1

BMI, body mass index; Dapa, dapagliflozin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; LOCF, last observation carried forward; SBP, systolic blood pressure; SEM, standard error of the mean

Efficacy analyses excluded data after rescue

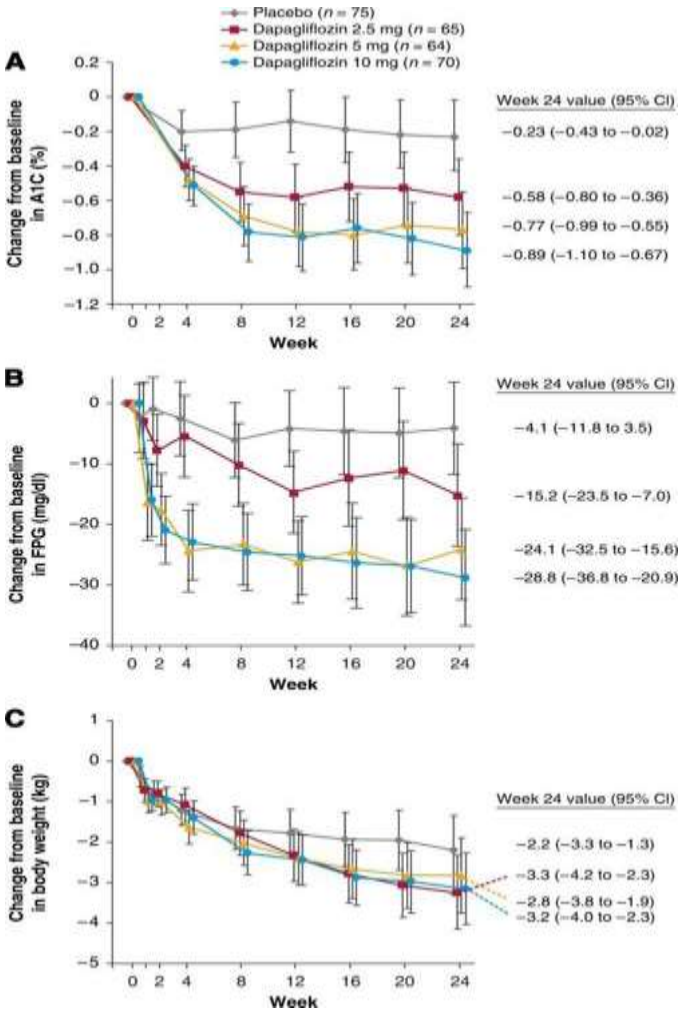
* Significant P-value: Primary endpoint was tested at alpha=0.019 applying the Dunnett adjustment, and secondary endpoints were tested following a sequential testing procedure at alpha=0.05.

[a] Assessed in patients without missing baseline and week 24 values with LOCF

[b] Data from CSR[32]

[a] Assessed in patients without missing baseline and week 24 values

Figure 3.1: **Adjusted mean changes over 24 weeks in: (a) HbA1c, %; (b) fasting plasma glucose, mg/dl; (c) total body weight, kg; (error bars represent 95% CIs)**



Source: Ferrannini et al., 2010 [27]

3.3.4 Efficacy outcomes of relevance at 102 weeks (long-term treatment period) in the main cohort

Only the main cohort results are presented in Bailey 2014, and thus presented here. The results from the exploratory cohorts from the CSR are shown in Appendix 8.1.2.4.

The mean reductions in HbA1c and FPG levels seen in the dapagliflozin 10 mg group at 24 weeks was maintained up to 102 weeks (Figure 3.2A and B). Compared with the placebo+low-dose metformin group, reductions in HbA1c levels from baseline at 102 weeks were significantly greater with dapagliflozin 10 mg (P=0.048,). Similarly, significantly greater reductions in FPG from baseline at 102 weeks were noted with dapagliflozin 10 mg compared with placebo+low-dose metformin (P=0.001; Table 3.6). The proportions of participants discontinued or rescued for failing to meet prespecified glycaemic targets by 102 weeks were 35.0% and 44.0% in the dapagliflozin 10 mg groups and placebo+low-dose metformin group, respectively, resulting in differences vs the placebo+low-dose metformin group of -9.0% (95% CI -24.1, 6.1).

For the dapagliflozin 10 mg group, the reduction in body weight seen after 24 weeks was maintained up to 102 weeks (P=0.016 compared with the placebo+low-dose metformin group;

Figure 3.2C).

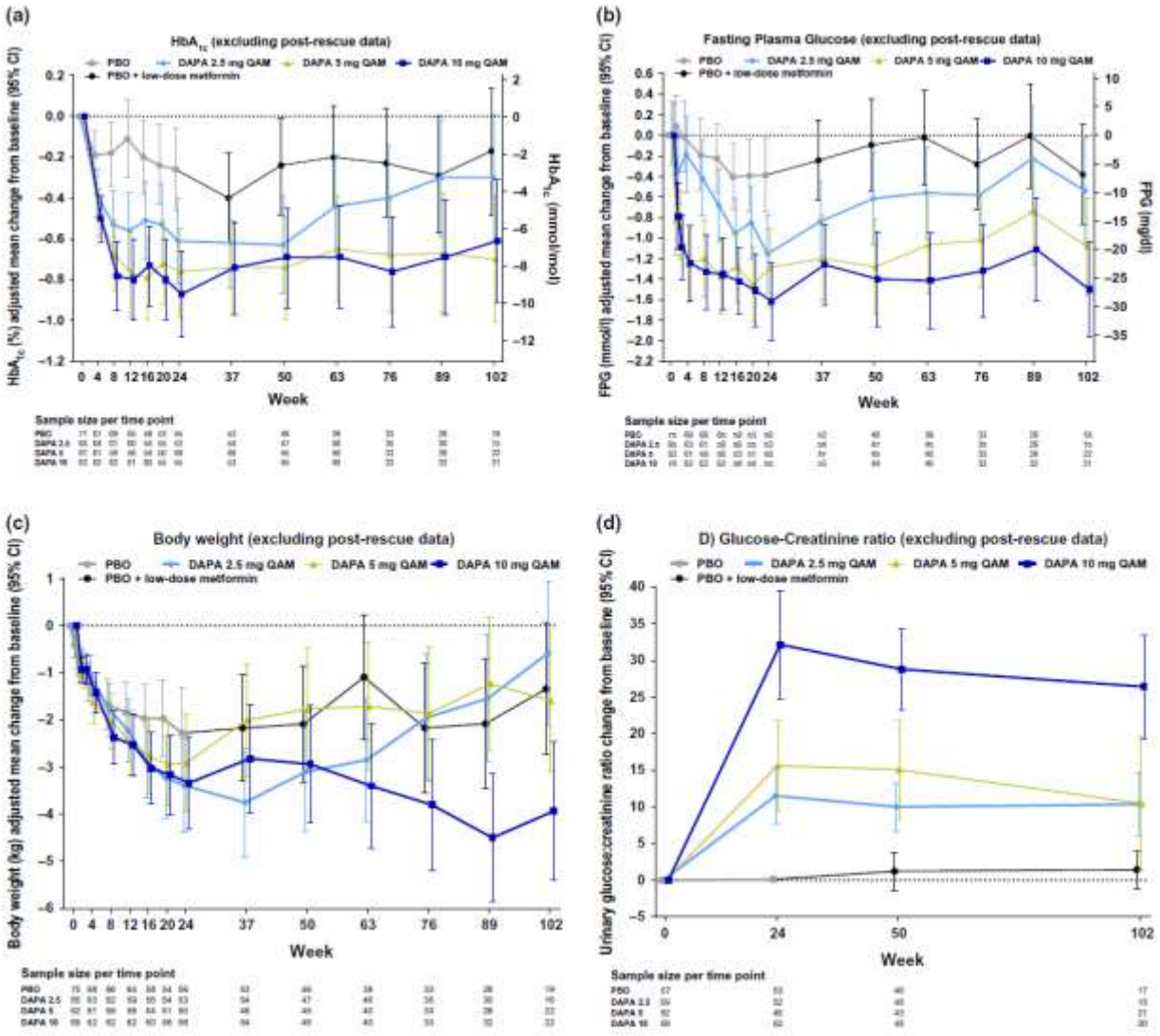
Dapagliflozin increased the urinary glucose: creatinine ratio in a dose-dependent manner (Figure 3.2D). Elevations evident at 24 weeks were maintained up to 102 weeks, showing the sustained pharmacodynamic activity of dapagliflozin throughout the study.

Table 3.6: Summary of the key outcome variables at 102 weeks

		Placebo+low dose metformin (n=75)	Dapa 10mg morning dose (main cohort) (n=70)
Glycaemic parameters			
HbA1c (mmol/mol)			
Week 102 (Longitudinal analysis)	n	18	21
	Adjusted mean change from baseline (95% CI)	-1.9 (-5.2, 1.5)	-6.7 (-9.9, -3.4)
	Difference vs. placebo+low dose metformin (95% CI)		-4.8 (-9.5, 0.0)
	P-value for difference vs. placebo+low dose metformin		0.048
HbA1c (%)			
Week 102 (Longitudinal analysis)	Adjusted mean change from baseline (95% CI)	-0.17 (-0.48, 0.14)	-0.61 (-0.91, -0.31)
	Difference vs. placebo+low dose metformin (95% CI)		-0.44 (-0.87, 0.00)
FPG (mmol/l)			
Week 102 (Longitudinal analysis)	n	18	21
	Adjusted mean change from baseline (95% CI)	-0.38 (-0.87, 0.11)	-1.50 (-1.97, -1.03)
	Difference vs. placebo+low dose metformin (95% CI)		-1.12 (-1.79, -0.44)
	P-value for difference vs. placebo+low dose metformin		0.001
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
Weight: total body weight			
Total body weight (kg)			
Week 102 (Longitudinal analysis)	n	19	22
	Adjusted mean change from baseline (95% CI)	-1.34 (-2.84, 0.16)	-3.94 (-5.41, -2.47)
	Difference vs. placebo+low dose metformin (95% CI)		-2.60 (-4.70, -0.49)
	P-value for difference vs. placebo+low dose metformin		0.016
Other outcomes of interest for the appraisal			
Seated blood pressure (mmHg)[c]			
Week 102 SBP	Mean change at week 102 (95% CI)	2.1 (-2.1, 6.3)	3.9 (0.5, 7.4)
Week 102 DBP	Mean change at week 102 (95% CI)	0.5 (-2.0, 3.0)	1.7 (-0.8, 4.2)
The proportion of subjects discontinued or rescued for failing to achieve prespecified glycaemic targets based on prespecified rescue criteria			
Week 102	%	44.0	35.0
	Difference vs. placebo+low dose metformin (95% CI)		-9.0 (-24.1, 6.1).

	Placebo+low dose metformin (n=75)	Dapa 10mg morning dose (main cohort) (n=70)
CI, confidence interval; Dapa, dapagliflozin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; SBP, systolic blood pressure Data are adjusted mean changes from baseline and 95% CIs based on a longitudinal repeated-measures mixed model with 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. Analyses excluded data after the initiation of rescue therapy. N is the number of randomised participants who took at least one dose of double-blind study medication. n is the number of randomised participants with available baseline and week 102 values. Placebo+low-dose metformin group received placebo (0–102 weeks) + low-dose metformin 500 mg/day (24–102 weeks) [a] Data from CSR[33] [redacted] [c] Observations include data after the initiation of rescue therapy		

Figure 3.2: **Adjusted mean changes over 102 weeks in: (a) HbA1c, %; (b) total body weight, kg; (c) fasting plasma glucose, mmol/l; and (d) glucose: creatinine ratio**



For panels a–c, data are adjusted mean changes from baseline and error bars are 95% CIs based on a longitudinal repeated-measures mixed model with 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. For panel d, data represent descriptive means and 95% CIs. Treatment symbols are shifted horizontally to prevent error bar overlapping. All analyses were conducted using the dataset comprising all randomised participants who received at least one dose of double-blind study medication and excluded data after the initiation of rescue therapy. DAPA, dapagliflozin; PBO, placebo (0–24 weeks); QAM, once daily in the morning. Placebo+low-dose metformin group received placebo + low-dose metformin 500 mg/day (24–102 weeks)

Source: Bailey et al., 2014 [13]

3.3.5 Safety outcomes of relevance at 24 and 102 weeks

Adverse events (AEs) in the main cohort, including those of special interest, over 24 and 102 weeks are presented in Table 3.7 and Table 3.8, respectively. The proportion of participants who experienced an AE over 24 weeks and 102 weeks was similar in each treatment group. The frequency of SAEs was also similar across the treatment groups; no SAEs were considered to be related to study medication and there were no SAEs related to hypoglycaemia. One death occurred in the dapagliflozin 10 mg group during the first 24 weeks as a result of a road traffic accident, which was not related to study medication in the opinion of the investigator.

Hypoglycaemic events were reported at a low level across all treatment groups. No major hypoglycaemic events were reported and no participant discontinued the study because of hypoglycaemia.

Events suggestive of genital infections and of UTIs occurred more frequently in the dapagliflozin groups compared with the placebo (+ low-dose metformin group). These events were more common in women, and most were single episodes. All AEs suggestive of genital infection and the majority of AEs suggestive of a UTI were mild or moderate in intensity and responded to standard treatment (there were two events suggestive of a UTI reported as severe both in the dapagliflozin 5-mg group). Three participants (one in each dapagliflozin group) discontinued the study because of events suggestive of a UTI and one participant in the dapagliflozin 2.5 mg group discontinued as a result of pyelonephritis. There were no other events of pyelonephritis reported in the study.

Neoplasms were reported in two participants in the placebo (+ low-dose metformin) group (single cases of malignant melanoma and thyroid neoplasm) and one participant in the dapagliflozin 2.5 mg group (a case of benign breast neoplasm). No cases of malignancy were reported across the other dapagliflozin treatment arms.

Table 3.7: Adverse events at 24 weeks

	Placebo	**Dapa 10mg morning dose**
Cohort	Group 1[a]	Group 1[a] main
n	75	70
AEs		
At least one AE	45 (60.0)	48 (68.6)
At least one SAE	3 (4.0)	1 (1.4)
Discontinuation for AE	1 (1.3)	5 (7.1)
Discontinuation for SAE	0	0
Deaths	0	1 (1.4)
Most common AEs (≥10% in any group) by MedDRA preferred term[b]		
Nasopharyngitis	4 (5.3)	2 (2.9)
Diarrhoea	1 (1.3)	1 (1.4)
Headache	5 (6.7)	4 (5.7)
Events by special interest category		
Hypoglycaemia[c]	2 (2.7)	2 (2.9)
Events suggestive of UTIs[d]	3 (4.0)	4 (5.7)
Events suggestive of genital infections[e]	1 (1.3)	9 (12.9)
Hypotensive events	1 (1.3)	1 (1.4)

Adverse event; Dapa, dapagliflozin; SAE, serious adverse event; UTI, urinary tract infection

Data are n (%) and include data after rescue

[a] The The arms also included 2.5 mg and 5 mg dapagliflozin administered once daily which are not included here because the recommended dose in normal clinical practise is 10 mg dapagliflozin once daily;[1] the text above includes any key safety data in these groups.

[b] Additional AEs with ≥5% incidence in any of the primary cohort and exploratory evening dose arms were arthralgia, pharyngitis, upper respiratory infection, UTI, back pain, dizziness, constipation, influenza, myalgia, peripheral oedema, pain in extremity, and insomnia

[c] None of the hypoglycaemic events led to discontinuation from the study, and none was a major episode, defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <54 mg/dl, and prompt recovery after glucose or glucagon administration

[d] These events included signs, symptoms, and other reports suggestive of UTIs

Table 3.8: Adverse events over 102 weeks

	Placebo+low dose metformin	Dapa 10mg morning dose
Cohort	Group 1[a] main	Group 1[a] main
n	75	70
AEs		
At least one AE	58 (77.3)	56 (80)
At least one drug-related AE	15 (20)	17 (24.3)
AE leading to discontinuation	4 (5.3)	5 (7.1)
At least one SAE	5 (6.7)	1 (1.4)
At least one drug-related SAE	0	0
SAE leading to discontinuation	1 (1.3)	0
Deaths	0	1 (1.4)
Most common AEs (≥10% in any group)		
Nasopharyngitis	7 (9.3)	10 (14.3)
Headache	9 (12)	6 (8.6)
Influenza	3 (4.0)	5 (7.1)
Events of hypoglycaemia		
At least one episode of hypoglycaemia	4 (5.3)	3 (4.3)
At least one major episode of hypoglycaemia[b]	0	0
Events suggestive of genital infections[c]		
Men	0/31	2/34 (5.9)
Women	1/44	9/36 (25.0)
Total participants	1/75 (1.3)	11/70 (15.7)
Single event	0	6 (54.5)
2–3 events	1 (100)	5 (45.5)
> 3 events	0	0
Events suggestive of UTI[c]		
Men	0/31	2/34 (5.9)
Women	3/44 (6.8)	4/36 (11.1)
Total participants	3/75 (4.0)	6/70 (8.6)
Single event	3 (100)	5 (83.3)
2–3 events	0	1 (16.7)
> 3 events	0	0
Renal impairment/failure		
Blood creatinine **>**132.6 µmol/l	0	3 (4.3)
Renal failure	0	0
Hypotensive events	1 (1.3)	1 (1.4)

Adverse event; Dapa, dapagliflozin; SAE, serious adverse event; UTI, urinary tract infection

Data are n (%) and include data after rescue

[a] Only data from the main cohort were presented in Bailey et al., 2014.[13] The arms also included 2.5 mg and 5 mg dapagliflozin administered once daily in the morning (main cohort) which are not included here because the recommended dose used in normal clinical practise is 10 mg dapagliflozin once daily. [1] Placebo**+**low-dose metformin group received placebo (0**–**102 weeks) **+** low-dose metformin 500 mg/day (24**–**102 weeks)

[b] Defined as symptomatic episodes requiring external assistance as a result of severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/l (< 54 mg/dl) and prompt recovery after glucose or glucagon administration

[c] A list of preferred terms was used to identify events suggestive of genital infection or UTI

3.4 Supportive clinical evidence

Here we briefly present the study design and efficacy and safety outcomes of relevance to this submission for two 24-week Phase 3 studies of dapagliflozin as monotherapy in Asian populations. The data presented are exclusively from the publications.[28,31]

3.4.1 Study D1692C00006: Dapagliflozin as monotherapy vs. placebo in a Japanese population

Summary for Study D1692C00006

Study design (Section 3.4.2)

- Study D1692C00006 is a 24 week phase 3 RCT evaluating the efficacy and safety of dapagliflozin as monotherapy compared to placebo in Japanese patients with T2DM inadequately controlled by diet and exercise.[28]

Efficacy (Section 3.4.3)

- Dapagliflozin 10 mg produced statistically significant reductions from baseline in HbA1c compared to placebo
  - The adjusted mean change from baseline to week 24 in HbA1c was significantly greater with dapagliflozin (10mg, −0.45%) than with placebo (−0.06%; P<0.0001)
  - Among patients with higher mean baseline HbA1c values (≥8.0–9%), the mean changes from baseline in the dapagliflozin 10 mg group was −0.94% vs. –0.03% with placebo
  - With dapagliflozin 10 mg 35.7% achieved a therapeutic response defined as HbA1c <7.0% compared with 18.8% of those who received placebo

- Dapagliflozin reduced body weight
  - Dapagliflozin 10 mg significantly reduced body weight compared to placebo at 24 weeks: −2.22 kg vs. −0.84 kg; P<0.0001
  - The approximate 2-kg weight loss seen in the dapagliflozin arm represents almost 3.0% of the patients' baseline body weights
  - In the subgroup of patients who had baseline BMI ≥25 kg/m^2 (48% of the study population) the adjusted mean changes in total body weight from baseline to week 24 was −2.89 kg in the dapagliflozin 10 mg group compared with −1.55 kg with placebo (P=0.0236 vs. placebo)

- Dapagliflozin patients showed a decrease in mean seated systolic blood pressure at 24 weeks: -3.2 mmHg for dapagliflozin 10 mg and -0.5 mmHg for placebo

Safety (Section 3.4.4)

- Dapagliflozin 10 mg was well-tolerated over 24 weeks
  - No major or minor hypoglycaemic events were reported throughout the study
  - Few events suggestive of UTI and genital infection were reported; all reported events were of mild or moderate intensity

3.4.2 Study design and patient population

The study design and characteristics for the 24 week RCT of dapagliflozin monotherapy in Japanese patients is presented in Table 3.9.[28]

Table 3.9: Study design characteristics

Study D1692C00006 (NCT01294423**)**	
Location	• Japan
Design	• Randomised, double-blind, parallel-group, multicentre, placebo-controlled trial
Duration of study	• 24 weeks + 3 weeks follow-up

Patient population	• Patients aged ≥20 years with a confirmed diagnosis of T2DM
	  ○ Treatment naïve[a] with HbA1c values ≥6.5 and ≤10%
	  or
	  ○ Receiving ongoing treatment for diabetes within 6 weeks of enrolment (not drug-naïve) with HbA1c values ≤8%; these patients would undergo a washout period before study treatments
	• At 1 week before randomisation, HbA1c was required to be ≥6.5 and ≤10% for all patients. The proportion of randomised patients with HbA1c ≥6.5%, but ≤7%, 1 week before randomisation was required to be ≤25%

Intervention(s) (n) and comparator(s) (n)	• Dapagliflozin 10 mg (n=88)[b] • Placebo (n=87)
Primary endpoint	• Change in mean HbA1c from baseline to week 24
Secondary endpoint	• Change from baseline to week 24 in FPG and body weight
Exploratory endpoints of relevance	• Change from baseline to week 24 in total body weight in patients with BMI ≥25 kg/m^2 • SBP overall and in patients with baseline seated SBP ≥130 mmHg • Proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7%) after 24 weeks in patients with baseline HbA1c ≥7% • Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FPG below prespecified rescue criteria after 24 weeks
Safety	• AEs, laboratory values, ECG, heart rate, blood pressure, hypoglycaemic events, calculated creatinine clearance, eGFR and physical examination findings
Analyses	• Efficacy was evaluated in the FAS[c] • Primary and most secondary efficacy analyses were performed using an ANCOVA with fixed terms for treatment group and gender (stratification factor) and baseline value as a covariate, using LOCF to calculate a least-squares estimate of the treatment difference • The proportion of patients achieving HbA1c levels <7.0% was analysed by logistic regression • Safety was evaluated in the safety analysis set[d]
Publication	• Kaku, K., A. Kiyosue, S. Inoue, N. Ueda, T. Tokudome, J. Yang and A. M. Langkilde. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. Diabetes Obes Metab 2014; 16(11): 1102-1110.[28]

AEs, adverse events; ANCOVA, analysis of covariance; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; LOCF, last observation carried forward; SBP, seated systolic blood pressure; T2DM, type 2 diabetes

[a] Defined as: never received medical treatment for diabetes or received treatment for <30 days after diagnosis, and during the 30-day period before screening did not receive oral antidiabetic agents for >3 consecutive or >7 non-consecutive days, or were previously treated for diabetes but not within 6 weeks of enrolment

[b] The arms also included 5 mg dapagliflozin (n=86) administered once daily which is not included in this submission because the recommended dose used in normal clinical practise is 10 mg dapagliflozin once daily[1]

[c] All randomised individuals who took at least one dose of double-blind study medication, had a non-missing baseline value and at least one post-baseline efficacy value for ≥1 efficacy variable

[d] Patients who took ≥1 dose of double-blind study medication and who provided any safety records

3.4.3 Summary of efficacy outcomes of relevance

Key results from the RCT of dapagliflozin monotherapy in Japanese patients is presented in Table 3.10.[28]

Table 3.10: Summary of the key outcome variables at 24 weeks

		Placebo (n=87)	Dapa 10mg (n=88)
HbA1c (%): Primary endpoint			
Week 24 (LOCF)	Baseline mean (s.d)	7.50 (0.63)	7.46 (0.61)
	Adjusted mean change from baseline (95% CI)	−0.06 (−0.18, 0.06)	−0.45 (−0.57, −0.33)
	Difference vs. placebo (95% CI)	−0.39 (−0.56, −0.23)	
	P-value for difference vs. placebo	<0.0001*	
Total body weight (kg): Secondary endpoint			
Week 24 (LOCF)	Baseline mean (s.d)	65.96 (12.91)	69.70 (13.82)
	Adjusted mean change from baseline (95% CI)	−0.84 (−1.36, −0.32)	−2.22 (−2.73, −1.71)
	Difference vs. placebo (95% CI)	−1.38 (−2.08, −0.69)	
	P-value for difference vs. placebo	0.0001*	
FPG (mg/dL [mmol/l]): Secondary endpoint			
Week 24 (LOCF)	Baseline mean (s.d)	139.8 (21.7) [7.76 (1.20)]	138.7 (22.3) [7.70 (1.24)]
	Adjusted mean change from baseline (95% CI)	5.8 (1.6, 10.1) [0.32 (0.09, 0.56)]	−13.7 (−18.0, −9.5) [−0.76 (−1.00, −0.53)]
	Difference vs. placebo (95% CI)	−19.5 (−25.2, −13.8) [−1.1 (−1.4, −0.8)]	
	P-value for difference vs. placebo	<0.0001*	
Subjects with HbA1c <7% in patients with baseline HbA1c ≥7.0%: Exploratory endpoint			
Week 24 (LOCF)	Baseline mean	7.74	7.66
	Percent adjusted (95% CI)	18.8 (9.9, 27.7)	35.7 (24.9, 46.5)
	Difference vs. placebo (95% CI)	16.9 (3.3, 30.6)	
	P-value for difference vs. placebo	0.0152	
Total body weight in patients with baseline BMI ≥25 kg/m2, kg: Exploratory endpoint			
Week 24 (LOCF)	Baseline mean (s.d)	74.80 (11.99)	77.10 (12.57)
	Adjusted mean change from baseline (95% CI)	−1.55 (−2.46, −0.63)	−2.89 (−3.71, −2.08)
	Difference vs. placebo (95% CI)	−1.35 (−2.51, −0.18)	
	P-value for difference vs. placebo	0.0236	
Proportion of patients discontinued for lack of efficacy: Exploratory endpoint			
Week 24	X/N (%)	0/87 (0)	0/88 (0)

		Placebo (n=87)	Dapa 10mg (n=88)
SBP (mmHg): Exploratory endpoint			
Week 24	Mean change from baseline (95% CI)	−0.5	−3.2
	P-value for difference vs. placebo	0.0964	
BMI, body mass index; CI, confidence interval; Dapa, dapagliflozin; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; N, number of subjects in the full analysis set; NR, not reported; s.d., standard deviation; SBP, seated systolic blood pressure; X, number of responders. Measurements of HbA1c and FPG were excluding data after rescue. Measurements of body weight were including data after rescue. *****Significant p value: <0.05: Dunnett's method was applied to control for type I error for the multiple comparisons of dapagliflozin with placebo for the primary endpoint, and hierarchical closed testing was applied to control for type I errors across the primary and secondary endpoints. For exploratory variables, nominal p values were reported for comparisons, although the statistical significance of the result could not be concluded.			

Source: Kaku et al., 2014.[28]

3.4.4 Summary of safety outcomes of relevance

A summary of the AE outcomes from the RCT of dapagliflozin monotherapy in Japanese patients is presented in Table 3.11.[28]

Table 3.11: Summary of adverse events at 24 weeks

	Placebo	Dapa 10mg
n	87	88
AEs		
At least one AE	51.7%	64.8%
At least one SAE	1 (1.1)[a]	1 (1.1)[a]
Discontinuation for AE	5.7%	8.0%
Most common AEs by Preferred Term ≥4%		
Nasopharyngitis	9 (10.3)	15 (17.0)
Dental caries	1 (1.1)	4 (4.5)
Pollakiuria	1 (1.1)	4 (4.5)
Renal impairment	3 (3.4)	4 (4.5)
Hypertension	5 (5.7)	1 (1.1)
Events by special interest category		
Hypoglycaemia	0	2 (2.3)[b]
AEs of UTIs	2 (2.3)	2 (2.3)
AEs of genital infections	1 (1.1)	2 (2.3)
Adverse evebt; Dapa, dapagliflozin; SAE, serious adverse event; UTI, urinary tract infection Data are n (%) or % The arms also included 5 mg dapagliflozin once daily, which are not included in this submission because the recommended dose for normal clinical practice is 10 mg dapagliflozin once daily.[1]		

3.4.5 Study MB102-054: Dapagliflozin as monotherapy vs. placebo in Asian populations

Summary for Study MB102-054

Study design (Table 3.12)

- Study MB102-054 is a 24 week phase 3 RCT evaluating the efficacy and safety of Dapagliflozin 10 mg as monotherapy compared to placebo in Asian populations with T2DM inadequately controlled by diet and exercise[31]

Efficacy (
Table 3.13)

- Dapagliflozin 10 mg demonstrated clinically and statistically significant improvements in HbA1c levels after 24 weeks of treatment compared with placebo,
  - The adjusted mean change from baseline to week 24 in HbA1c was significantly greater with dapagliflozin 10mg (-1.11%) than with placebo (-0.29%; P<0.0001)
  - Among patients with higher mean baseline HbA1c values (≥9%), the mean changes from baseline in the dapagliflozin 10 mg group was -1.78% vs –0.46% with placebo
  - With dapagliflozin 10 mg 49.8% achieved a therapeutic response of HbA1c <7.0% compared with 21.3% of those who received placebo

- Dapagliflozin reduced body weight
  - Dapagliflozin 10 mg significantly reduced body weight compared to placebo at 24 weeks: -2.25 kg vs -0.27 kg; P<0.0001

- Dapagliflozin patients showed a decrease in mean seated systolic blood pressure at 24 weeks: -2.3 mmHg for dapagliflozin 10 mg and 0.8 mmHg for placebo

Safety (Table 3.14)

- Dapagliflozin 10 mg was well-tolerated over 24 weeks
  - AEs and SAEs were balanced across treatment groups
  - No major episodes of hypoglycaemia were reported and no patient discontinued the study due to hypoglycaemia
  - Few patients experienced UTIs or genital infections
    - All reported events were of mild or moderate intensity and responded to standard treatment
    - Proportions of patients with UTIs or genital infections were higher in the dapagliflozin group than the placebo group

3.4.6 Study design and patient population

The study design and characteristics for the 24 week RCT of dapagliflozin monotherapy in Asian patients is presented in Table 3.12.[31]

Table 3.12: Study design characteristics

Study MB102-054 (NCT01095653**)**	
Location	• 40 sites in Asia (26 in China, 5 each in Korea and Taiwan, and 4 in India)
Design	• Randomised, double-blind, placebo- controlled, parallel-group, phase 3 study
Duration of study	• 24-week double-blind treatment period, and a 28-day follow-up period
Patient population	• Drug naïve[a] adults ≥18 years with inadequately controlled T2DM[b]
Intervention(s) (n) and comparator(s) (n)	• Dapagliflozin 10 mg (n=133)[c] • Placebo (n=132)
Primary endpoint	• Change in mean HbA1c from baseline to week 24
Secondary endpoint	• Change from baseline at week 24 in FPG • Proportion of patients achieving a therapeutic glycaemic response (HbA1c <7%) • HbA1c for patients with baseline HbA1c ≥9% • Change from baseline at week 24 in total body weight • Change from baseline in 2-hour PPG (after a liquid meal challenge) at week 24
Safety	• AEs and SAEs, discontinuations due to AEs, laboratory tests, changes in vital signs, hypoglycaemia, and other AEs of special interest
Analyses	• Efficacy was evaluated in patients randomised to treatment who received at least 1 dose of double-blind study medication and had both a baseline and postbaseline measurement • Primary and most secondary efficacy analyses were performed using an ANCOVA with treatment group as a fixed effect and the baseline value as a covariate, using LOCF • The proportion of patients achieving HbA1c levels <7.0% was analysed by logistic regression • Safety was evaluated in patients who received at least 1 dose of double-blind study medication
Publication	• Ji, L., J. Ma, H. Li, T. A. Mansfield, L. T'Joen C, N. Iqbal, A. Ptaszynska and J. F. List. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther 2014; 36(1): 84-100 e109.[31]

AEs, adverse events; ANCOVA, analysis of covariance; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; LOCF, last observation carried forward; PPG, postprandial glucose; SAEs, serious adverse events; T2DM, type 2 diabetes

[a] Never received prescription medication, including Chinese traditional medicines for diabetes, or have received prescription medication for diabetes for <24 weeks since original diagnosis

[b] Defined as HbA1c levels ≥7.5% and ≤10.5% (≥58 and ≤91 mmol/mol) at the enrolment visit and ≥7.0% and ≤10.5% (≥53 and ≤91 mmol/mol) at the lead-in day -14 visit

[c] The arms also included 5 mg dapagliflozin (n=128) administered once daily which is not included in this submission because the recommended dose used in normal clinical practise is 10 mg dapagliflozin once daily[1]

3.4.7 Summary of efficacy outcomes of relevance

The main results for the RCT of dapagliflozin monotherapy in Asian patients are presented in Table 3.13.[31]

Table 3.13: Summary of the key outcome variables at 24 weeks

		Placebo (n=132)	**Dapa 10mg (n=133)**
HbA1c (%): Primary endpoint			
Week 24 (LOCF)	Baseline mean	8.33	8.28
	Adjusted mean change from baseline (95% CI)	-0.29 (-0.43, -0.16)	-1.11 (-1.24, -098)
	Difference vs. placebo (95% CI)	-0.82 (-1.01, -0.63)	
	P-value for difference vs. placebo	< 0.0001*	
Total body weight (kg): Secondary endpoint			

		Placebo (n=132)	Dapa 10mg (n=133)
Week 24 (LOCF)	Baseline mean	72.18	70.76
	Adjusted mean change from baseline (95% CI)	-0.27 (-0.72, 0.18)	-2.25 (-2.70, -1.80)
	Difference vs. placebo (95% CI)	-1.98 (-2.62 to -1.34)	
	P-value for difference vs. placebo	< 0.0001**	
FPG (mg/dL): Secondary endpoint			
Week 24 (LOCF)	Baseline mean	166.6	161.8
	Adjusted mean change from baseline (95% CI)	2.5 (-1.9, 6.9)	-31.6 (-36.1, -27.2)
	Difference vs. placebo (95% CI)	-34.2 (-40.4, -27.9) [-1.90 mmol/L (2.24, 1.55)]	
	P-value for difference vs. placebo	< 0.0001**	
Subjects with HbA1c <7% in patients: Secondary endpoint			
	Percent adjusted (95% CI)	21.3 (14.8, 27.8)	49.8 (41.9, 57.7)
	Difference vs. placebo (95% CI)	28.5 (18.6, 38.3)	
	P-value for difference vs. placebo	< 0.0001**	
HbA1c for patients with baseline HbA1c ≥9% (%): Secondary endpoint			
Week 24 (LOCF)	Baseline mean	9.69	9.54
	Adjusted mean change from baseline (95% CI)	–0.46	-1.78
SBP (mmHg): Safety			
Week 24	Baseline mean (SD)	123.5 (14.7)	123.5 (14.7)
	Adjusted mean change from baseline (SE)	0.8 (1.2)	-2.3 (1.1)

CI, confidence interval; Dapa, dapagliflozin; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; SBP, seated systolic blood pressure; SD, standard deviation

Analyses exclude data after rescue therapy, except SBP (including data after rescue)

* P< 0.0001 at α = 0.027 applying Dunnett's adjustment

** P< 0.0001 after sequential testing procedure at α = 0.05

3.4.8 Summary of safety outcomes of relevance

The main safety results for the RCT of dapagliflozin monotherapy in Asian patients are presented in Table 3.14.[31]

Table 3.14: Summary of adverse events at 24 weeks

	Placebo	Dapa 10mg
n	132	70
AEs		
At least one AE	84 (63.6)	8 1 (60.9)
At least one SAE	2 (1.5)	4 (3.0)
Discontinuation for AE	1(0.8)	3(2.3)
Most common AEs by Preferred Term ≥3%		
Nasopharyngitis	5 (3.8)	4 (3.0)
UTI	4 (3.0)	5 (3.8)
Events by special interest category		
Hypoglycaemia	2 (1.5)	1(0.8)
AEs of UTIs	4 (3.0)	7(5.3)
AEs of genital infections	1 (0.8)	6(4.5)
Renal impairment	2 (1.5)	3 (2.3)
Malignancy	0	0[a]

Adverse event; Dapa, dapagliflozin; SAE, serious adverse event; UTI, urinary tract infection

Data are n (%) or %

The arms also included 5 mg dapagliflozin once daily, which are not included here because the recommended dose for normal clinical practise is 10 mg dapagliflozin once daily [1]

[a] An SAE of pancreatic carcinoma was observed in 1 patient in the dapagliflozin 5 mg group

3.5 Discussion and conclusions

Using a set of criteria to assess bias in RCTs study quality all three studies reported above and included in the NMA (the pivotal, Phase 3, 102 week MB102-013 study, and the two phase 3 studies in Asian populations) can be considered to be good quality (See Appendix 8.4). These phase 3 RCTs had sufficient power to detect differences between treatment arms. Blinding was conducted adequately, and continued in the extension phase i.e. double-blind methodology continued in the 102-week extension period in Study MB102-013. Baseline demographic characteristics were comparable between study arms. All end-points were calculated using ITT analyses, which provided robust results for both efficacy and safety.

Clinically relevant reductions in HbA1c levels, FPG and body weight were demonstrated across all three studies in treatment-naive patients treated with dapagliflozin compared to placebo. Achieving early effective glycaemic control is often challenging, especially when metformin is contraindicated or not tolerated; alternatives such as a SU, repaglinide or a TZD may be unsuitable owing to the risk of either hypoglycaemia and/or weight gain. The studies show that dapagliflozin 10 mg is well placed as an alternative for monotherapy when metformin is contraindicated or not tolerated, offering short-term and durable reductions in HbA1c level with a low risk of hypoglycaemia and with the added benefits of weight loss and reductions in systolic and diastolic blood pressure.

The main limitations of the evidence base for dapagliflozin in monotherapy include:

- In study MB102-013 at 24 weeks there was a large placebo effect out of line with other evidence for dapagliflozin used in dual or triple therapy settings (impacting both HbA1c and weight). The effect was considered to be due to an impact of diet and exercise counselling on motivated patients with newly diagnosed diabetes in a clinical trial setting (see section 4.2.4).[27]

However, reductions in weight and HbA1c with dapagliflozin 10 mg were statistically significantly greater compared to placebo+low dose metformin at week 102,[13] which demonstrates that improvements in glycaemic control and weight reduction are maintained over time with dapagliflozin, and are statistically significant versus an active comparator

- For study MB102-013 over the long-term period (102 weeks) a proportion of participants discontinued or received rescue therapy because of a failure to maintain prespecified glycaemic targets by 102 weeks, although this occurred less frequently in the dapagliflozin 10 mg group (35%) than placebo+low dose metformin (44%).[13] Regulatory authorities stipulate that placebo-controlled randomised trials should give participants rescue therapy according to a predefined algorithm. Given the progressive nature of T2DM, it is therefore not uncommon to observe substantial rates of rescue therapy in diabetes trials.[38] However, this need to allow for rescue therapy may complicate the interpretation of the analysis. In the studies presented here, the analysis of efficacy excluding data after the initiation of rescue therapy was used, enabling the efficacy of dapagliflozin to be assessed without the confounding effect of additional glucose-lowering rescue therapy; although this may have limited the numbers of participants available for analysis, especially as time progresses

- Two of the dapagliflozin monotherapy studies were conducted in Asian populations.[28,31] The Asian populations with T2DM may differ to non-Asian populations due to ethnic differences in PPG regulation,[39] and a lower average BMI of Asian versus non-Asian patients, restricting their generalisability to patients in England and Wales.[40] Despite these potential differences between Asian and Caucasian populations, these studies confirmed the efficacy of dapagliflozin as monotherapy with regards to reductions in HbA1c, weight and SBP/DBP, together with its acceptable safety and tolerability profile

The Asian studies were included in the NMA as a number of studies across drug classes are wholly in Asian populations, hence this data enhanced the amount of evidence available for the NMA. The impact of removing exclusively Asian studies was explored in sensitivity analysis, and was found to not have a large impact on the results of the indirect comparisons (see Section 4).

The occurrence of UTIs and genital infections, which is more common in people with T2DM than in those without diabetes,[41] is increased with the SGLT2 class.[42] However, in the monotherapy studies presented here, the majority were single episodes, and all were of mild or moderate intensity and responded to standard management. Furthermore in the long-term study MB102-013 most events occurred during the first 6 months of dapagliflozin therapy (n=4 UTIs and n=9 genital infections in the dapagliflozin 10 mg group at 24 weeks; n=2 UTIs and n=2 genital infections from 24-102 weeks.[13,27]

The frequency of hypoglycaemia was low and there were no major episodes; such findings are consistent with other trials assessing dapagliflozin in combination with other OADs.[29,30] In contrast to agents dependent on insulin secretion or action, which are known to be associated with hypoglycaemia, the mechanism of action of dapagliflozin is largely dependent on filtered glucose load, not insulin, which confers a low intrinsic propensity for hypoglycaemia.[43,44]

Key conclusions from the dapagliflozin clinical evidence:

- The clinical evidence in monotherapy is of good quality and has shown both short term (24 weeks) and longer term (up to 2 years) durable reductions in HbA1c levels, weight and blood pressure, and with a low intrinsic risk for hypoglycaemia.

- This is consistent with evidence from pooled analyses of dapagliflozin clinical trials, also including studies in other indications, showing that the benefits and tolerability of dapagliflozin as monotherapy are consistent with findings from other phase 3 RCTs for dapagliflozin as add-on therapy.

4. Systematic review and network meta-analysis

Systematic Search (Section 4.1)

- A systematic review was conducted to identify all RCTs that investigated OADs as monotherapy for the treatment of T2DM in adults with inadequate glycaemic control through diet and exercise alone including the following drug classes: SGLT2s, DPP4s, TZD (only pioglitazone), SUs, and repaglinide

- Most OAD monotherapy trials include treatment naive patients. Therefore in order to generate sufficient evidence for the NMA the patient population included were patients who were drug treatment naïve. It was assumed that this evidence is generalisable the NICE scope population and to a patient population with intolerance or contraindicated to metformin (which represents the specific licensed indications of dapagliflozin, canagliflozin and empagliflozin[1,7,8])

- 32 RCTs were identified for inclusion in the NMA covering the following drug classes: SGLT2s, DPP4s, TZD and SUs. There were no studies that met NMA inclusion/exclusion criteria for the meglitinide class (i.e. repaglinide); however it is not considered a key comparator due to low use in current clinical practice

NMA methods (Section 4.2)

- Outcomes included: change in HbA1c from baseline, change in body weight from baseline, change in systolic blood pressure from baseline, proportion of patients experiencing hypoglycaemia; all outcomes were assessed at 24 (±6) week

- Due to limitations in the monotherapy evidence, and given the expectation of comparable efficacy and safety between SGLT2s, individual SGLT2 treatments were pooled as a class rather than compared as individual therapies

NMA results (Section 4.3)

- All treatment classes had statistically significant reductions in HbA1c from baseline compared to placebo. There were no statistically significant differences between the SGLT2 and DPP4, TZD and SU comparators

- SGLT2s were associated with a statistically significant reduction in mean body weight from baseline compared to placebo (mean difference = -2.06 kg), whereas all other treatment classes were associated with weight gain (0.63 kg, 0.83 kg and 3.37 kg for DPP4, SU and TZDs respectively). SGLT2s were associated with a statistically significant reduction in mean body weight vs. DPP4s, TZDs and SUs of 2.7 kg, 5.4 kg and 2.9 kg respectively

- SGLT2s were associated with a greater mean reduction in systolic blood pressure compared to all comparator classes, with a statistically significant difference relative to DPP4s, and TZDs (mean difference = -4.25 mmHg, and -4.45 mmHg respectively), and a numerical difference of -5.12 mmHg compared to SUs

- SGLT2s had a similar likelihood of hypoglycaemic events as placebo and a statistically significant lower likelihood relative to SU (Odds Ratio for ≥1 hypoglycaemic event of 0.18)

- The results were not highly sensitive to baseline HbA1c adjustment, and exclusion of 9 RCTs

conducted in only Asian populations

Limitations and conclusions (Section 4.4 and 4.5)

- Limitations included limited data for SGLT2s to enable robust and meaningful individual SGLT2 comparisons, and an unusually high placebo effect in the pivotal dapagliflozin study, thought due to the impact of diet/exercise counselling provided without active drug therapy on motivated patients with newly diagnosed diabetes

- In addition, it was only possible to perform robust NMA at 24 weeks follow-up due to limited comparable data over longer follow-up durations. As a consequence SU HbA1c efficacy is likely to have been overestimated as the SUs tend to be associated with good short term efficacy that wanes over time, and relatively rare hypoglycaemic events are likely to be underestimated over short term follow-up

- Due to inconsistency in reporting, and limited evidence available, it was not possible to analyse, in an NMA, some of the outcomes within the NICE scope (mortality; complications of diabetes; BMI [weight was more consistently reported]; change in CV risk factors; adverse events; and HRQoL). Although not meta-analysed, UTIs and genital infections have been included in the economic model through calculation of a weighted pooled average of the AE incidence data (Section 5.6)

- In conclusion, despite limitations in the NMA, the SGLT2s have comparable HbA1C reduction efficacy relative to all other classes, and appear to have greater effectiveness compared to pioglitazone, SUs and DPP4s in weight reduction, and are associated with less hypoglycaemia risk than SUs

4.1 Systematic Review

4.1.1 Search strategy and sources

As there was no direct evidence for dapagliflozin or any other SGLT2 versus comparators in the NICE scope (see Table 1.1), systematic searches and a Network Meta-analysis (NMA) were conducted in order to address the following research question:

What is the relative efficacy and safety of dapagliflozin 10 mg and/or SGLT2s as a class as monotherapy compared to other classes of anti-diabetic agent for the treatment of T2DM in adults with inadequate glycaemic control through diet and exercise alone?

An original systematic literature search was performed from database inception to June 2012, as well as abstracts from selected 2010 and 2011 conference proceedings and clinical trial registries. The systematic literature search was updated using the original search strategy which was run from June 2012 to March 2015. Additional comparators were included in the systematic review update; original search strings were run from database inception to March 2015 to include: canagliflozin, empagliflozin, alogliptin, tolbutamide, and gliclazide modified release. The following databases were searched in the original and update searches using the OVID platform for the electronic databases:

- CENTRAL (Cochrane Central Register of Controlled Trials)
- Medline and Medline in Process: 1946 to March 2015

- Embase: 1980 to March 2015

Further details on the electronic databases search strategy and the search terms used are provided in Appendix 8.2. In addition, relevant conference proceedings were searched (see Appendix 8.2). However, due to limitations in level of detail from conference abstracts for data extraction only published studies were included in the NMA, so the outputs of the conference abstract and clinical trial search were not included. This was also the reason the update search and review did not include the same additional sources, and focussed instead on the electronic database search.

4.1.2 Study selection

The inclusion and exclusion criteria for studies identified from the search are provided in Table 4.1.

Table 4.1: Summary of inclusion/exclusion criteria (PICOS framework)

Inclusion criteria	
Population	Adults (≥ 18 years of age) with T2DM for whom diet and exercise do not provide adequate glycaemic control

Interventions (drug class and individual drugs covered within each class)	• Sodium glucose transporter 2 inhibitors
	  ○ dapagliflozin 10mg
	  ○ canagliflozin (100mg or 300mg)
	  ○ empagliflozin 10mg and 25mg
	• Dipeptidyl peptidase 4 inhibitors
	  ○ saxagliptin
	  ○ sitagliptin 100mg
	  ○ linagliptin 5mg
	  ○ vildagliptin
	  ○ alogliptin
	• Sulfonylureas (SUs)
	  ○ glimepiride
	  ○ glipizide
	  ○ glyburide (also known as glibenclamide)
	  ○ gliclazide (including gliclazide modified release)
	  ○ tolbutamide
	• Meglitinides
	  ○ repaglinide
	• Thiazolidinedione (TZD)
	  • pioglitazone

Comparators	• Placebo • Any active treatment
Study design	RCTs of at least 12 weeks duration
Outcomes **(at least one of)**	Efficacy outcomes - included in NMA: • Change in HbA1c from baseline • Change in weight from baseline • Change in systolic blood pressure from baseline Efficacy outcomes – not included in NMA*: • Proportion of patients achieving glycaemic control • Change in body mass index from baseline • Change in high-density lipoprotein cholesterol from baseline

	• Change in low-density lipoprotein cholesterol from baseline • Change in total cholesterol from baseline • Change in triglycerides from baseline Safety outcomes - included in NMA: • Proportion of patients with ≥ 1 hypoglycaemia event (definition as provided by study authors) Safety outcomes – not included in NMA*: • Number of hypoglycaemic events (including definition as provided by study authors) • Proportion of patients who discontinued treatment due to lack of efficacy • Proportion of patients who discontinued treatment due to an adverse event • Proportion of patients who reported an adverse event (overall, severe) • Proportion of patients who experienced urinary tract infections, genital infections, malignancies, renal complications, or eye complications Other - not included in NMA*: • Mortality • HRQoL
Exclusion criteria	
Population	• Studies that limited enrolment to a specific sub-population where the sub-population was not generalisable to the population of diabetic patients • Only metformin-intolerant population**
Study design	Pooled analyses of RCTs
*These outcomes were included in the NICE scope. However, very few studies included in the NMA contained consistent data on change in BMI, other CV risk factors, the safety/AE outcomes, hence it was not possible to meta-analyse these outcomes. There were also no studies reporting mortality, HRQoL outcomes in a consistent way to include in the NMA. ** Trials with metformin-intolerant populations were excluded to ensure comparison between similar trial designs and similar patient populations: only one trial was excluded for this reason	

RCTs that reported efficacy and safety of at least one of the interventions of interest for the treatment of T2DM in adults who had inadequate glycaemic control on diet and exercise alone, and reported at least one outcome of interest, were suitable for selection for review. As most OAD monotherapy trials include treatment naive patients, the patient population included patients who were drug treatment naïve in order to generate sufficient evidence for the NMA. It was assumed that this evidence is generalisable to the patient population in scope with intolerance or contraindicated to metformin (which represents the specific licensed indications of dapagliflozin, canagliflozin and empagliflozin).[1,7,8]

A two-step selection process for study selection was employed. Two reviewers independently determined whether studies meet inclusion criteria. Reasons for rejections and exclusions of studies were recorded. Discrepancies between reviewers were resolved by consensus - a third reviewer adjudicated unresolved disputes; the judgment of the third reviewer was considered final.

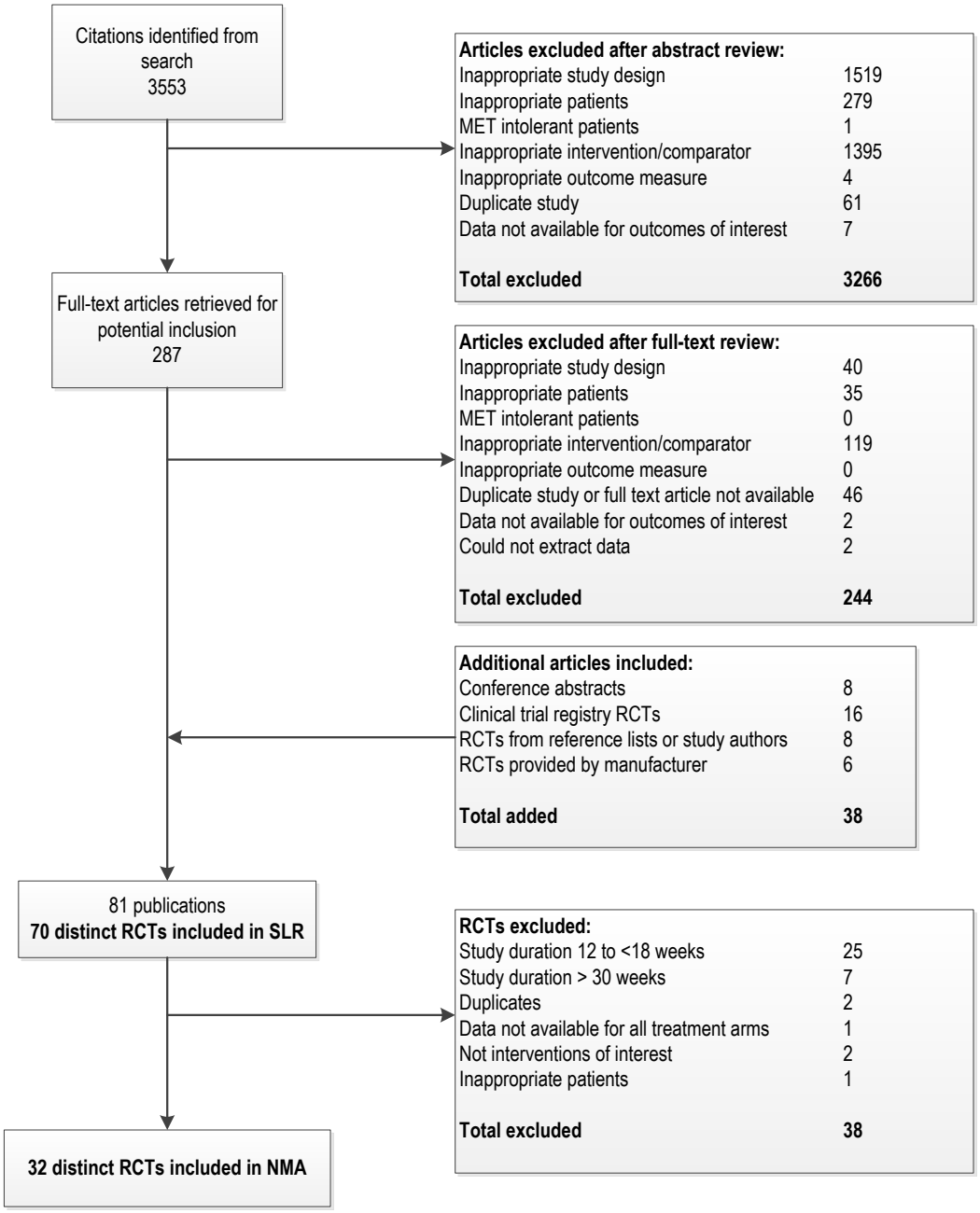
4.1.3 RCTs identified

A flow diagram detailing the selection of studies for review and inclusion in the NMA from the systematic searches conducted is provided in Figure 4.1. In total 32 RCTs that met inclusion criteria were identified as eligible for the NMAs of key outcomes in monotherapy.

Although the NMA aimed to compare drug classes over a longer duration than 24 weeks (>50 weeks), limited data were identified. There is unpublished RCT evidence in monotherapy for

dapagliflozin up to 102 weeks (although compared to metformin),[33] published 52 weeks for canagliflozin (although compared to metformin),[45] and up to 78 weeks as a randomised open label extension,[27] and 76 weeks RCT evidence (available in abstract form) for empagliflozin.[46] The systematic review only identified only a further three studies with a duration up to 54 weeks (for Gliclazide modified release vs. pioglitazone,[47] sitagliptin vs. pioglitazone[48] and alogliptin vs. glipizide.[49] Subsequently, the decision was made to include evidence only from studies with data for a 24 weeks (± 6 weeks) follow-up timepoint, for which there was a relatively large body of evidence. Where reported, data for 24 weeks (±6 weeks) were included from studies of 52 weeks or more. In total there were 21 studies excluded due to duration below 18 weeks and 12 with duration >30 weeks (see Appendix 8.3 for list of references).

Figure 4.1: Flow diagram summarising study selection process for the NMA covering the original and updated systematic search



*Exclusion criteria from the systematic review related to studies shorter than 18 weeks. However, there were considered insufficient studies with long term data for a consistent time point to enable robust NMA for durations >30 weeks, hence longer duration studies were excluded (unless they also reported 18-30 week follow-up data).

4.2 The Network Meta-Analyses

4.2.1 Overview of studies in the NMA

The following specific efficacy and safety outcomes were selected for the NMAs:

- **Efficacy endpoints**
  - Mean change in HbA1c from baseline
  - Mean change in weight from baseline
  - Mean change in SBP from baseline

- **Safety outcomes**
  - Proportion of patients experiencing hypoglycaemia

These outcomes were chosen for the following reasons:

a) Priority and relevance of the outcome, with regards to NICE scope and in particular these represent key outcomes included in the economic model the SGLT2s (see Section 5).
b) Availability of data (availability of studies reporting that endpoint for each pair of comparators). Data was extracted for the endpoints of change from baseline in BMI, and for a range of lipid outcomes (change from baseline in HDL, LDL, total cholesterol, and in triglycerides), but there was insufficient data for meta-analysis (1 RCT for BMI, 5 RCTs for each of HDL, LDL and triglycerides outcomes, and 3 for total cholesterol).
c) The endpoint is clearly defined.

For efficacy outcomes, the preferred estimate was based on an intention-to-treat population (with LOCF); however, where data were unavailable, estimates were extracted as reported by the author. For safety outcomes, the population of interest was the safety population, typically defined as subjects receiving at least one dose of study drug. Data for specific adverse events (AEs) apart from hypoglycaemia were not analysed in the NMA due primarily to variations in reporting, but data on incidence of urinary tract infections (UTIs) and genital infections (GIs), and discontinuations due to adverse events were extracted from the studies included in the NMA for use in the economic analysis.

As a general rule only published RCT evidence was included. The exceptions were two unpublished studies for saxagliptin. As AZ are the manufacturer of saxagliptin, the Clinical Study Reports (CSRs) were available, and hence were used for data extraction in order to include this evidence in the NMA (Table 8.13, Appendix 8.4).[50,51]

4.2.2 Study characteristics

Study design and key patient characteristics of the 32 RCTs included in the NMA are reported in Table 8.16 in Appendix 8.7. RCTs were conducted between 1994 and 2014, and about half (n=17) were multinational trials. Nine RCTs were conducted among only Asian subjects.[28,31,50-52,56,65,68,69] Study duration ranged from 18 to 102 weeks, but only data reported for 18 to 30 weeks were included in the NMA.

Baseline participant characteristics from all included RCTs are presented in Appendix 8.7. Baseline mean age was similar across studies, with all treatment arms ranging between 48-60 years, with the exception of one RCT which had a mean age of 70 years.[49] All except one RCT had a mean baseline HbA1c within the range of 7.45% to 9.1%; the remaining RCT, by Aronoff *et al*., enrolled subjects whose mean baseline HbA1c was between 10.2 and 10.4%, hence may be considered an outlier. Baseline weight tended to be greater than 70kg (ranging up to 94.2 kg), with the exception of eight of the RCTs that were conducted in Asian countries,[28,31,50-52,56,65,68,69] (weight ranged from 64.8 to 72kg). The overall average duration of diabetes among patients ranged from less than one year to just over six years. There was some variation in baseline BMI across studies.

4.2.3 Study quality

Study quality has been assessed using a set of criteria for bias: blinding of patients, clinicians and researchers, adequate generation of randomisation sequence, adequate concealment of randomisation, adequate reporting of patient baseline characteristics, adequate reporting of study design, and similar groups in terms of prognostic factors.

Overall, the quality of studies included in the NMAs was reasonable with a low risk of bias. Most studies were double blinded, although details on randomisation process and allocation concealment were not always reported. All studies were industry sponsored. Appendix 8.5 provides an assessment of bias for the three dapagliflozin studies and the studies for the other SGLT2s included in the NMA.

4.2.4 The networks for each outcome

4.2.4.1 Overview

The networks for each outcome comparing SGLT2s to all viable comparator classes are presented in the following sub-sections (i.e. no comparison to meglitinides as no evidence was available).

A decision was taken to perform the NMAs to compare SGLT2s as a class compared to other classes of treatment (vs. DPP4s, SUs and TZDs), rather than comparing dapagliflozin with other individual SGLT2s, or versus other individual DPP4s, SUs or TZDs (although only one TZD is considered – pioglitazone). Grouping agents within a class is relatively common in meta-analyses of anti-diabetes agents, in part due to the large number of available agents and the similarity in efficacy and safety profiles within most drug classes. The reasons for adopting this approach for the submission were as follows:

- The systematic search retrieved limited amounts of evidence for individual SGLT2 drug treatments used in monotherapy for each outcome. Three dapagliflozin studies were identified, although two of these were in Asian patients only[31] (see Appendix 8.7). There were two studies identified for canagliflozin 100mg; only one of these also reports data for canagliflozin 300mg.[45] Only one eligible RCT was identified for empagliflozin, and only 33% of patients in this study were Caucasian[54] (Appendix 8.7).

- The SGLT2s are considered as a group in the draft NICE clinical guidelines for T2DM,[3] and have in previous NICE technology appraisals been considered to have similar efficacy and safety (see Section 4.4 of the empagliflozin TA336 guidance),[11] and this also appears to be the expectation of the Warwick Technology Assessment Team for the MTA (see TAR team protocol section 6 where it is concluded that based on NMA evidence “it is probably unsafe to conclude that any one flozin is best”).[75]

- There were differences in key characteristics for the available studies for dapagliflozin, canagliflozin and empagliflozin. Patients in the pivotal dapagliflozin study in monotherapy have significantly higher baseline weight and BMI (94 kg and 33.6 BMI) compared to the canagliflozin and empagliflozin studies (ranging from 69-88 kg, and 25-32 BMI) (Appendix 8,7). There was a relatively low proportion of male patients in the pivotal dapagliflozin RCT and one of the canagliflozin studies[27,45] (Appendix 8.7). In addition, there is variation in duration of diabetes across the dapagliflozin studies of 0.5 – 4.9 years, whereas the range is narrower for the canagliflozin studies (4.2 – 5.9 years) and not specifically reported for empagliflozin, although patients ranged from ≤1 year to >10 years (Appendix 8.7).

The limited evidence combined with variation in the patient characteristics across SGLT2 studies means that a meaningful comparison of the individual SGLT2 treatments is not possible, and would be associated with a substantial risk of bias.

There are additional concerns over a differential placebo effect across the dapagliflozin and comparator SGLT2 studies, as previously discussed (Section 3.5), which is out of line with other evidence for dapagliflozin used in dual or triple therapy settings. Table 4.4 below illustrates that for key outcomes of change in HbA1c and change in body weight from baseline, the pivotal study[27] for dapagliflozin had a much higher reduction in HbA1c and body weight in the placebo arms than in the canagliflozin and empagliflozin trial placebo arms.

The particularly large placebo effect for body weight in the Ferrannini study was suggested by the authors to probably be due to the impact of diet/exercise counselling provided alone without active drug therapy on motivated patients with newly diagnosed diabetes (hence, would not have received diet/exercise counselling previously) in a clinical trial setting. Counselling was conducted according to American Diabetes Association recommendations.[27] In contrast, in one trial for canagliflozin patients continued diet and exercise unchanged from before the study[52], while the second trial did not report the diet and excercise regimen[53]; the empagliflozin trial included diet and exercise councelling to local recommendations[54]. The duration since diagnosis of diabetes in the Ferrannini study was also much shorter than in the canagliflozin and empagliflozin studies (mean of only 0.5 years compared to 4.2 – 5.9 years across treatment arms in the canagliflozin studies – see Appendix 8.7). Due to the longer mean baseline duration of diabetes in these studies, placebo patients do not appear to be benefitting to the same extent from any possible non-pharmacological intervention.

Table 4.2: Placebo effects for HbA1c and body weight change from baseline from SGLT2 studies included in the NMA

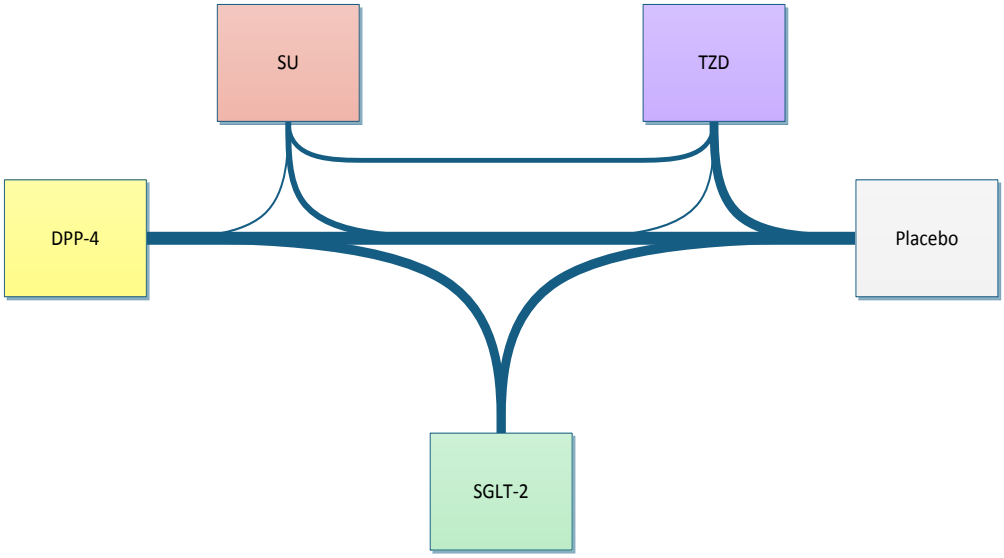
Monotherapy active treatment arm	Study	Placebo baseline HbA1c %	Placebo HbA1c% change	Placebo body weight (kg)	Placebo body weight change (kg)
Dapagliflozin	Ferrannini et al., 2010	7.8	-0.23	88.8	-2.20
	Ji et al., 2014	8.4	-0.29	72.2	-0.27
	Kaku et al., 2014	7.5	-0.06	66.0	-0.84
Canagliflozin	Inagaki et al., 2014	8.0	0.29	68.6	-0.76
	Stenlof et al., 2013	8.0	0.14	87.6	-0.60
Empagliflozin	Roden et al., 2013	7.9	0.08	78.2	-0.33

(see Appendix 8.4 for individual study results)

4.2.4.2 Network diagrams

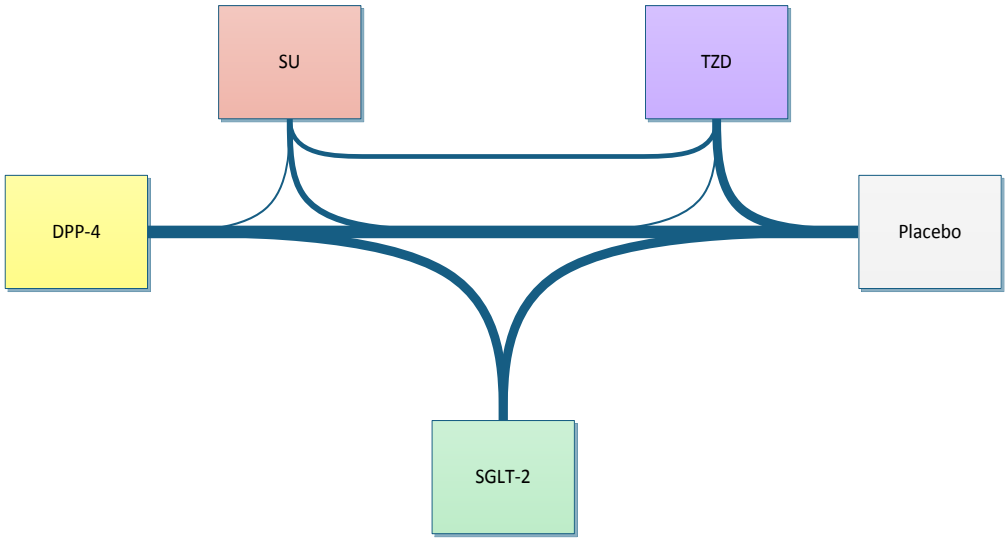
- Figure 4.2 shows the network diagram for mean change from baseline in HbA1c. This is based on data extracted from all 32 RCTs.
- Figure 4.3 shows the network diagram for mean change from baseline in body weight, based on data extracted from 27 RCTs.
- Figure 4.4 shows the network diagram for mean change from baseline in SBP, based on data extracted from 13 RCTs.
- Figure 4.5 shows the network diagram for proportion of patients experiencing one or more hypoglycaemic events, based on data extracted from 24 RCTs.

Figure 4.2: Network diagram for: mean change from baseline in HbA1c*



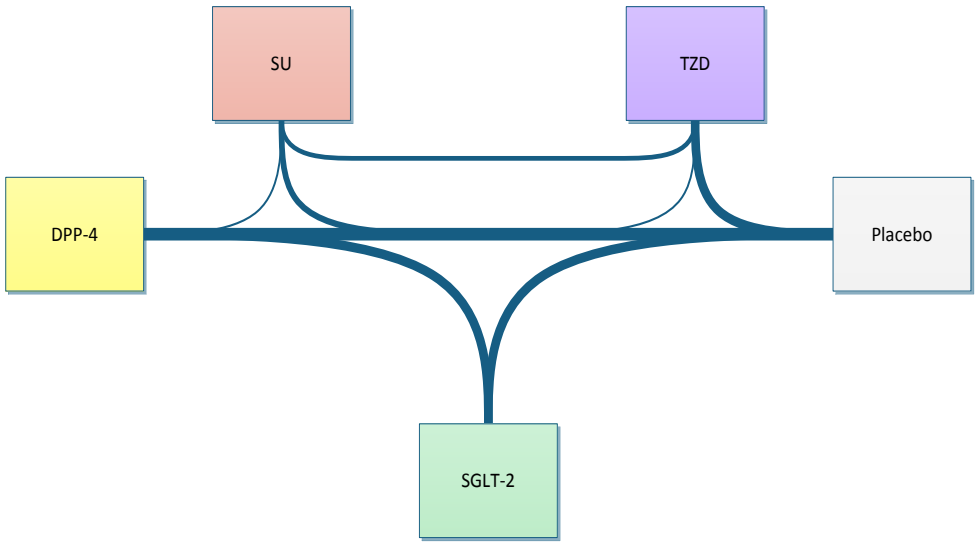
*The thickness of lines connecting treatments in this figure indicates the relative amount of evidence linking the treatments. Treatments are assessed grouped by class.

Figure 4.3: Network diagram for: mean change from baseline in body weight (kg)*



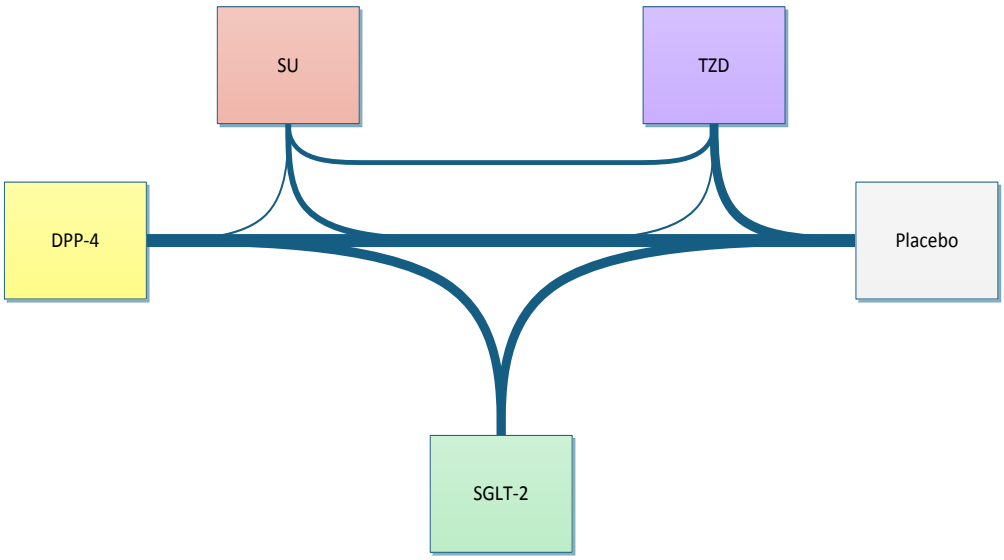
*The thickness of lines connecting treatments in this figure indicates the relative amount of evidence linking the treatments. Treatments are assessed grouped by class.

Figure 4.4: Network diagram for: mean change from baseline in SBP (mmHG)*



*The thickness of lines connecting treatments in this figure indicates the relative amount of evidence linking the treatments. Treatments are assessed grouped by class.

Figure 4.5: Network diagram for: proportion of patients experiencing one or more hypoglycaemic events*



*The thickness of lines connecting treatments in this figure indicates the relative amount of evidence linking the treatments. Treatments are assessed grouped by class.

4.2.5 NMA methods

4.2.5.1 Modelling methods

An NMA can be performed using a fixed effect (FE) approach or a random effects (RE) approach. Guidance suggests that a random effects model should be used when included trials are relatively small (i.e. not mega-trials), and are heterogeneous in terms of patient population and design.[76] 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.[77] In addition, the posterior distribution of the between studies standard deviation was investigated to ensure that it was updated from the prior distribution based on the available evidence. A fixed effect (FE) model was selected over a RE model only if any of the following conditions held: 1) it offered better model fit, based on the Deviance Information Criteria (DIC); 2) the posterior distribution of the between-studies variance is not updated from the prior distribution (i.e. no information was provided by the data).[78]

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.[78] 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. A thin parameter of 10 was used. Convergence was assessed by visualising the histories of the chains, of relevant parameters, against the iteration number; overlapping histories provided an indication of convergence. 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 provided in Appendix 8.6.

The approach to study data extraction and the raw data from each study in the NMA for each outcome is presented in Appendix 8.7. Further details on the data preparation for use in the NMAs are provided in Appendix 8.8.

4.2.5.2 Analysis

The mean change in HbA1c, weight and SBP were analysed using the mean difference scale, and the proportion of subjects with hypoglycaemia was analysed based on an odds ratio.

4.2.5.3 Heterogeneity and consistency testing

Sources of clinical heterogeneity were summarised, and inconsistency between the direct and indirect evidence were evaluated. Statistical heterogeneity was estimated for pairwise comparisons based on the I^2 statistic. Consistency of study results was explored through pairwise meta-analysis of active treatments vs. placebo (HbA1c only).

4.2.5.4 Sensitivity analyses

Sensitivity analysis consisted of reporting the NMA results based on the alternative model to that used in the base case (e.g. fixed effect if random effects used in base case). In addition, the following sensitivity analyses were performed for the key efficacy outcomes of change from baseline in HbA1c, and change from baseline in body weight:

- Adjustment for baseline HbA1c: for this analysis a meta-regression was performed to adjust for baseline HbA1c

- Exclusion of studies containing only Asian patients: in total 9 RCTs were excluded for this analysis.[28,31,50-52,56,65,68,69]

4.3 NMA Results

4.3.1 Overview

4.3.2 HbA1c mean change from baseline

The model fit statistics for the random and fixed effect models for the HbA1c change from baseline outcome are presented in Table 4.3. The random effects (RE) model was selected in the base case over the fixed effect model as the DIC was considerably lower, and the between-studies SD was updated by the data.

Table 4.3: Model fit statistics for HbA1c mean change from baseline outcome

	Random Effects	Fixed effect
Deviance information criterion	-48.024	3.67
Between-study SD, mean (95% CrI)	0.22 (0.14, 0.32)	

Based on an RE model all regimens performed better than placebo at reducing HbA1c levels, and there was no significant difference between the SGLT2s and other classes of drugs in HbA1c change from baseline (Table 4.4).

Table 4.4: Relative effect sizes for mean change in HbA1c (%) in monotherapy – random effects model

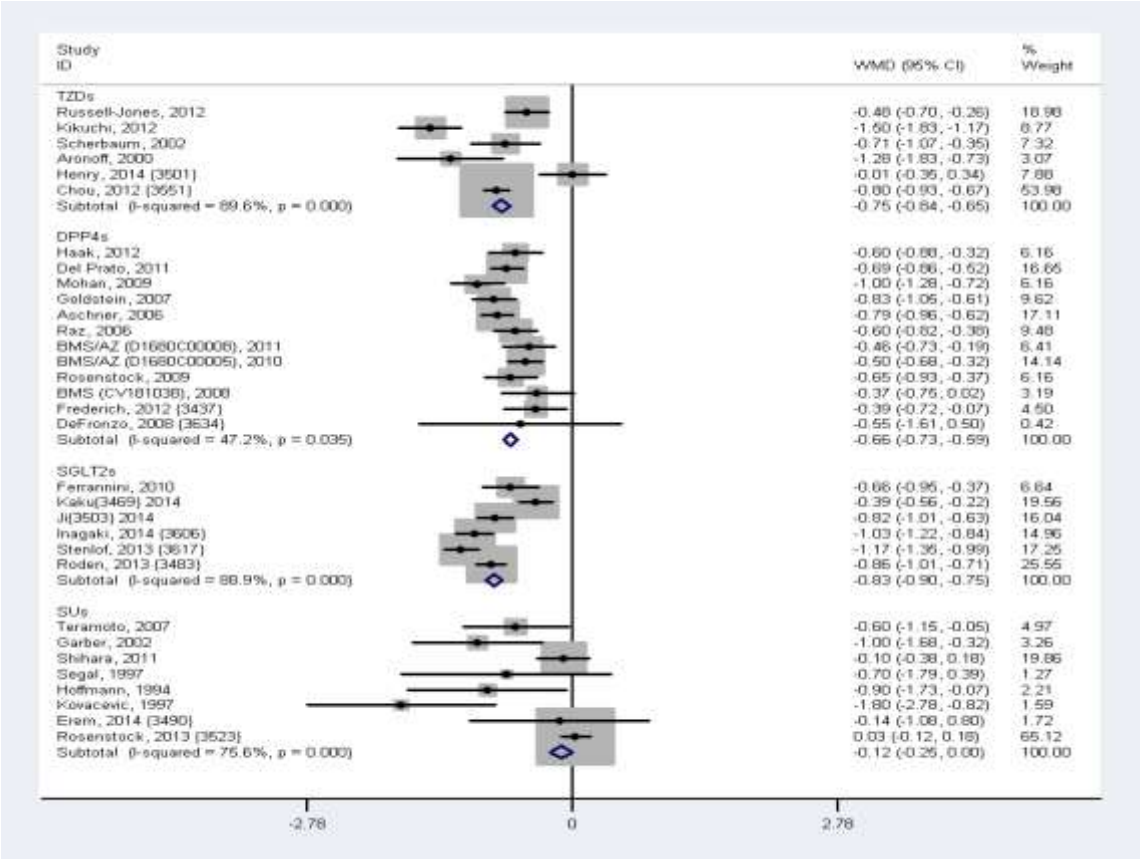
Drug	Comparison vs. placebo	SGLT2 vs. comparators
	Mean difference (95% CrI)	Mean difference (95% CrI)
Placebo (reference treatment)	-	-0.78 (-0.98, -0.59)*
SGLT2s	-0.78 (-0.98, -0.59)*	-
DPP4 inhibitors	-0.68 (-0.81, -0.54)*	-0.11 (-0.34, 0.11)
TZDs	-0.94 (-1.15, -0.73)*	0.15 (-0.13, 0.43)
Sulfonylureas (SU)	-0.99 (-1.28, -0.72)*	0.21 (-0.11, 0.55)

CrI: credible interval; * indicates statistically significant result

There was some heterogeneity in the data: the mean of the posterior distribution of the between study standard deviation (SD) was 0.22.

The forest plots presenting direct pairwise comparisons against placebo for the HbA1c outcome are presented in Figure 4.6, while the caterpillar plot with estimates produced by the NMA is presented in Appendix 8.9. Direct evidence for SUs suggest a more moderate effect relative to placebo, than the estimate obtained through the NMA (-0.12 and -0.98, resplectively) (Table 4.6) [72]. The observed difference in estimates is likely due to the indirect evidence informing the comparison of SUs against placebo, carrying a heavier weight than the direct evidence. Trials informing SUs were less and of smaller size than those for the other classes contributing indirect evidence. Sensitivity analysis results based on the fixed effect model are presented in Appendix 8.10

Figure 4.6: Pairwise meta-analysis of change in HbA1c versus placebo



4.3.3 Body weight (kg) mean change from baseline

The model fit statistics for the random and fixed effect models for the body weight change from baseline outcome are presented in Table 4.5. The random effects (RE) model was selected in the base case over the fixed effect model on the grounds that the mean of the posterior distribution of the between study SD was updated by the data.

Table 4.5: Model fit statistics for weight mean change from baseline outcome

	Random Effects	Fixed effect
Deviance information criterion	80.977	82.538
Between-study SD, mean (95% CrI)	0.27 (0.02, 0.59)	

Based on an RE model, the only class statistically superior to placebo for weight reduction was SGLT2s – all other classes were associated with significant increases in weight relative to placebo. Consequently, the SGLT2s had a statistically significantly favourable weight change relative to DPP4s, TZDs, and SUs (Table 4.6 below).

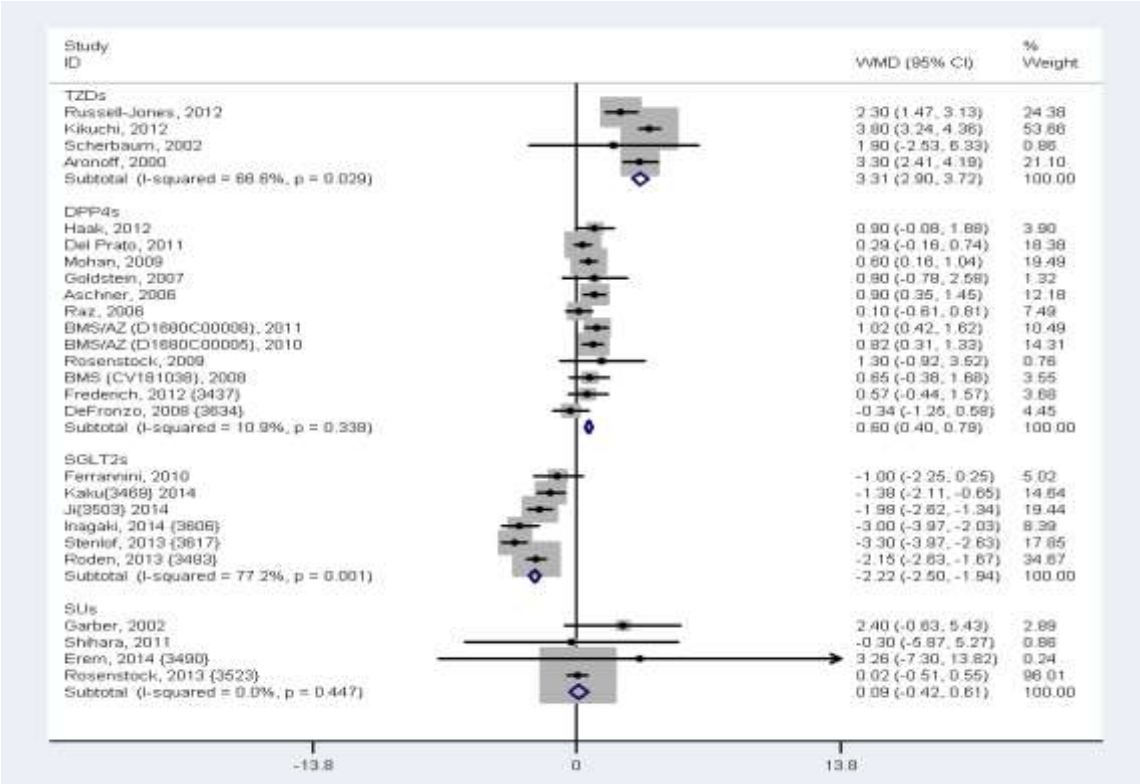
Table 4.6: Relative effect sizes for mean change in body weight in monotherapy – random effects model

Drug	Comparison vs. placebo	SGLT2 vs. comparators
	Mean difference (95% CrI)	Mean difference (95% CrI)
Placebo (reference treatment)	-	-2.06 (-2.44, -1.68)*
SGLT2s	-2.06 (-2.44, -1.68)*	-
DPP4 inhibitors	0.63 (0.37, 0.89)*	-2.69 (-3.12, -2.25)*
TZDs	3.37 (2.79, 3.90)*	-5.43 (-6.07, -4.73)*
Sulphonylureas (SU)	0.83 (0.06, 1.71)*	-2.89 (-3.83, -2.03)*

CrI: credible interval; * indicates statistically significant result

The forest plots presenting direct pairwise comparisons against placebo for the body weight outcome are presented in Figure 4.7, while the caterpillar plot with estimates produced by the NMA is presented in Appendix 8.9. Sensitivity analysis results based on the fixed effect model are presented in Appendix 8.10.

Figure 4.7: Pairwise meta-analysis of change in body weight versus placebo



In terms of assessing heterogeneity the mean of the posterior distribution of the between study standard deviation (SD) was 0.27, showing mild heterogeneity in the data.

4.3.4 SBP mean change from baseline

The model fit statistics for the random and fixed effect models for the SBP change from baseline outcome are presented in Table 4.7. The fixed effect model had a slightly lower DIC than the random effects model; additionally, the CrI of the posterior SD was considerably wide. This could have been due to either not having enough evidence with only 13 studies informing this outcome with which to accurately estimate the between-study SD, or due to heterogeneity in the evidence base that was not accounted by the model. Because of this, the fixed effect (FE) model was selected over the random effects model.

Table 4.7: Model fit statistics for SBP mean change from baseline outcome

	Random Effects	Fixed effect
Deviance information criterion	102.193	100.405
Between-study SD, mean (95% CrI)	0.67 (0.03, 2.02)	

Based on an FE model, Table 4.8 below shows the SGLT2s were superior to placebo in SBP reduction, and statistically superior to DPP4s and TZDs.

Table 4.8: Relative effect sizes for mean change in SBP (mmHg) in monotherapy – fixed effect model

Drug	Comparison vs. placebo	SGLT2 vs. comparators
	Mean difference (95% CrI)	Mean difference (95% CrI)
Placebo (reference treatment)	-	-3.82 (-5.02, -2.62)*
SGLT2s	-3.82 (-5.02, -2.62)*	-
DPP4 inhibitors	0.42 (-0.87, 1.72)	-4.25 (-5.83, -2.67)*
TZDs	0.62 (-1.93, 3.19)	-4.45 (-7.19, -1.74)*
Sulphonylureas (SU)	1.30 (-4.03, 6.54)	-5.12 (-10.47, 0.27)

CrI: credible interval; * indicates statistically significant result

Pairwise plots for the indirect comparisons performed for the SBP outcome are presented in Appendix 8.9, and sensitivity analysis results based on the random effects model are presented in Appendix 8.10.

In terms of assessing heterogeneity the mean of the posterior distribution of the between study standard deviation (SD) was 0.27, showing moderate to high heterogeneity in the data.

4.3.5 Proportion ≥ 1 hypoglycaemic event

The model fit statistics for the random and fixed effect models for the hypoglycaemia outcome are presented in Table 4.9. The fixed effect model had a slightly lower DIC than the random effects model; and the CrI of the posterior SD was considerably wide. Hence, the fixed effect (FE) model was preferred.

Table 4.9: Model fit statistics for proportion of subjects with hypoglycaemia event

	Random Effects	Fixed effect
Deviance information criterion	158.774	157.011
Between-study SD, mean (95% CrI)	0.40 (0.01, 1.14)	

Based on an FE model, only SUs were likely to be associated with a greater likelihood of hypoglycaemic events compared to placebo, although wide credible intervals suggest considerable heterogeneity is likely. There was a statistically significant difference in OR for hypoglycaemia for the SGLT2s versus SUs but not versus other comparators, although the trend was for a lower likelihood of hypoglycaemic events for the SGLT2s (Table 4.10).

Table 4.10: Relative effect sizes for proportion of subjects with hypoglycaemia event in monotherapy – fixed effect model

Drug	Comparison vs. placebo	SGLT2 vs. comparators
	Odds Ratio (95% CrI)	Odds Ratio (95% CrI)
Placebo (reference treatment)	-	0.91 (0.26, 3.02)
SGLT2s	0.91 (0.26, 3.02)	-
DPP4 inhibitors	1.46 (0.81, 2.68)	0.62 (0.17, 2.24)
TZDs	2.22 (0.83, 6.30)	0.41 (0.08, 1.88)
Sulphonylureas (SU)	4.97 (1.77, 15.53)*	0.18 (0.03, 0.89)*

CrI: credible interval; * indicates statistically significant result

Pairwise plots for the indirect comparisons performed for the hypoglycaemia outcome are presented in Appendix 8.9, and sensitivity analysis results based on the random effects model are presented in Appendix 8.10.

In terms of assessing heterogeneity the mean of the posterior distribution of the between study standard deviation (SD) was 0.27, showing mild-moderate heterogeneity in the data.

4.3.6 Sensitivity analysis results

The results for the use of the alternative models to those used in the base case for each outcome are presented in Appendix 8.10. There were only small differences in results showing choice of model is not a major area of sensitivity.

The results of the sensitivity analysis adjusting for HbA1c, and exclusion of studies in Asian only patients are also presented in Appendix 8.10. These analyses show that the results are not highly sensitive to variations in baseline HbA1c across studies, or due to the inclusion or exclusion of Asian studies.

4.4 Limitations of the NMA

The following bullets provide a summary of the main limitations of the NMA. In general, the limitations surround a lack of data identified within the monotherapy setting for T2DM; despite these limitations the analysis of the NMA remains robust, and results are considered valid.

- There is a high placebo effect in particular on body weight reduction (and HbA1c reduction) in the pivotal dapagliflozin monotherapy study (Ferrannini *et al.*) and in one of the Asian studies,[31] which is not seen in other dapagliflozin and SGLT2 studies across the T2DM treatment pathway. This appears to be likely to be related to the short duration since T2DM diagnosis of patients in this study and a motivated placebo group who are receiving an active diet and exercise counselling intervention for the first time (see Section 4.2.4.1 for further discussion).

- There is a lack of direct evidence in the patient population of interest i.e. metformin intolerant population. Hence the NMA was based on monotherapy evidence in a treatment naïve patient population, with the assumption that this generalises to the metformin intolerant population. This has also been recognised in the NICE TAR team protocol for the NMA.[75]

- There is limited evidence for the individual treatments in each treatment class, and the evidence in Caucasian patients is limited for meaningful comparisons between the individual SGLT2s. There is also some variation in patient characteristics between the dapagliflozin (especially the Ferrannini study) and the canagliflozin and empagliflozin RCTs (see Section 4.2.4.1 for further discussion, and Section 5.2).

- The duration of follow-up for the studies in the NMA is only 18-30 weeks, which is relatively short, and is too short a duration for fully assessing safety outcomes. There is some longer term evidence in monotherapy, particularly for dapagliflozin which shows durable efficacy and body weight reduction over two years (see Section 3.3.4). However, there is insufficient evidence across treatment classes to enable a robust NMA for follow-up durations >30 weeks.

- Due to the short follow-up (24 weeks), SU efficacy is likely to be overestimated, and hypoglycaemic events underestimated. SUs tend to have a large initial drop in HbA1c during the first four to six months in trials which is followed by a gradual increase over the longer term; this trajectory is termed a 'J-curve' and has been found for SUs, but less so in other antidiabetic drugs such as dapagliflozin or sitagliptin.[79,80] It is related to SU dose increase in trials until patient has an adverse event to ensure maximal efficacy. In clinical practice SU dose adjustment occurs over a longer period and is not necessarily maximised to the same degree, thus cutting the data at the 24 week point results in an artificially high HbA1c reduction that is unlikely to be replicated in clinical practice.

- There were generally wider CrIs associated with the comparisons versus SU, so higher uncertainty in the comparisons vs. this class of drug

- Caution must also be used in interpreting the hypoglycaemia results due to differences in the definition used across studies (see Appendix 8.7, Table 8.20)

- Due to inconsistent reporting across studies it was not possible to meta-analyse safety outcomes such as individual adverse events, or discontinuation due to AEs. There was also a lack of data reported for meta-analysis of BMI change from baseline, which was one of the outcomes included in the NICE scope

- No data were included in the systematic review for repaglinide, and as such no comparison could be made to the meglitinide class; however as repaglinide is now no longer/very rarely used in clinical practice it is not considered a true comparator to be displaced by SGLT2s.

Despite the limitations the results can be considered to be generalisable to those seen in clinical practice for the SGLT2 class relative to other classes and is consistent with results for other positions in the treatment pathway.[81]

4.5 Conclusions

Key conclusions from the NMA:

- As there was insufficient evidence to compare the individual SGLT2s in this NMA, as anticipated, the SGLT2s were grouped as a class, in line with the NICE scope for the comparator classes.

- SGLT2s are effective at HbA1c reduction compared to placebo, and have comparable HbA1c efficacy relative to all other drug classes.included in the NMA.

- The SGLT2s as a class have greater efficacy than pioglitazone, SUs and DPP4s in weight reduction, and are associated with less hypoglycaemia risk than SUs.

- There is greater uncertainty in the relative efficacy of SGLT2 and SU based on the 95% CrIs from the NMA for HbA1c and weight change.

5. Cost-effectiveness

Economic model and methods (Sections 5.1-5.4)

- The economic analysis performed in this submission is to assess the cost-effectiveness of the SGLT2 class of drugs as a monotherapy in T2DM patients who are not achieving adequate glycaemic control with diet and exercise alone and are intolerant to metformin

- The model uses the same validated economic model structure (stochastic simulation diabetes model) as was used for the previous submission of dapagliflozin to NICE for T2DM (the Cardiff Diabetes model – CDM), updated for the most recent UKPDS risk equations for CV complications of T2DM

- Comparators were DPP4, TZD (only pioglitazone) and SU classes. DPP4 is considered the primary monotherapy likely to be displaced by dapagliflozin, canagliflozin or empagliflozin

- The model accommodates three treatment lines – in the base case baseline HbA1c and treatment switch were set to 7.5% in line with NICE guidelines in T2DM.[2]

Clinical, utility and cost parameters (Sections 5.7-5.10)

- Baseline characteristics and treatment effect/safety parameters for SGLT2 and comparator classes were derived from the NMA.

- Utility and cost estimates for complications were largely derived from the UKPDS, and the utility estimates for weight change from an EQ-5D study used in previous HTA submissions for T2DM (Bagust and Beale)[82]

Results (Section 5.11)

- The base case ICER was estimated for SGLT2 at £5,904 per QALY gained vs. DPP4s, with the ICER below £10k/QALY in all sensitivity analyses, £20k vs. pioglitazone, and £52k vs. SU.

- The sensitivity analysis indicates there is high variability in the ICER for the comparison with SU associated with uncertainty in the relative efficacy of SGLT2 and SU based on the 95% CrIs from the NMA for HbA1c and weight change, and in utility range applied to BMI unit decrease.

- Probabilistic sensitivity analysis indicates a 66%. 51% and 13% probability of SGLT2 being cost-effective at a £20,000/QALY threshold vs. DPP4, TZD and SU respectively.

Conclusions (Section 5.12)

- Compared to the primary comparator of DPP4s, the SGLT2 can be considered highly cost-effective, with an ICER of £6k QALY.

- The incremental QALYs estimated for the SGLT2s and incremental QALY over DPP4s are primarily driven by the weight reduction advantages of these drugs (which are similar between the SGLT2 drugs).

- The ICER is higher vs. pioglitazone (although still acceptable at £20k/QALY) and SU due to the relatively low cost of pioglitazone and SUs, but there are significant benefits for the SGLT2s in terms of weight reduction and lower hypoglycaemia risk.

- The ICER for the SU comparison is likely to be an overestimate due to SUs tending to have a large initial impact on HbA1c in the first 6 months (for which NMA data in the model was used) which then drops off.

- Based on the NMA and cost-utility results the optimal positioning for the SGLT2s in monotherapy when metformin is contraindicated or not tolerated is likely to be as an effective alternative therapy to DPP4s, and to pioglitazone, in patients who are unsuitable for SUs due to risk of hypos or weight gain

5.1 Introduction

The economic analysis performed in this submission assesses the cost-effectiveness of SGLT2s as a monotherapy in T2DM patients who are not achieving adequate glycaemic control with diet and exercise alone and are intolerant to metformin. The economic evaluation for monotherapy uses the same economic model structure as was used for the previous submission of dapagliflozin to NICE for T2DM (the Cardiff Diabetes model – CDM).[9] Since that submission, the model has been updated with three main modifications to model structure and inputs:

- The use of updated UKPDS risk equations (UKPDS 82) to replace UKPDS 68 risk equations, derived from longer follow-up of the UKPDS patient cohort [83] (see Section 5.4.1)

- Updated baseline characteristics that can be accommodated by the model (see Section 5.5).

- The use of updated T2DM complication costs derived from the more recent UKPDS data (UKPDS 84)[18] (see Section 5.8.3).

The primary assessment consisted of assessment of the cost-effectiveness of the class of SGLT2s vs. DPP4s as the main monotherapy comparator that would be expected to be displaced in clinical practice, and versus TZD and SU classes as secondary analyses (see Section 5.2 below).

5.2 Patient population and comparator

The patient cohort for the model are adults aged ≥18 years who are not achieving adequate glycaemic control with diet and exercise alone and are intolerant to metformin. The core clinical data used in the economic model is derived from the NMA reported in section 4 which, due to limits to data availability in a metformin intolerant patient population, was conducted in treatment naïve patients. It was assumed that this evidence is generalisable to a patient population with intolerance or contraindicated to metformin (which represents the specific licensed indications of dapagliflozin, canagliflozin and empagliflozin).[1,7,8]

The comparators considered were those presented in the NICE scope for the MTA for which there was evidence to enable comparisons. The key comparator was considered to be the DPP4s (sitagliptin, vildagliptin, saxagliptin and linagliptin), which have a similar price to the SGLT2s and are the most likely monotherapy drugs to be displaced by an SGLT2 in clinical practice. Based on UK prescription data for the use of treatments for monotherapy in T2DM, of the comparators in the NICE scope SU use has the largest market share (representing 80% of patients receiving monotherapy).[84] The DPP4s market share is 13% of patients, followed by TZDs (4%)[84] Comparisons were made with the SUs although these were not considered to represent a key comparator as due to their low cost they are likely to be used ahead of the SGLT2s and DPP4s in clinical practice in a metformin intolerant patient population, and are considered a first choice alternative to metformin monotherapy.[3] TZDs are little used as monotherapy in clinical practice, but

when considered for use (typically when hypoglycaemia is seen as a risk with SU use[3] may also be potentially displaced by the introduction of SGLT2s.

There was no evidence identified from the systematic review in order to inform a comparison with repaglinide, which was included within the NICE scope. However, this is also not considered to represent a key comparator due to low use as monotherapy in clinical practice.

The comparators were grouped by class in the economic evaluation as this was the approach used in the NMA, and in order to increase the rigour of the comparisons. There was only one TZD considered (pioglitazone). The individual SUs are considered comparable in efficacy and safety and as are DPP4s which is supported by published systematic review and NMA evidence.[81,85]

It was decided to also consider the SGLT2s as a class on the grounds that these are also considered in previous NICE technology appraisals to have similar efficacy and safety (see Section 4.4 of the empagliflozin TA336 guidance), [11] as expected by the Warwick Technology Assessment Team for the MTA (see TAR team protocol section 6 where it is concluded that based on NMA evidence "it is probably unsafe to conclude that any one flozin is best").[75] There were also limits in the monotherapy evidence for the individual treatments (in particular for empagliflozin and canagliflozin 300mg) rendering it not possible to perform a robust indirect comparison of dapagliflozin versus other SGLT2s (see Section 4.2.4.1).

The results presented in this section for the SGLT2 comparisons with other classes of drugs are considered to generalise to dapagliflozin specifically.

5.3 Type of economic evaluation

A cost-utility analysis (CUA) has been performed for the comparison of the SGLT2s with the comparators as per the NICE scope with health benefits measured as QALYs. As is appropriate for a chronic disease and standard in diabetes models a lifetime horizon was adopted consisting of a base case of 40 years. This was varied in sensitivity analysis. A summary of the key structural features of the model are provided in Table 5.1 below, and further details on the model used provided in Section 5.4.

Table 5.1: Key features of the economic analysis

Component	Chosen values	Justification
Time horizon	Lifetime (maximum of 40 years)	T2DM is a chronic, progressive disease. Treatments have impact on costs and outcomes over a patient's lifetime.
Cycle length	6 months	Standard duration of trial follow-up and treatment decisions
Half-cycle correction	Yes	Standard practice
Primary outcome measure	QALYs	As in NICE methods guide
Discount for QALYs/costs	3.5%	As in NICE methods guide
Perspective	NHS + PSS	As in NICE methods guide

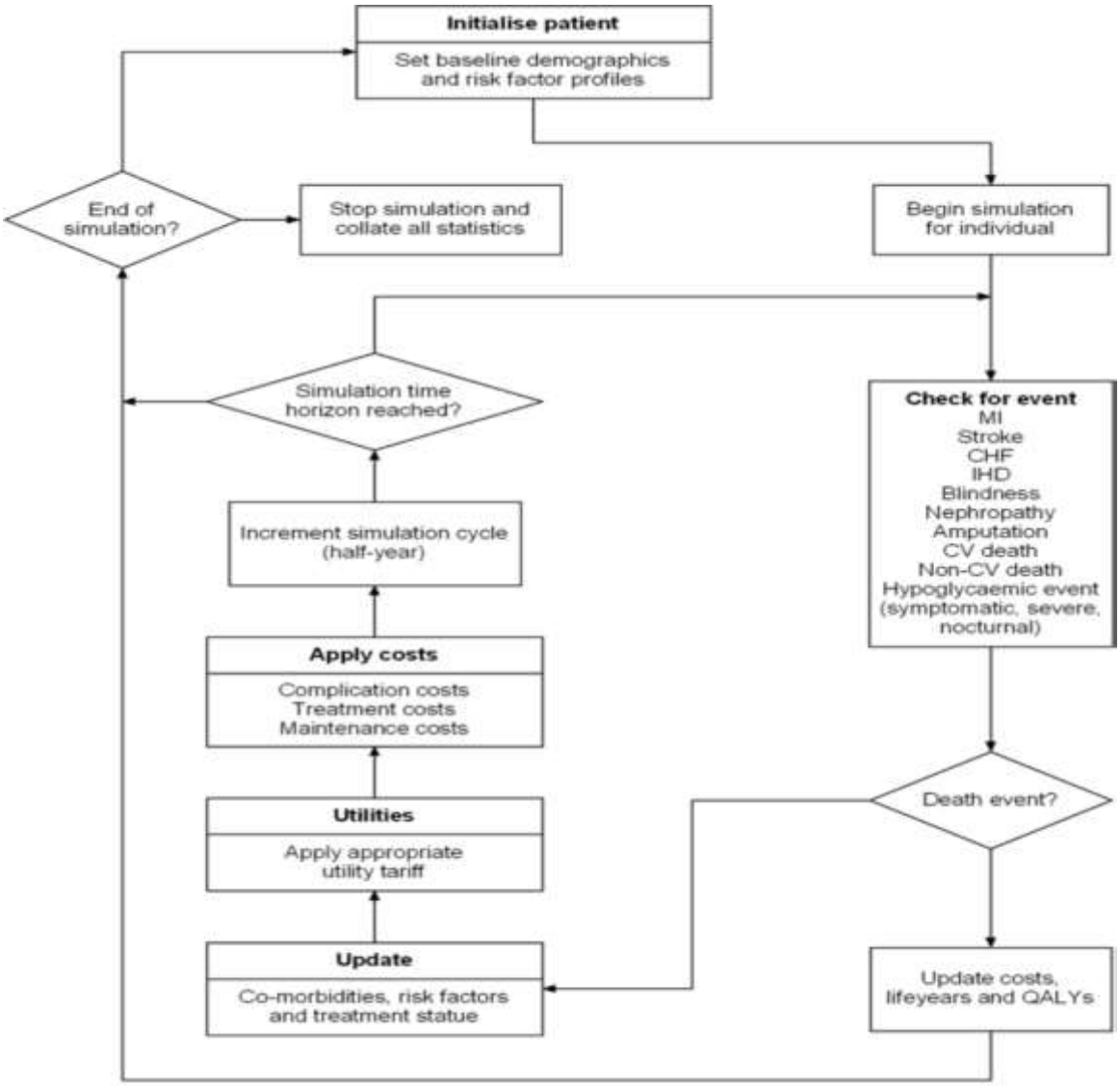
5.4 Modelling methods

5.4.1 Model structure and risk of CV complications

T2DM 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 T2DM.

The economic evaluation utilises a stochastic simulation diabetes model run within an Excel front-end.[2] The simulation uses C++ programming compiled into dll format. The model is similar to other established diabetes models used in the UK previously with NICE and/or published including the CORE Diabetes model,[86] and the UKPDS Health Outcomes Model – 2,[83] in that it utilises UKPDS risk equations to estimate long run micro- and macro-vascular complications, diabetes and non-diabetes mortality, and time paths for risk factors such as HbA1c and systolic blood pressure. All these models have incorporated the latest UKPDS 82 risk equations, which are based on a 5,102 patients over a 30 year period up to 2007.[83] The original CDM model has been subject to systematic validation and regularly features alongside the other established models at the Mount Hood Challenge (a forum for determining the validity of diabetes models), including the most recent forum held in Stanford after the ADA meeting of 2014.[87] The model has been used for numerous economic evaluations of drug interventions for T2DM in a range of country settings, the most recent publication for a UK healthcare setting being an assessment of the cost-effectiveness of dapagliflozin versus SU as an add-on to metformin.[88] A schematic of the model is provided in Figure 5.1.

Figure 5.1: Schematic of the model structure



The patient cohort enters the model with a set of baseline characteristics and modifiable risk factors for long run micro and macrovascular complications. The modifiable risk factors in the

model are as follows: HbA1c, total body weight, total cholesterol (TC), high density lipoprotein (HDL) cholesterol (TC/HDL ratio) and systolic blood pressure (SBP). The value of these variables will change as the model simulation progresses, through treatment effects and through natural progression. The model uses updated risk equations from the UK Prospective Diabetes Study (UKPDS) 82 to estimate long run macro- and micro-cardiovascular complications, as well as diabetes related and all-cause mortality.[89]

The model predicts the incidence of seven specific macro and micro-vascular complications.

Macro-vascular events predicted in the model are:

- ischaemic heart disease (IHD);
- myocardial infarction (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 derived from the systematic literature review. Treatment effect estimates for dapagliflozin and comparators for HbA1c, SBP and lipids are applied for the first year after treatment initiation. Patients in the intervention and comparator groups are simulated through the model in six month cycles, over the 40-year base case time horizon.

For the dapagliflozin economic analysis the cohort size was 30,000 patients to ensure stability in the simulation results. At the end of the first six month cycle, the UKPDS risk equations determine the occurrence of fatal and non-fatal complications, and non-cardiovascular (all-cause) and direct diabetes deaths; the order in which these events occur was generated randomly within the model. If the patient survives beyond the first cycle they transition to the next cycle whereby they remain at risk of treatment related AEs, long run complications and death. Once a fatal event or death from other causes occurs, life years and QALYs are updated and the simulation ends for that patient. 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).

5.4.2 HbA1c natural progression

T2DM 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 T2DM by including a gradual increase in HbA1c over time. In the model the introduction of a new treatment results in a reduction in HbA1c according to the efficacy of the drugs from clinical trial evidence, which is applied for one year. After this initial one year reduction in HbA1c, natural progression consists of a gradual rise in HbA1c (estimated by regression analysis from the UKPDS 82 study)[89] associated with a natural decline in the capacity to secrete endogenous insulin whilst patients continue on drug therapy. When the natural increase in HbA1c reaches a target HbA1c threshold a treatment change is triggered (see Section 5.4.5 below) and the 12 month treatment effect of the next treatment in the sequence is applied followed by natural HbA1c progression until a further treatment switch is triggered by Hba1c reaching the defined threshold level of 7.5.

5.4.3 Treatment lines and HbA1c switching thresholds

The economic model is able to accommodate up to two additional therapy lines after the initial treatment line. It was assumed that this would consist of monotherapy with NPH insulin as 2nd line treatment, and intensified insulin as 3rd line (assumed to consist of 50% insulin dose escalation):

- *Any monotherapy (SGLT2, pioglitazone, SU) -> NPH insulin -> intensified NPH insulin*

These 2nd and 3rd line regimens were selected on the grounds that on disease progression following monotherapy with either an SGLT2, or with the main comparators to SGLT2 of a DPP-4 or TZD the expectation in clinical practice is that a significant proportion of patients will require insulin monotherapy in order to provide adequate glycaemic control. In addition, the choice of 2nd and 3rd line agents in the sequence was driven by the availability of clinical evidence on HbA1c impact of the selected agents. Furthermore, as the 2nd and 3rd line treatments are the same for both the SGLT2 and comparator cohorts the choice of agent has little impact on the cost-effectiveness results (see results Tables 5.13 to 5.15 which show similar duration of 2nd and 3rd line therapy across treatment cohorts). The NICE TAR team protocol for the MTA cost-effectiveness analysis specifies second and third line treatments that differ according to the first line monotherapy treatment adopted.[75] Whilst this is stated to be accordance with the current draft NICE clinical guideline for patients contraindicated to or intolerant of metformin, this means that the economic evaluation becomes an assessment of the cost-effectiveness of alternative T2DM treatment pathways rather than an evaluation of the relative cost-effectiveness of SGLT2s used as monotherapy, which is the objective of the MTA. The sequences proposed in the TAR team protocol would not allow a fair comparison of SGLT2 cost-effectiveness as monotherapy. In addition, the most likely positioning in clinical practice for SGLT2s will be in patients for whom an SU is unsuitable due to risk of hypoglycaemia (or weight gain), hence a pathway in which SUs are added onto 1st line monotherapy with an SGLT2, as indicated in the TAR team protocol (page 7), would not be appropriate.[75]

In the base case the HbA1c threshold at which a switch of treatment to the next line of therapy is assumed to be initiated in clinical practice is ≥7.5% which is in line with current NICE guidelines, and the current draft guidelines for T2DM management HbA1c of 7.5% is the base case for pre-monotherapy baseline HbA1c, and for treatment switch to second and third line treatments. In clinical practice treatment switching may occur at higher levels of HbA1c; this was therefore explored in scenario analyses, as a higher baseline HbA1c corresponding to the mean baseline value from the studies included in the NMA (which was 8.19%).

5.4.4 Weight progression

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 whilst on treatment and with CV risk over time. CV risk is modelled using the UKPDS derived CV risk equations based on BMI values converted from changes in patient body weight over time.

The clinical trial evidence for dapagliflozin reported in this submission and NMA has demonstrated the SGLT2s are associated with significant weight loss. The weight loss is associated with the SGLT2 inhibitor mechanism of action which leads to the excretion of glucose/calories in the urine.[90] The majority of the weight reduction with dapagliflozin has been observed to be loss of body fat, including visceral fat rather than lean tissue or fluid loss.

In the model it is assumed the weight loss associated with the SGLT2s (see Table 4.5 in Section 4.3.3) is assumed to be maintained for a 2 year period. There is two year data for dapagliflozin in monotherapy showing the initial weight reduction is durable and maintained over this time period at least (see Section 3.3.4). There is also up to 4 year clinical trial data showing weight reduction maintenance for dapagliflozin in dual therapy as an add-on to metformin and in pooled trial data

(see also Appendix 8.1.4).[91,92] After 2 years it is assumed that patients will regain all the weight back to the baseline starting weight in a linear manner over the course of one year. This is an important assumption that has been made due to limited data beyond two years for the maintenance of weight effect with SGLT2s in monotherapy. It can be considered a conservative assumption given the evidence of weight maintenance for up to 4 years for those patients who remained on treatment.[91] Based on the NMA evidence (Table 4.5, Section 4.3.3), only one of the comparator drug classes are associated with any weight reduction (a modest reduction for DPP4s, which are considered weight neutral – see Table 5.3). In the model base case the weight change for the comparators is assumed to be maintained for 1 year. Where there is an increase in body weight from baseline estimated (as is the case with TZD and SUs) this is assumed to not return to baseline weight after the initial 1 year period. For all treatment cohorts, the rate of natural weight progression is assumed to be a rate of 0.1 kg per year.

5.4.5 Mortality

All-cause mortality events were estimated using gender specific life tables for the UK.[93] These life tables show the annual probability of death at each age in male and female patients. Since mortality events relating to CV events and diabetes have already been accounted for in the UKPDS risk equations, all-cause mortality does not include deaths from these variables (i.e. CV and diabetes-related deaths were subtracted from all-cause mortality).

Section 5.10.1 (Table 5.12) summarises the alternative baseline/switch scenarios.

5.5 Baseline characteristics and risk factors

A list of baseline patient characteristics and risk factors applied in the economic model is provided in Table 5.2. Age, duration of diabetes and modifiable risk factor parameters change as the simulation progresses due either to treatment effects or natural progression. The baseline patient characteristics comparing SGLT2 to each comparator class were primarily sourced from the NMA, supplemented by published sources (Table 5.2). Baseline HbA1c in the base case was set at 7.5% to be consistent with the treatment switch threshold used. In scenario analysis the baseline HbA1c from the NMA was used (8.2% - see Section 5.4.5). It was assumed that patients entering the model have no history of prior macro or micro vascular complications.

Table 5.2: Baseline demographics and modifiable risk factors applied in the model

Baseline Characteristics	Value	Source
Current Age (yrs)	55.0	NMA
Proportion female (%)	45.4	NMA
Duration diabetes (yrs)	3.6	NMA
Height (m)	1.65	NMA
Proportion Afro-Caribbean	0.062	Nauck et al., 2011[79]
Proportion smokers	0.369	UKPDS 33 [94]
Modifiable risk factors		
HbA1c	7.5	NICE Clinical Guideline 87 [2]
Total-Cholesterol (mg/dL)	195.90	NMA
HDL Cholesterol (mg/dL)	46.3	NMA
SBP (mmHg)	128.3	NMA

Baseline Characteristics	Value	Source
Weight (kg)	79.6	NMA
eGFR (ml/min/1.73m^2)	77.5	UKPDS 33 [94]
Haemoglobin (g/dL)	145	UKPDS 33 [94]
Albuminuria (mg/l)	47	UKPDS 33 [94]
White blood cell count	6.8	UKPDS 33 [94]
Heart rate	72	UKPDS 33 [94]

Abbreviations: AC, Afro-Caribbean; DPP4, dipeptidyl peptidase 4 inhibitor; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure.

5.6 Clinical parameters

5.6.1 Treatment effects and data source

The treatment effects associated with the modifiable risk factors of change in HbA1c %, body weight and systolic blood pressure (SBP) for SGLT2s and the comparators have been derived from the NMA in monotherapy. A summary of these outcomes are presented in Table 5.3.

The NMA demonstrated that the only significant difference was in the weight outcome, with SGLT2s estimated to lead to a -2.69kg average body weight reduction relative to DPP4s, -5.43kg relative to pioglitazone, and -2.89kg relative to SUs, based on the best fitting model (random effects model) (see Table 4.5, Section 4.3.3). The data used in the economic model for each outcome are the absolute treatment effects for each treatment class extracted from the NMA, with the mean placebo effect for each outcome derived from the NMA used as the anchor. For example, the mean change from baseline for HbA1c for SGLT2s relative to placebo was -0.78 over 24 (±6) weeks (see Table 4.3 in Section 4.3.2), and the mean placebo effect on HbA1c from the NMA was +0.04, hence the estimated absolute HbA1c change treatment effect for SGLT2s was estimated to be -0.74 (Table 5.3). The 95% CrIs for HbA1c reduction and weight change from baseline for each treatment were used in sensitivity analysis.

Table 5.3: Absolute treatment effect values for the modifiable risk factors used in the economic model

Modifiable risk factors/parameter	Reference (placebo)∞	SGLT2	DPP4	TZD (pio)	SU
Change in HbA1c *95% CrI¥ (LL, UL)*	0.04	-0.74 *(-0.93, -0.55)*	-0.64 *(-0.50, -0.77)*	-0.90 *(-1.10, -0.69)*	-0.95 *(-1.23, -0.69)*
Change in weight* (kg) *95% CrI¥ (LL, UL)*	-0.76	-2.81 *(-3.18, -2.44)*	-0.13 *(-0.38, 0.12)*	2.61 *(2.06, 3.16)*	0.07 *(-0.74, 0.89)*
Change in SBP* (mmHG) *95% CrI (LL, UL)*	-1.95	-5.78 *(-6.97, -4.58)*	-1.53 *(-2.82, -0.24)*	-1.31 *(-3.89, 1.23)*	-0.65 *(-5.94, 4.63)*
Other modifiable risk factors in the model:					
Change in total cholesterol* (mg/dL)†	0.00	0.00	0.00	0.00	0.00
Change in HDL-C* (mg/dL)†	0.00	0.00	0.00	0.00	0.00

∞Placebo values not applied in the model – the absolute values under each drug in the table are applied

* Effects apply to the first year after treatment initiation.
† no estimate available from the NMA - zero value assumed.
¥The 95% CrIs (from the NMA) were used as upper and lower limits for sensitivity analysis of the HbA1c and weight treatment effect parameters

5.6.2 Hypoglycaemia

The NMA included an assessment of the OR of hypoglycaemic events associated with the anti-diabetic drug therapies included in the economic analysis (Table 4.9 in Section 4.3.5). All events were assumed to be severe, and the absolute probability of a hypoglycaemic event was included in the economic analysis (Table 5.4). As can be seen in Table 5.4, the absolute probability of hypoglycaemic episodes is very low but is estimated to be highest for SUs.

Table 5.4: Probability of hypoglycaemic events applied in the model (derived from the NMA)

Hypoglycaemic event	SGLT2	DPP4	TZD (pio)	SU
Probability. of severe hypoglycaemic event	0.010	0.016	0.024	0.055
95% CrI (LL, UL)	*(0.003, 0.036)*	*(0.008, 0.031)*	*(0.007, 0.076)*	*(0.015, 0.176)*

5.6.3 UTI and GI adverse events, and treatment discontinuation due to AEs

Adverse events that may be associated with dapagliflozin and other SGLT2s due to their mechanism of action, and so were expected to have a higher incidence than for comparators included: urinary tract infections (UTIs), and genital infections. Both adverse events were included in the base case. Although not meta-analysed the percentage of patients experiencing a UTI or GI adverse event was derived from a weighted pooled average of the AE incidence data at 24 (±6) week studies for each treatment class identified in the systematic review for the NMA (Table 5.5). Data for the probability of treatment discontinuation due to AEs for SGLT2s and comparators at 24 weeks was also obtained from the studies included in the NMA (but not meta-analysed) and applied in the first 6 month model cycle only. This shows a lower probability of discontinuation for the SGLT2s compared to each comparator (Table 5.5).

Table 5.5: Probability of UTI and GI adverse events, and discontinuations due to AEs

Adverse event/parameter	SGLT2	DPP4i	TZD (pio)	SU
Probability of a UTI*	0.092	0.022	0.153	0.000¥
Probability of a GI*	0.074	0.002	0.000¥	0.000¥
Discontinuation probability**	0.034	0.039	0.177	0.061

a) Of the studies identified in the systematic literature review (SLR) and eligible for the NMA that reported discontinuation events, 11 of them were related to DPP4s, 9 studies were related to SGLT2s, 7 trials were related to pioglitazone and only 4 were related to SUs.
b) Of the adverse events identified in the SLR and eligible for the NMA, UTI and GI were the most frequently reported events for the regimens of interest. With respect to the UTI events, the probability estimated in the table above was based on 7 studies for DPP4s, 7 for SGLT2s and 3 studies for pioglitazone. None of the studies identified for SU reported relevant events. With respect to the GI events, the presented average was based on 1 study for DPP4 and 7 studies for SGLT2s. None of the studies identified for SU and pioglitazone reported relevant events.

*Probabilities of adverse events were applied during every model cycle.
**Probability of discontinuation was applied during the first model cycle (i.e. first 6 months).
¥No data available from NMA hence conservatively assumed zero probability

5.6.4 Clinical parameters for the subsequent therapy lines

Treatment effect and hypoglycaemia data for the subsequent therapy lines after SGLT2s or comparator treatments were derived from published sources, consisting of the following:

- Insulin (second-line therapy). Efficacy was drawn from a study by Monami et al.,[95]
- Intensified insulin (third-line therapy in the dual therapy analysis) consisted of an increased dose relative to the initial dose on starting insulin treatment. Efficacy was derived from a published HTA performed for NICE.[96]

The clinical parameters entered in the model for the subsequent therapy lines for these regimens are presented in Table 5.6. These were applied for the first year after treatment switch before the natural progression in HbA1c was applied. The same second- and third-line treatment regimen was applied to both the SGLT2 and comparator treatment arms.

Table 5.6: Clinical parameters used for subsequent lines of therapy after SGLT2 and comparators in monotherapy

Clinical parameter	2nd line therapy NPH insulin†	3rd line therapy Intensified NPH insulin‡
Change in HbA1c *	-1.1	-1.11
Change in weight (kg)	1.084	1.90
Change in SBP (mmHG)	0.00*	0.00*
Change in total cholesterol (mg/dL)	0.00*	0.00*
Change in HDL-C (mg/dL)	0.00*	0.00*
No. of hypoglycaemic episodes (symptomatic)	0.0108	0.616
% hypoglycaemic episodes that are severe	0.037	0.022

† Monami et al., 2009.[95] Intensified insulin consisted of 50% escalation in the dose of NPH insulin
‡Waugh et al., 2010.[96]
* no estimate available - zero value assumed.

5.7 Utility estimates

5.7.1 T2DM complications disutilities

In the model patients are assigned an age adjusted utility associated with T2DM 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.[97] Table 5.7 presents the reduction in quality of life, in terms of incremental disutilities, associated with the seven non-fatal macro and microvascular complications included in the model. These are drawn from the UKPDS 62 sub-study whereby utility values for T2DM patients experiencing CV complications were assessed using the EQ 5D.[98] 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 T2DM economic models and has provided utility data for most previous technology appraisals of T2DM drugs in the UK, including the NICE Clinical Guideline 87.[2] 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 T2DM patients in Wales were used.[99]

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.[98] After the event the disutility was assumed to apply in the first and subsequent years.

Table 5.7: Utility decrements associated with complications and BMI related utilities

T2DM related complications	Utility decrements*	Source:
Ischemic Heart Disease	-0.090	Clarke et al., (UKPDS 62), 2002 [98]
Myocardial Infarction	-0.055	
Congestive Heart Failure	-0.108	
Stroke	-0.164	
Blindness	-0.074	
Amputation	-0.280	
ESRD	-0.263	Currie et al., 2005¥ [99]
For each unit decrease in BMI	±0.0061**	Bagust and Beale, 2005 [82]

¥ The estimate is derived from bespoke analysis of the HODAR database – the publication cited describes the database.
*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.

5.7.2 Utilities associated with weight change

In the base case utility estimates associated with weight change were derived from an OLS regression analysis of EQ 5D and BMI data from an observational dataset of over 4,600 T2DM patients in the UK, Belgium, Spain, Italy, Netherlands and Sweden (Bagust and Beale, 2005).[82] 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 of ±0.0061 for weight gain and loss was applied to each treatment induced weight/BMI change data in the economic model (Table 5.7 above). The utility estimates from this study were used for the base case on the grounds that it has been used in previous technology appraisals performed by NICE of T2DM interventions, including in the economic model used for the assessment of treatments covered by NICE Clinical Guideline 87.[2]

A published systematic review of utilities associated with weight change that covered both T2DM and non-T2DM 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.[100] 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.

5.7.3 Hypoglycaemia disutilities

The disutility associated with hypoglycaemia in terms of the fear associated with different types of event occurring was incorporated in the economic analysis. The 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.[101] 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. The resultant disutility is calculated as follows:

*Severe event (binary variable: if ≥1 event then [1], else [0]) * 0.047 + number of symptomatic events * 0.0142 + number of nocturnal events * 0.0084*

It should be taken into account that no data were available for number of symptomatic and nocturnal events. Data related to severe hypoglycaemia were available and applied in the model as presented in Table 5.4

Table 5.8: Utility decrements associated with hypoglycaemic events and other adverse events (UTIs/GIs)

Event	Utility decrement	Source:
Hypoglycaemic event		
Severe	0.047	Currie et al., (2006)[101]
Symptomatic	*0.0142*	
Nocturnal	*0.0084**	
Other adverse event:		
UTI	-0.00283	Barry et al., (1997)[102]
GI	-0.00283	

*there was no data for the analysis for symptomatic or nocturnal hypoglycaemia, hence not used in the economic analysis

5.7.4 Disutilities associated with UTI/GI adverse events

The UTI/GI events were assumed to be associated with a utility decrement of 0.00283 per event (Table 5.8 above). This estimate was obtained from a published economic evaluation of ambulatory care interventions for UTIs in women[102] and was used as it represents the mid-estimate from five studies reporting UTI related utilities that were identified from a PubMed search of UTI/GI disutilities conducted in February 2012.[102-106]

The literature search revealed no specific utility estimates were available for GI adverse events; hence the same disutility was applied as for UTIs.

5.8 Resource use and costs

5.8.1 Drug acquisition costs

The drug acquisition costs used to represent specific drugs and classes of drugs in the model are presented in Table 5.9. For the group comparisons the weighted average cost of the SGLT2 and DPP4 class was used based on current market share data in monotherapy for the UK.[107] The cost of pioglitazone was used for TZD, and a mid-cost SU was applied.

Table 5.9: Drug acquisition costs applied in the model

Therapy	Price per pack[Φ]	Tablets per pack	Price per tablet [Φ]	Dose per tablet	Daily dose	Annual cost (£)
SGLT2s						
Dapagliflozin 10mg	£36.59	28	£1.31	10mg	10mg	£476.92
Canagliflozin 100mg	£39.20	30	£1.31	100mg	100mg	£476.93
Canagliflozin 300mg	£49.99	30	£1.67	300mg	300mg	£608.21
Empagliflozin 10mg	£36.59	28	£1.31	10mg	10mg	£476.98
Empagliflozin 25mg	£36.59	28	£1.31	25mg	25mg	£476.98
Weighted average of SGLT2s*						**£481.79**
DPP4is:						
Sitagliptin	£33.26	28	£1.19	100mg	100mg	£433.57
Saxagliptin	£31.60	28	£1.13	5mg	5mg	£411.92
Vildagliptin	£31.76	56	£0.57	50mg	100mg	£414.00
Linagliptin	£33.26	28	£1.19	5mg	5mg	£433.57
Alogliptin	£26.60	28	£0.95	25mg	25mg	£346.75
Weighted average of DPP4is*						**£429.13**
TZDs						
Pioglitazone	£1.46	28	£0.05	30	30	£19.03
SUs						
Gliclazide (reference SU as mid-price)	£3.36	28	£0.12	40mg	60mg	£65.70
Insulin (for 2nd/3rd line treatment)						
NPH Insulin	£22.90	5[ϒ]	£0.0076 per kg/day**			
Intensified NPH insulin	£22.90	5[ϒ]	£0.0115 per kg/day**			

Φ pack price/tablets per pack derived from BNF69.[26]

*

[redacted] - note, there is no specific data from this source for use of the 100mg vs 300mg doses of canaglilflozin in monotherapy or 10mg vs 25mg doses of empagliflozin. hence an assumption has been made that the market share is 50% for each dose in each case, based on the assumption made in the NICE costing template for the canagliflozin STA.[108]

Weighted DPP4 cost based on prescription estimates for UK [redacted]

ϒ 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 79.6kg patient (the average weight from the NMA – see Table 5.2) representing a daily dose per kg of 0.50 and 0.75 respectively.

5.8.2 Drug administration and monitoring

As SGLT2s and the primary comparators are oral antidiabetic drugs, no administration costs have been assumed. In addition, insulin is assumed to be self-administered.

Efficacy of the SGLT2s is dependent on renal function, and hence renal monitoring is recommended in the SPCs at least annually.[1,7,8] Patient monitoring, including renal monitoring, is

part of the routine clinical management of T2DM hence an additional cost for this has not been included. However, we have included in the economic analysis a single incremental cost associated with the introduction of renal monitoring on initiation of any SGLT2 treatment. This is estimated to include one GP visit (unit cost of £46)[109] and a 24 hour urine creatinine clearance test (unit cost of £2.70, NHS Kidney Care).[110]

5.8.3 T2DM complications costs

First year costs for the following diabetes-related events: IHD, MI, CHF, stroke, blindness, amputation, were classified as fatal or non-fatal, and derived from the recent updated analysis of data on non-inpatient resource use data for the UKPDS cohort up to 2007 (UKPDS 82).[18] This covered direct inpatient (hospital admissions and day cases) and other healthcare resource use (e.g. GP visits, nurse and other health professional outpatient or community visits) based on 2791 hospitalisation records in England, and resource use questionnaires (for non-inpatient resource use) administered to 3589 UK patients with T2DM. The same source was used for the subsequent annual maintenance costs for patients experiencing blindness and amputation events. Data for patients who survive an IHD, MI, CHF or stroke event were derived from the previous UKPDS sub-study (UKPDS 65).[111] Costs were uprated to 2014 values using the Community Health Services inflator[109] (Table 5.10). The estimated costs are initially applied within the cycle in which the event occurs. Maintenance costs for non-fatal events are applied in all subsequent years until either the end of the simulated time horizon or until the subject dies.

A cost for ESRD/renal failure was not covered by UKPDS 84 study; hence estimates for the costs of dialysis from a study in the UK setting by Baboolal et al., 2008 was used instead,[112] uprated to 2014 levels using the Community Health Services inflator.[109] The annual cost of £18,776 represents the average cost for continuous ambulatory peritoneal dialysis. This represented the lowest cost estimate for dialysis in the Baboolal et al., study hospital haemodialysis, hence could be considered conservative. The same cost as in the first year was assumed for maintenance costs associated with ESRD (patients on dialysis). The cost of blindness can only be incurred once as patients were assumed to incur severe vision loss/blindness in both eyes simultaneously. This may be a conservative total cost estimate for vision loss as resource use incurred for less severe eye impairment (e.g. loss of vision in one eye) has not been included.

The annual costs of complications used in the economic model are presented in Table 5.10.

Table 5.10: Microvascular and macrovascular event complication costs

Event	Costs			
	Fatal	Non-fatal 1st year	Maintenance costs	Source
Ischaemic Heart Disease		£ 12,762	£ 1395	Alva 2015 UKPDS 84 [18]/ Clarke 2003 UKPDS 65 [111]
Myocardial Infarction	£ 2,605	£ 7,938	£ 2177	Alva 2015 UKPDS 84 [18]
Congestive Heart Failure		£ 5,180	£ 1656	Alva 2015 UKPDS 84 [18]/ Clarke 2003 UKPDS 65 [111]
Stroke	£ 5,188	£ 11,450	£ 1378	Alva 2015 UKPDS 84 [18]/ Clarke 2003 UKPDS 65 [111]
Amputation		£ 13,499	£ 4618	Alva 2015 UKPDS 84 [18]
Blindness		£ 6,502	£ 2307	Alva 2015 UKPDS 84 [18]
ESRD (including dialysis)	-	£ 18,776	£ 18,776	Baboolal et al., 2008 [112]
*Costs inflated to 2014 values using the hospital and community health services (HCHS) pay and prices index.[109]				

5.8.4 Costs associated with hypoglycaemia

Costs were included in the model for severe hypoglycaemic events only, based on evidence from a published study by Hammer et al., of health service resource use covering 320 T2DM patients in Germany, Spain and the UK (approximately one third of the patients), who had experienced more than one hypoglycaemic event in the previous year.[113] From data on direct healthcare costs in this study an estimated cost of £424 per severe episode was applied in the dapagliflozin economic model (Table 5.12). This cost has been converted back to GBP from Euros presented in the publication and uprated from the original 2007 cost year to 2014 values using the hospital and community health services (HCHS) inflator.[109] It was assumed no costs were associated with non-severe symptomatic and nocturnal hypoglycaemic events, in line with most other economic evaluations of T2DM treatments.

5.8.5 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 £46, derived from Curtis, 2014.[106,109] 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 £46.

Table 5.11 summarises the hypoglycaemic and UTI/GI costs included in the model.

Table 5.11: Costs of hypoglycaemic episodes and UTI/GI AEs included in the economic model

Adverse event	Cost per episode	Source
Severe hypoglycaemic episode	£424*	Direct healthcare costs from Hammer et al, 2009 [113]
UTI or GI	£46	Cost of GP visit (11.7 min consultation), from Curtis 2014 [109]

*Costs inflated to 2014 values using the hospital and community health services (HCHS) pay and prices index.[109]

5.9 Discounting

Costs, life years and QALYs were discounted at 3.5% in the base case, with 0% and 6% investigated in sensitivity analysis.

5.10 Sensitivity and Scenario Analysis

5.10.1 Univariate sensitivity analysis and scenario analysis

Univariate sensitivity analysis was performed, varying treatment effect and BMI utility parameters around the 95% confidence/credible intervals available (see Table 5.3), varying disutilities for T2DM complications by ±10%, and total non-drug costs by ±25%.

A number of scenario analyses were performed to examine the impact of changing key assumptions and parameter estimates (listed in Table 5.12).

Table 5.12: Scenario analyses performed

Scenario analysis	Change from base case and rationale
HbA1c threshold 8.0% (for 2nd and 3rd line switch) and baseline value 7.5%	To explore the impact of a higher treatment switch threshold than recommended in NICE clinical guidelines
HbA1c threshold 8.19% (for both lines) and baseline value to 8.19%	To explore impact of applying baseline HbA1c as estimated from the NMA
HbA1c threshold 2nd line switch: 7.5% and 3rd line switch: 8.0%, baseline value 7.5%	To explore a further variant on switch thresholds whereby only third line switch is at a higher threshold
Weight reduction maintenance for SGLT2s set to 1 year	To show the impact of a conservative assumption for maintenance of weight reduction with the SGLT2s, but also to reflect that the weight change data is derived from a 24 week follow-up (±6 weeks) from the NMA
Weight maintenance period for comparators set to 2 years	As above, conservative assumption regarding weight change maintenance for the comparators
Weight convergence assumed between SGLT2 and TZD monotherapy patients at 2nd (i.e. final) treatment switch.	The small base case difference in weight that remains between the SGLT2 and TZD regimens after switching to the final line of treatment is removed in this scenario
Discontinuation rates for AEs set to zero	To explore sensitivity of results to the base case differences estimated
No disutility associated with AEs	To explore sensitivity of results to the base case differences estimated
Market shares for cana 100 and 300mg increased to 10%	In the base case the market share of canagliflozin was estimated at 3.7% for each of the 100mg and 300mg doses (50:50 split) – see Table 5.9 footnote. As the prices of these doses vary an alternative higher market share of canagliflozin was assumed to test the impact of a higher SGLT2 weighted cost on the ICER.
Discounting of costs/QALYs at 6%	Variation around 3.5% represents standard practice
Applying the highest (sitagliptin) and lowest (alogliptin) DPP4i prices	To assess impact of comparator drug acquisition cost uncertainty as a weighted cost of DPP4is was used in the base case.

5.10.2 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was performed to examine the combined effect of the uncertainty in all the variable parameters. Values were sampled from the uncertainty distributions associated with each parameter, with normal distributions assumed for treatment effect/outcome parameters, beta distributions for utility parameters, probabilities and rates, gamma distributions for costs and normal distributions for all other parameters. Cost-effectiveness acceptability curves were derived using bootstrapping sampling techniques. For the probabilistic analysis the model simulated 1,000 cohorts of 30,000 patients.

5.11 Results

5.11.1 Base case results

The following tables present the base case results for SGLT2s versus each of the DPP4, TZD (pioglitazone) and SU drug classes used as monotherapy in patients who are metformin intolerant.

- Compared to the primary comparator of DPP4s, SGLT2s have an estimated base case ICER of £5,904 per QALY gained, based on incremental costs and QALYs of £106 and 0.018 respectively over a 40 year time horizon (Table 5.13).

- Compared to TZDs (pioglitazone), the SGLT2s have an estimated base case ICER of £20,089 per QALY gained, based on incremental costs and QALYs of £1,912 and 0.095 respectively over the 40 year time horizon (Table 5.14). Whilst pioglitazone has the lowest drug acquisition cost of the comparators, a larger relative QALY gain is estimated.
- Compared to SUs, the SGLT2s have an estimated base case ICER of £52,047 per QALY gained, based on incremental costs and QALYs of £1,397 and 0.027 respectively over the 40 year time horizon (Table 5.15).

In each comparison the incremental cost associated with the SGLT2s is primarily due to an additional drug acquisition cost, whereas the QALY gain estimated is associated with the superior weight reduction outcome and its impact on health related quality of life for the SGLT2s. The modelled predictions for the progression of the modifiable risk factor outcomes over a 40 year time horizon and the predicted incidence of T2DM events are presented in Appendix 8.10. It should be noted that the ICER relates to very small difference in costs and QALYs over this time horizon.

Table 5.13: Cost-effectiveness of SGLT2s vs. DPP4s

	SGLT2	DPP4i	Incremental cost/outcome
Treatment duration by line			
1st line with SGLT2 or comparator (yrs)	3.85	3.89	-
2nd therapy: met+insulin duration (yrs)	3.80	3.80	-
3rd therapy: met+intensified insulin duration (yrs)	16.72	16.67	-
Costs			
Drug costs	£5,638	£5,449	£190
Macrovascular complications costs*	£9,179	£9,251	-£ 72
Microvascular complications costs**	£12,924	£12,938	-£ 14
Hypoglycaemia costs	£175	£184	-£9
Other AE costs (inc. renal monitoring)	£63	£51	£12
Total discounted costs	**£27,979**	**£27,873**	**£106**
Outcomes			
Discounted Life years gained (LYG)	15.769	15.765	0.000
Discounted QALYs gained	**13.206**	**13.188**	**0.018**
Incremental cost per QALY	**£5,904**		
NB: There is rounding of costs and QALYs in the table. *IHD, CHF, MI and stroke; **Blindness, Nephropathy, Amputation			

Table 5.14: Cost-effectiveness of SGLT2s vs. TZDs (pioglitazone)

	SGLT2	TZD (pioglitazone)	Incremental cost/outcome
Treatment duration by line			
1st line with SGLT2 or comparator (yrs)	3.85	3.88	**-**
2nd therapy: met+insulin duration (yrs)	3.80	3.80	**-**

	SGLT2	TZD (pioglitazone)	Incremental cost/outcome
3rd therapy: met+ intensified insulin duration (yrs)	16.72	16.71	-
Costs			
Drug costs	£5,638	£4,066	£1,572
Macrovascular complications costs*	£9,179	£9,319	-£140
Microvascular complications costs**	£12,924	£12,433	£491
Hypoglycaemia costs	£175	£197	-£22
Other AE costs (inc. renal monitoring)	£63	£53	£10
Total discounted costs	**£27,979**	**£26,067**	**£1,912**
Outcomes			
Discounted Life years gained (LYG)	15.769	15.780	-0.010
Discounted QALYs gained	**13.206**	**13.111**	**0.095**
Incremental cost per QALY	**£20,089**		
NB: There is rounding of costs and QALYs in the table. *IHD, CHF, MI and stroke; **Blindness, Nephropathy, Amputation			

Table 5.15: Cost-effectiveness of SGLT2s vs. SUs

	SGLT2	SU	Incremental cost/outcome
Treatment duration by line			
1st line with SGLT2 or comparator (yrs)	3.85	3.83	-
2nd therapy: insulin duration (yrs)	3.80	3.80	-
3rd therapy: intensified insulin duration (yrs)	16.72	16.73	-
Costs			
Drug costs	£5,638	£4,128	£1,510
Macrovascular complications costs*	£9,179	£9,226	-£47
Microvascular complications costs**	£12,924	£12,935	-£11
Hypoglycaemia costs	£175	£244	-£69
Other AE costs (inc. renal monitoring)	£63	£49	£14
Total discounted costs	**£27,979**	**£26,582**	**£1,397**
Outcomes			
Discounted Life years gained (LYG)	15.769	15.767	0.003
Discounted QALYs gained	**13.206**	**13.179**	**0.027**
Incremental cost per QALY	**£52,047**		
NB: There is rounding of costs and QALYs in the table. *IHD, CHF, MI and stroke; **Blindness, Nephropathy, Amputation			

5.11.2 Scenario and sensitivity analysis results

The results of the univariate sensitivity and scenario analyses are presented in Table 5.16 and Table 5.17

- In all sensitivity analyses, including varying the HbA1c and weight change outcomes by the 95% CrIs, compared to DPP4 the ICER for the SGLT2s is <£10,000/QALY gained (Table 5.16).
- The most sensitive variable for the comparison vs. TZD is disutility associated with BMI increase (Range £14.6 - £32k/QALY based on 95% CIs).
- The ICER for SGLT2 vs. SU is sensitive to uncertainty over the relative efficacy of SGLT2 and SU based on the 95% CrIs from the NMA for HbA1c and weight change, and in utility range applied to BMI unit decrease (£4.4k to £62k/QALY, Table 5.16). These ICERs reflect the greater relative uncertainty in the NMA for the comparison of SGLT2 versus SU, compared to the DPP4 and TZD comparisons.

Scenario analysis shows the only parameter that the comparison with DPP4 is sensitive to is varying the price of the comparator. For the comparison with TZD assuming no differences in AE disutility reduces the ICER to £5,685/QALY, whereas assuming weight convergence at 2nd treatment switch increases the ICER to £38,199/QALY (Table 5.17). However, this seems an unlikely scenario in practice as it assumes post treatment TZD patients lose the additional weight they gained whilst on treatment, whilst SGLT2 patients regain all the weight they lost. For comparisons with SU the ICER remains above £40k/QALY across scenarios (Table 5.17). However, it is likely that the base case and the scenario analysis ICERs are overestimates due to a J effect associated with SUs,[79,80] which results in an overestimate of SU efficacy in HbA1c reduction over the first 4-6 months (see Section 4.4). This is a limitation of the NMA as there was only sufficient evidence to perform the analysis at 24 (±6) weeks, whereas it is likely that SU treatment effect is lower over a longer duration of follow-up, whereas efficacy of dapagliflozin has shown durability in monotherapy up to 2 years (see Section 3.3.4).

Table 5.16: Sensitivity Analyses results

SGLT2	**vs. DPP4**			**vs. TZD (pioglitazone)**			**vs. SU**		
Sensitivity/Scenario analysis	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**
Base case	**£106**	**0.018**	**£5,904**	**£1,912**	**0.095**	**£20,089**	**£1,397**	**0.027**	**£52,047**
Sensitivity analysis									
SGLT2 and comparator change in HbA1c:									
NMA 95% CrI Lower limit SGLT2	£71	0.019	£3,713	£1,876	0.096	£19,512	£1,361	0.028	£48,928
NMA 95% CrI Upper limit SGLT2	£128	0.015	£8,700	£1,934	0.092	£21,045	£1,419	0.024	£60,248
NMA 95% CrI Lower limit Comparator	£139	0.020	£6,917	£2,151	0.083	£25,857	£1,584	0.010	£165,409
NMA 95% CrI Upper limit Comparator	£196	0.031	£6,357	£1,841	0.098	£18,713	£1,328	0.031	£42,724
SGLT2 and comparator change in weight:									
NMA 95% CrI Lower limit SGLT2	£114	0.021	£5,501	£1,920	0.098	£19,604	£1,405	0.030	£47,462

SGLT2	vs. DPP4			vs. TZD (pioglitazone)			vs. SU		
Sensitivity/Scenario analysis	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**
NMA 95% CrI Upper limit SGLT2	£106	0.019	£5,675	£1,912	0.096	£19,939	£1,397	0.028	£50,694
NMA 95% CrI Lower limit Comparator	£107	0.015	£6,961	£1,884	0.082	£22,882	£1,399	0.021	£68,366
NMA 95% CrI Upper limit Comparator	£103	0.026	£3,960	£1,963	0.114	£17,251	£1,461	0.051	£28,422
Disutility for increase in BMI:									
95% CI Lower limit	£106	0.018	£5,922	£1,912	0.131	£14,626	£1,397	0.0280	£49,854
95% CI Upper limit	£106	0.018	£5,885	£1,912	0.060	£32,065	£1,397	0.0257	£54,442
Utility for decrease in BMI:									
95% CI Lower limit	£106	0.014	£7,874	£1,912	0.091	£21,109	£1,397	0.0222	£62,810
95% CI Upper limit	£106	0.023	£4,722	£1,912	0.100	£19,163	£1,397	0.031	£4,434
Disutilities for complications									
+10%	£106	0.018	£5,802	£1,912	0.095	£20,085	£1,397	0.027	£51,577
-10%	£106	0.018	£6,009	£1,912	0.095	£20,093	£1,397	0.027	£52,526
Total non-drug costs:									
+25%	£86	0.018	£4,749	£1,997	0.095	£20,982	£1,369	0.027	£50,993
-25%	£127	0.018	£7,058	£1,827	0.095	£19,196	£1,425	0.027	£53,102

Table 5.17: Scenario Analyses results

SGLT2	vs. DPP4			vs. TZD (pioglitazone)			vs. SU		
Scenario Analysis	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**
HbA1c threshold 8.0% (for 2nd and 3rd line switch) and baseline value 7.5%	£225	0.021	£10,799	£3,059	0.106	£28,970	£2,335	0.037	£63,783
HbA1c threshold 8.19% (for both lines) and baseline value to 8.19%	£198	0.023	£8,694	£3,327	0.101	£32,982	£1,846	0.021	£88,934
HbA1c threshold 2nd line switch: 7.5% and 3rd line switch: 8.0%, baseline value 7.5%	£100	0.020	£4,977	£1,902	0.101	£18,884	£1,382	0.026	£53,057
Weight reduction maintenance for SGLT2s set to 1 year	£22	0.014	£1,583	£1,828	0.091	£20,077	£1,313	0.023	£57,839
Weight maintenance period for comparators set to 2 years	£115	0.014	£8,137	£1,913	0.101	£19,032	£1,435	0.028	£51,166
Weight convergence assumed between SGLT2	NA	NA	NA	£1,818	0.048	£38,199	NA	NA	NA

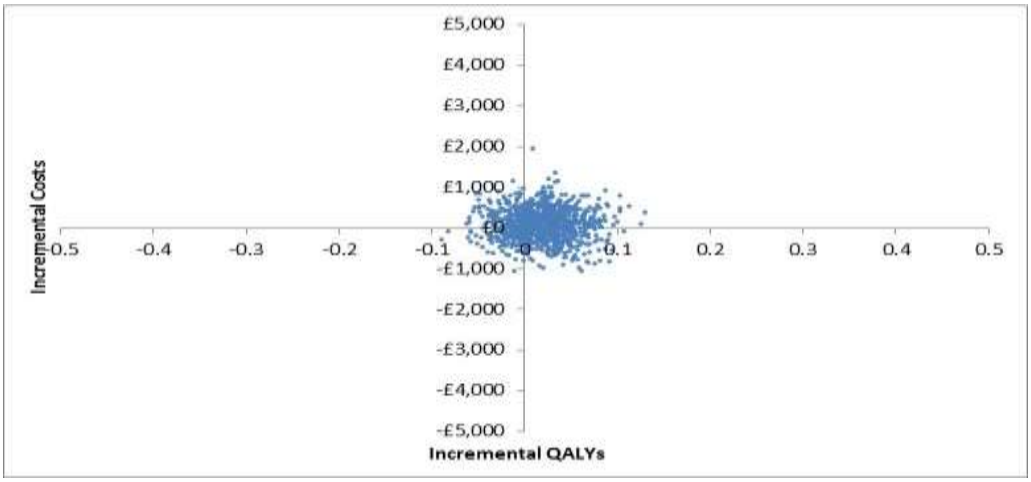
SGLT2	vs. DPP4			vs. TZD (pioglitazone)			vs. SU		
Scenario Analysis	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**	**Inc. Cost £**	**Inc. QALY**	**Inc. cost per QALY £**
and TZD monotherapy patients at 2nd (i.e. final) treatment switch.									
Discontinuation rates for AEs set to zero	£69	0.023	£3,035	£69	0.023	£3,035	£1,431	0.028	£51,718
No disutility associated with AEs	£106	0.019	£5,685	£106	0.019	£5,685	£1,397	0.028	£50,456
Market shares for cana 100 and 300mg 10%	£137	0.018	£7,585	£1,943	0.095	£20,407	£1,427	0.027	£53,176
Applying the highest DPP4i prices (sitagliptin)	£90	0.018	£4,996	NA	NA	NA	NA	NA	NA
Applying the lowest DPP4i prices (alogliptin)	£410	0.018	£22,756	NA	NA	NA	NA	NA	NA
Time horizon of 20 years	£100	0.020	£5,093	£1,841	0.089	£20,611	£1,399	0.028	£49,275
Discounting of costs/QALYs at 0%	£59	0.022	£2,718	£2,115	0.134	£15,772	£1,412	0.033	£43,393
Discounting of costs/QALYs at 6%	£100	0.020	£5,093	£1,802	0.079	£22,914	£1,368	0.024	£56,122

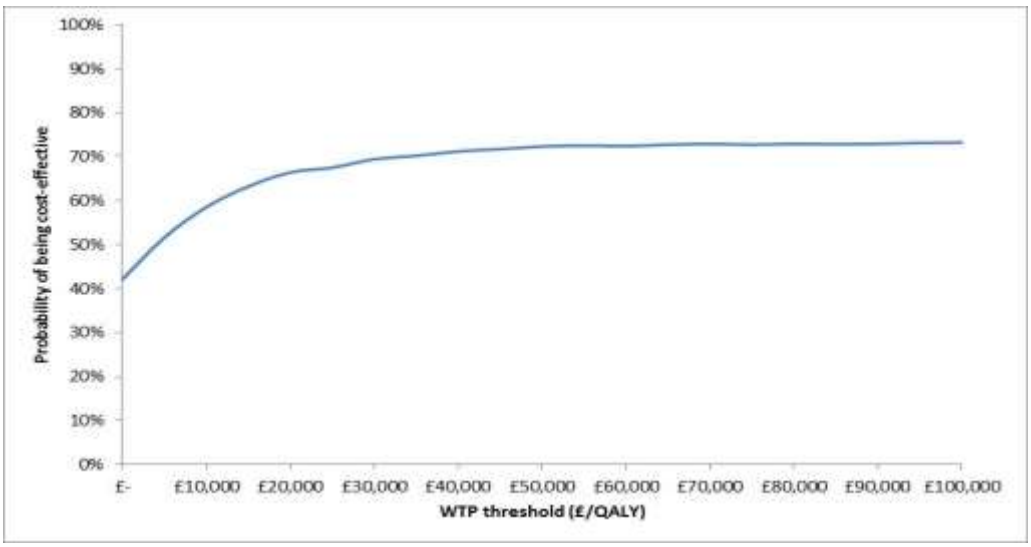
5.11.3 Probabilistic sensitivity analysis results

The scatterplot and cost-effectiveness acceptability curves from the PSA are presented in Figure 5.2. At a willingness to pay of £20,000 the probability that the SGLT2 class are cost-effective compared to DPP4s in monotherapy is 66%. Compared to TZD and SUs the probability is 51% and 13% respectively at a threshold of £20,000/QALY.

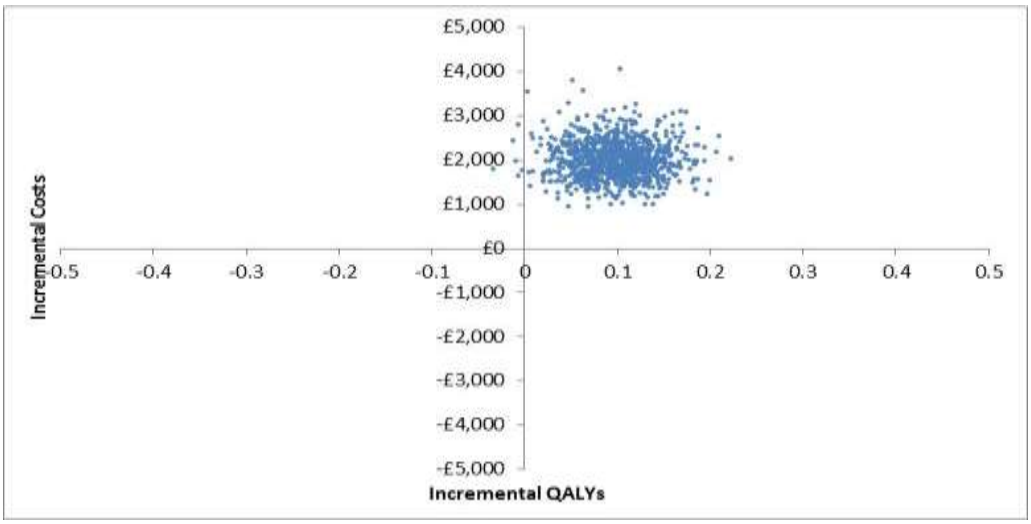
Figure 5.2: Scatterplots and cost-effectiveness acceptability curve for incremental costs and QALYs for SGLT2s vs. a) DPP4s b) TZD c) SUs in monotherapy

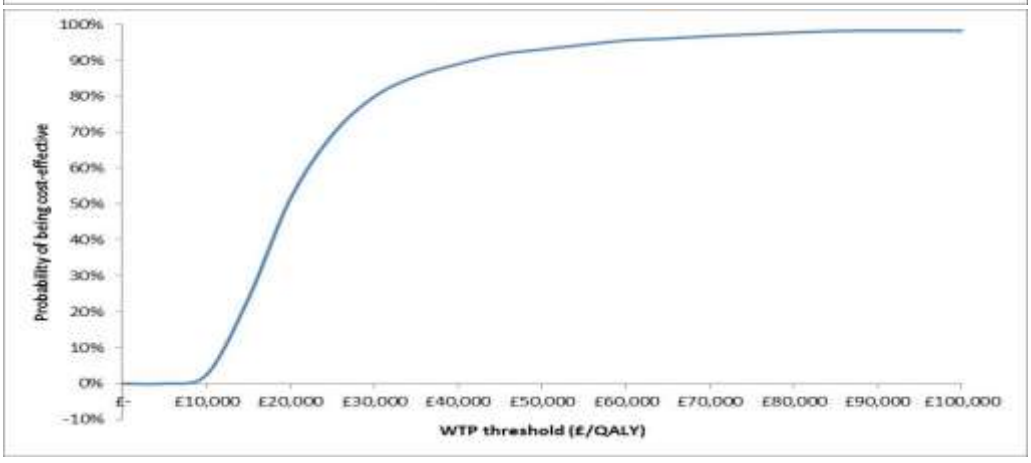
a) SGLT2s vs. DPP4s



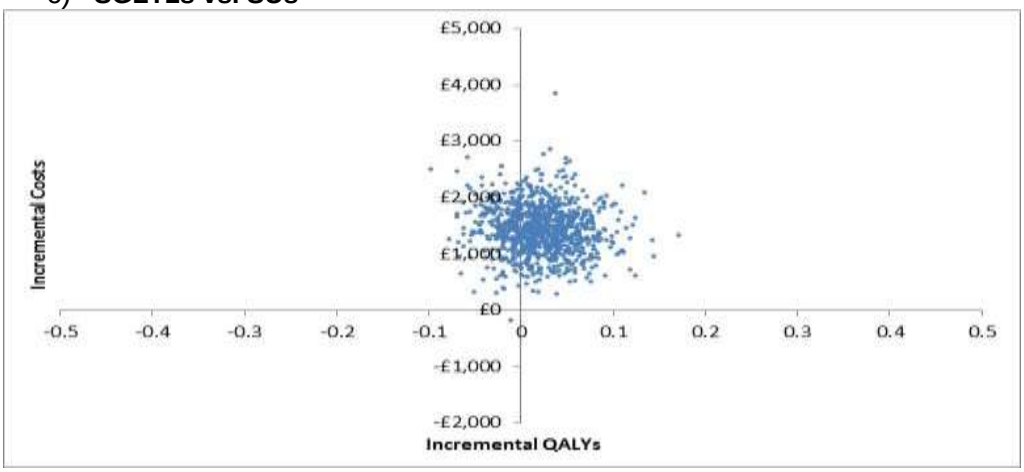


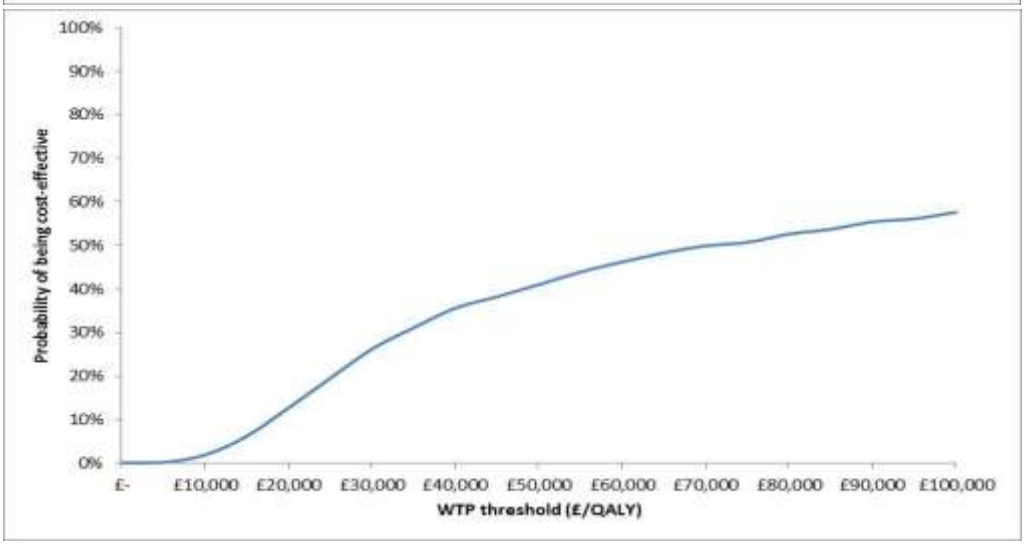
b) **SGLT2s vs. TZDs**





c) **SGLT2s vs. SUs**





5.12 Conclusions

Based on the NMA and cost-utility results the optimal positioning for the SGLT2s in monotherapy when metformin is contraindicated or not tolerated is likely to be as a cost-effective alternative therapy to DPP4s, and to pioglitazone, in patients who are unsuitable for SUs due to risk of hypos or weight gain

- Compared to the primary comparator of DPP4s, SGLT2s can be considered highly cost-effective, with an ICER of £6k/QALY, with all sensitivity analyses attaining an ICER <£10k/QALY.
- The incremental QALYs estimated for the SGLT2s and incremental QALY over DPP4s are primarily driven by the weight reduction advantages of these drugs (which are similar between the SGLT2 drugs), with a numerical benefit in HbA1c reduction.
- The ICER is higher v. pioglitazone (although still acceptable at around £20k/QALY) and high vs. SU due to the relatively low cost of pioglitazone and SUs; however there are significant benefits for the SGLT2s in terms of weight reduction and lower hypoglycaemia risk.
- Further, the ICER for the SU comparison is likely to be an overestimate due to SUs tending to be associated with a large initial reduction in HbA1c in the first 6 months (corresponding to the time point in the NMA and used in the model) which then increases gradually over a longer time period.

6. Budget Impact

- The prevalence of type 2 diabetes is increasing in the general population, with an estimated net patient number of 2,798,201 by 2020
- Although the usage of the SGLT2s in monotherapy is small, it is gradually increasing. Of the SGLT2s, dapagliflozin currently has the largest estimated market share (92.38%) in monotherapy
- It is estimated that after 5-years dapagliflozin will still maintain the largest market share for SGLT2s. Furthermore, SGLT2s are expected to gain market share from DPP4s, and TZDs
- Overall annual net budget impact estimate for SGLT2 class is estimated to be [redacted] in
  2015-2016 increasing to [redacted] by 2019-2020.

6.1 Overview

Estimates of projected NHS impact of dapagliflozin and SGLT2 inhibitors in England and Wales post NICE recommendation are provided for use as a T2DM monotherapy for patients inadequately controlled by diet and exercise as monotherapy when metformin is not tolerated. Equivalent efficacy is assumed as described and validated in this submission.

There may be potential for some patients to receive a SGLT2 and actually not be metformin intolerant, but this is very likely to be very small population as guidelines have specific treatment recommendations, so therefore any associated budget overestimation is not likely to be significant. In terms of overall drug budget, SGLT2 inhibitors are not expected to have a major impact on resources.

6.2 Resource impact estimation

6.2.1 Epidemiological assumptions

The population size of England and Wales was obtained from Office of National Statistics (ONS)[114] data with the adult population determined to be 79.42% from the 2011 Census.[115] The prevalence of diabetes (type 1 and type 2) was obtained from Quality and Outcomes Framework (QOF) general practice data report for England for 2013-2014.[116] The prevalence rate was shown to have increased to 6.2% from 6% in 2012-2013.[116] Type 2 diabetes comprises 90% of patients with diabetes around the world.[117] In terms of type 2 diabetes incidence, a crude incidence rate was reported in 2010 as 515 per 100,000 population.[118] In terms of mortality associated with type 2 diabetes, the National Diabetes Audit (2011-2012)[19] reported that 70,941 observed deaths occurred in England and Wales. Table 6.1 presents the estimated net number of patients with type 2 diabetes in England and Wales based upon the above epidemiological assumptions.

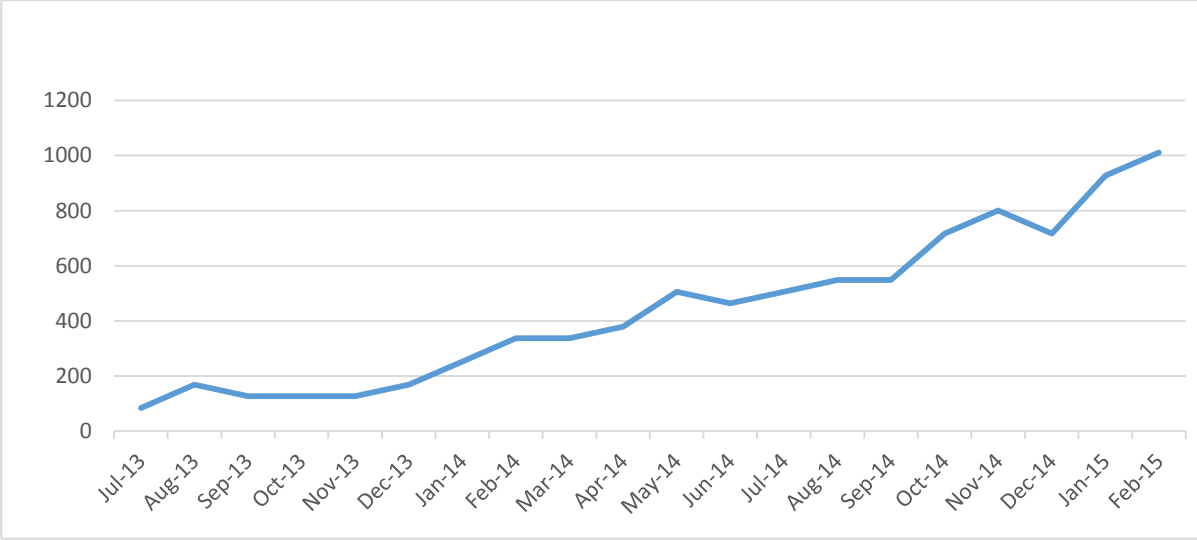
Table 6.1: Estimated and projected adult type 2 diabetes population of England and Wales, 2013 to 2020

	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2019-2020
Population size of England & Wales	56,927,000	57,323,000	57,721,000	58,139,000	58,546,000	58,956,000	59,355,000
Adult population (79.42%)	45,211,423	45,525,927	45,842,018	46,173,994	46,497,233	46,822,855	47,139,741
Adults with diabetes (prevalence)	2,803,108	2,822,607	2,842,205	2,862,788	2,882,828	2,903,017	2,922,664
Adults with type 2 diabetes (90%)	2,522,797	2,540,347	2,557,985	2,576,509	2,594,546	2,612,715	2,630,398
Type 2 incidence	232,839	234,459	236,086	237,796	239,461	241,138	242,770
Diabetes mortality	71,900	72,400	72,903	73,431	73,945	74,462	74,966
Net number of patients	2,683,737	2,702,405	2,721,168	2,740,874	2,760,062	2,779,391	2,798,201

6.3 Uptake of dapagliflozin

Based upon current market research data (February 2015) in terms of the overall type 2 diabetes monotherapy market the majority of monotherapy usage is metformin (72.9%) followed by sulphonylureas (9.5%), DPP4s (1.6%), TZDs (0.45%), glucagon-like peptide (0.24%), other monotherapies (0.22%), and SGLT2s (0.1%) with some patients also receiving insulin (15%).[107] The SGLT2 inhibitors are an alternative monotherapy option and IMS market research data indicates that SGLT2 inhibitors use in monotherapy is gradually increasing (Figure 6.1).

Figure 6.1: Patients in England and Wales prescribed SGLT2 monotherapy



The SGLT2 dapagliflozin has been available to the NHS in England and Wales since 2012. Internal company estimates show that dapagliflozin had a patient share representing [redacted] of the total SGLT2 monotherapy market in 2014. This is estimated to gradually decline whilst newer entrants offer additional clinician choice and gain some market share.

The number of patients estimated to be prescribed monotherapy was based upon IMS Information Solutions market research data. Based on assumptions by Astra Zeneca, this has been calculated as an average of 1,246,153 patients between January 2014 and January 2015 who received monotherapy, which was equivalent to 46.11% of the net number of patients in England and Wales with type 2 diabetes. Internal company estimates of the monotherapy market share for the overall SGLT2 market ([redacted] for 2014-2015) was obtained for the years between 2014 and 2020. Using these estimates the proportion of patients receiving each of the different SGLT2 inhibitors between 2015 and 2020 was calculated ([redacted] 6.2)

Table 6.2: Estimated proportions of patient receiving SGLT2 inhibitors from 2014-2020 (CIC)

	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2019-2020
Number of treated patients receiving monotherapy (46.11%)	1,246,153	1,254,731	1,263,817	1,272,665	1,281,577	1,290,250
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The annual budget impact for years 2014-2020 was calculated based upon BNF[26] list prices and previously calculated proportion of patients by product, assuming market share is displayed from DPP4s and TZDs (see Table 6.3). It was assumed that 50% of patients receiving canagliflozin received either the 100mg or 300mg strengths. This assumption was based upon the NICE costing template for canagliflozin (TA 315)[108] which based upon expert opinion suggests that although

people are likely to start on the 100 mg dose, around 50% will progress to the 300 mg dose. Assuming patients switch from DPP-4 inhibitors (5% year one, 10% year two onwards with DPP-4 accounting for 1.59% of total monotherapy market in Feb 2015) and thiazolidines (TZD) (2.5% year one and 5% year two onwards accounting for 0.45% of the monotherapy market in Feb 2015)[107] then the net budget impact is illustrated in Table 6.3.

Table 6.3: [redacted]

	2015-2016	2016-2017	2017-2018	2018-2019	2019-2020
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

The values shown in this table are based on assumptions made by Astra Zeneca and have been calculated from internal forecasts and adjusted market research data for England and Wales. *Weighted DPP4 annual cost (£429.13) based on prescription estimates for UK [redacted]. Thiazolidines cost £19.03 Estimates of DPP-4 and TZD market share from Patient Data of the type 2 diabetes market, IMS Information Solutions UK Ltd, Feb 2015.[107]

6.4 Conclusions

The prevalence of type 2 diabetes continues to increase meaning there is therefore increased need for monotherapy treatments for patients intolerant to metformin. The use of SGLT2s as monotherapy is increasing; dapagliflozin currently has an estimated market share of SGLT2s [redacted] which is anticipated to decline with new entrants to the SGLT2 market. Overall the SGLT2 inhibitors are expected to have a gross annual budget impact in monotherapy in year 2015-2016 of [redacted] rising to [redacted] by 2019-2020. If patients are switched from DPP4 inhibitors and TZDs, the net annual budget impact for the SGLT2 class is estimated at [redacted] in 2015-2016 rising to [redacted] by 2019-2020.

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Boehringer Ingelheim

Empagliflozin (Jardiance®)

For the treatment of type II diabetes mellitus in adult patients

Multiple Technology Appraisal (MTA)

Submission date: 15th June 2015

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ADA	American Diabetes Association
AHA	Anti-hyperglycaemic agent
ANCOVA	Analysis of covariance
BD	Twice daily
BI	Boehringer Ingelheim
BMI	Body mass index
CEAC	Cost-effectiveness acceptability curves
CEP	Cost-effectiveness plane
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CrI	Credible interval
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DPP-4	Dipetidyl-peptidase 4
DSU	Decision Support Unit
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
eCrCl	Estimated creatinine clearance
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FAS	Full analysis set
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GI	Gastrointestinal
GLP-1	Glucagon like peptide-1
HbA_{1c}	Glycosylated haemoglobin (haemoglobin A_{1c})
HDL	High density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance index
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LY	Life year
MACE	Major adverse cardiovascular event

MCMC	Markov chain Monte Carlo
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Met	Metformin
MMRM	Mixed model repeated measures
MR	Modified release
NA	Not applicable
NCF	Non completers considered failure
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
OAD	Oral antidiabetic drug
OC	Observed cases
OD	Once daily
OHEM	Original Health Economic Model
OLS	Open label set
OR	Odds ratio
PP	Per protocol
PPG	Postprandial plasma glucose
PSA	Probabilistic sensitivity analyses
QALY(s)	Quality-adjusted life year(s)
qw	Once weekly
RCT	Randomised controlled trial
REML	Restricted maximum-likelihood
RS	Randomised set
SBP	Systolic blood pressure
SCR	Screened patient set
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium-glucose co-transporter-2
SPC	Summary of product characteristics
SR	Systematic review
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
tid	Three times daily
TS	Treated set

TSD	Technical support document
TZD	Thiazolidinedione
UKPDS OM1	United Kingdom Prospective Diabetes Study Outcomes Model version 1
UTI	Urinary tract infection
WTP	Willingness-to-pay

Executive Summary

Empagliflozin, marketed as Jardiance®, is a sodium dependent glucose cotransporter 2 (SGLT-2) inhibitor: a relatively new class of oral anti-diabetics (OADs). These reduce hyperglycaemia by blocking reabsorption of filtered glucose through the proximal tubule of the nephron in the kidney, the site of reabsorption of nearly all filtered glucose under normal physiological conditions. This leads to increased urinary glucose excretion, resulting in lower serum glucose levels, as well as weight loss and a reduction in blood pressure from osmotic diuresis (1).

Empagliflozin (Jardiance®) was granted EU marketing authorisation in May 2014. It is licensed in the UK for the treatment of type 2 diabetes to improve glycaemic control in adults as monotherapy, when diet and exercise alone do not provide adequate glycaemic control and where metformin is inappropriate due to intolerance, or in combination with other glucose-lowering medicinal products. This submission relates to the use of empagliflozin as monotherapy in treatment naïve or metformin intolerant/contraindicated patients.

Empagliflozin is available as orally administered film-coated tablets. The recommended starting dosage is 10 mg once daily (OD); this dosage can be increased to a maximum of 25 mg OD for patients who tolerate empagliflozin well and need tighter glycaemic control (i.e. estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or more). There are no restrictions for the use of empagliflozin within its marketing authorisation. The list price for empagliflozin is £36.59 for a 28-day supply (28 × 10 mg or 25 mg tablets) (2, 3).

There are a number of other OADs which can be used as comparators for empagliflozin monotherapy, including other SGLT-2 inhibitors (canagliflozin and dapagliflozin) sulfonylureas (SUs), dipeptidyl peptidase-4 (DPP-4) inhibitors and thiazolidinedione (pioglitazone). These are indicated for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy for patients in whom metformin is contraindicated or not tolerated. NICE currently recommends SUs as an alternative where patients cannot take metformin, however these are associated with high incidence of hypoglycaemia and weight gain (4). Thus there is a need for additional recommended treatment options in this setting.

Clinical effectiveness

Evidence of the efficacy and safety of empagliflozin is provided by two pivotal phase III randomised controlled trials (RCTs; study 1245.20 and study 1275.1) involving 2,327 patients, 1,077 of whom received empagliflozin 10 mg or 25 mg monotherapy (1, 5). Long-term efficacy and safety were also studied in a 76-week extension study (study 1245.31). Overall, both doses of empagliflozin resulted in clinically significant improvements in glycaemic control. In study 1275.1, a reduction in baseline HbA_{1c} was observed in both the metformin treated (-0.06% for empagliflozin 10 mg and 25 mg vs. -0.07% for the comparator linagliptin) and treatment naïve patient groups (-0.84% for empagliflozin 10 mg and -0.95% for empagliflozin 25 mg vs. -0.69% for linagliptin); a comparable or greater difference vs. linagliptin (6, 7). In study 1245.20, empagliflozin 10 mg and 25 mg resulted in a mean HbA_{1c} treatment difference vs. placebo of -0.74% and -0.85% respectively (24 weeks; $p<0.0001$) compared with -0.73% for sitagliptin (1, 5). This benefit was also seen in the group of patients with very poor glycaemic control

studied in the open-label extension (mean change from baseline HbA_{1c} was -3.10% at week 24). The improved glycaemic control demonstrated by empagliflozin was also shown to continue up to 76 weeks, based on the results of the 1245.31 extension study (mean HbA_{1c} difference from placebo of -0.78 and -0.89 for empagliflozin 10 mg and 25 mg respectively; mean HbA_{1c} difference vs. sitagliptin was -0.12 and -0.22 for the 10 mg and 25 mg dose, respectively) (8, 9). In addition, empagliflozin was associated with a generally low incidence of hypoglycaemia, and significant reduction in body weight vs. placebo.

Overall, empagliflozin was well tolerated, with a similar frequency of adverse events (AEs) to comparators in both pivotal studies (81.5% and 68.9% for empagliflozin 10 mg and 25 mg vs. 71.9% for linagliptin 5 mg in study 1275.1 (6, 7); 55% and 61% for empagliflozin 10 mg and 25 mg, vs. 61% and 53% for placebo and sitagliptin in study 1245.20) (1, 5). The majority of AEs were mild to moderate in intensity; 7.4% patients in the empagliflozin 10 mg group and 6.7% patients in the empagliflozin 25 mg group reported serious AEs in study 1275.1 and 3.6% patients in the empagliflozin 10 mg group and 2.2% patients in the empagliflozin 25 mg group reported serious AEs in study 1245.20. The most common AEs reported included urinary tract infection (UTI), nasopharyngitis, upper respiratory tract infection, hyperglycaemia, headache, arthralgia and dyslipidaemia. The 76 week tolerability profile was consistent with that seen in the pivotal trials (8, 9).

Indirect treatment comparison

A network-meta analysis (NMA) was conducted in order to estimate the efficacy and safety of empagliflozin in comparison with other OADs, as outlined in the NICE scope. These included SGLT-2 inhibitors (canagliflozin and dapagliflozin), SUs, DPP-4 inhibitors, pioglitazone and repaglinide used as monotherapy.

The results of this analysis showed that empagliflozin, as well as the other SGLT-2 inhibitors, DPP-4 inhibitors and most doses of pioglitazone and repaglinide, resulted in significant reductions in HbA_{1c} at 24 weeks compared with placebo. Empagliflozin, the only SGLT-2 inhibitor for which data were available, also demonstrated a significantly greater reduction in HbA_{1c} at 52 weeks and ≥ 52 weeks. In addition, empagliflozin and all other SGLT-2 inhibitors showed a significantly greater reduction in weight compared with placebo at 24 weeks. This reduction in weight was maintained for empagliflozin at 52 weeks. Empagliflozin and the other SLGT-2 inhibitors also significantly reduced systolic blood pressure (SBP) compared with placebo at 24 weeks.

Base case cost-effectiveness

The cost-effectiveness analysis was based on two models (A and B), both of which used a United Kingdom Prospective Diabetes Study (UKPDS) backbone. Model A, a simple 1 year decision tree, showed that empagliflozin is cost-effective compared with current monotherapy options. The SGLT-2 class show similar levels of cost effectiveness; both doses of empagliflozin dominate both doses of dapagliflozin, but both are dominated by canagliflozin 100 mg. Model B, a more complex model closer to the recent OHEM from the GDG and NICE, validated the results from Model A. Thus, empagliflozin has been demonstrated to be cost effective in patients unable to take metformin, with consistent direction of results across the two modelling approaches.

1. Background

Burden of disease

- T2DM contributes to considerable global morbidity and mortality, including reduced life expectancy and increased risk of complications, such as cardiovascular disease (CVD), kidney failure, blindness and limb amputation (10, 11).
- T2DM is a prevalent disease; in 2014 there were an estimated 3.3 million adults with diabetes in the UK, of which 90% are estimated to have T2DM (10).
    - The prevalence of T2DM is expected to rise, due to increased prevalence of obesity, decreased physical activity and other lifestyle related factors (10).
- Treating T2DM and its complications is estimated to cost the National Health Service (NHS) £8.8 billion a year, with indirect costs estimated at £13 billion.

Current management of disease

- Current management of T2DM is based on a step-wise approach, with metformin monotherapy as first-line treatment after diet and exercise management. SU monotherapy is recommended as an alternative to metformin monotherapy, where metformin is contraindicated or not tolerated (4, 12).
    - Other classes of therapy, including SGLT-2 inhibitors, DPP-4 inhibitors and thiazolidinediones are indicated for monotherapy use in patients who cannot take metformin; however these have yet to be included in the NICE care pathway.
- SUs are associated with weight gain and hypoglycaemia. There is therefore a need for alternative therapies with a reduced risk of these effects.
- There is also a need for improved adherence to diabetes medication, as poor adherence is thought to predict poor long-term glycaemic control (13, 14).

Empagliflozin (Jardiance®)

- Empagliflozin (Jardiance®) is indicated for the treatment of T2DM as:
    - Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin use is considered inappropriate due to intolerance.
    - Add-on to other glucose-lowering products, including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (15).
- This submission relates to the use of empagliflozin as monotherapy in patients who cannot take metformin due to intolerance.

1.1 Remit of NICE appraisal

The National Institute for Health and Care Excellence (NICE) are conducting a Multiple Technology Appraisal "to appraise the clinical- and cost-effectiveness of canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes".

The purpose of this submission document is to provide a balanced summary of the clinical- and cost-effectiveness data for the use of empagliflozin monotherapy compared with other OADs.

1.2 Disease background

1.2.1 Disease overview

T2DM is a chronic, metabolic disease characterised by hyperglycaemia, caused by a combination of insulin resistance and an insufficient insulin secretory response by pancreatic beta cells (16) It is frequently underdiagnosed with approximately 50% of individuals with T2DM being unaware of their condition (17).

1.2.2 Epidemiology of disease

In 2014 there were an estimated 3.3 million adults with diabetes in the UK, of which 90% are estimated to have T2DM (10), while there are approximately 2.2 million patients in England and Wales on anti-diabetic medication (18). Furthermore, the prevalence of type 2 diabetes in the UK is expected to rise as a result of an increased prevalence of obesity, decreased physical activity and other lifestyle related factors, with around 5 million cases estimated by 2025 (10). As such, it is likely to remain an important disease in the UK in the near future.

1.3 Burden of disease

1.3.1 Impact on the patient

1.3.1.1 Morbidity and mortality

T2DM substantially contributes to global morbidity and mortality (19); life expectancy is reduced by up to 10 years in people with diabetes (11). The effects of chronic hyperglycaemia result in microvascular and macrovascular complications such as kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin; these all contribute to the significant clinical and economic burden of T2DM (20). Cardiovascular disease is the most common complication, with type 2 diabetes patients having at least a two-fold increased risk compared to those without diabetes (21-24). At the same time it is the greatest cause of morbidity and premature death in diabetic patients (25). Kidney disease is another important co-morbidity, accounting for 11% of deaths in T2DM. Around one in four people with diabetes will develop some stage of kidney disease during their lifetime (10), which can lead to the requirement for further treatment. In fact, diabetes is the single most common cause of end stage renal disease requiring dialysis or transplant.

1.3.1.2 Quality of life

People with diabetes have a worse quality of life than people with no chronic illness, even though duration and type of diabetes are not consistently associated with reduced quality of life (26). Intensive treatment does not impair quality of life, and having better glycaemic control is associated with better quality of life (26).

Besides the physical co-morbidities that have an impact on the daily life of patients, multiple studies and meta analyses have shown the association between diabetes and

depression (27). It is estimated that the prevalence of depression in the diabetic population was 24% compared with 17% in the non-diabetic population (28).

1.3.2 Societal and healthcare burden

While treating type 2 diabetes and its complications costs the NHS approximately £8.8 billion a year (12), the indirect costs associated with type 2 diabetes are estimated at £13 billion. These comprise costs related to an increase in premature deaths and illness, loss of productivity and the need for informal care (12). Furthermore, the total cost of diabetes is predicted to rise to £39.8 billion by 2035/6, suggesting that the considerable burden is likely to increase in the coming years.

1.4 Current management of disease

1.4.1 Diagnosis/measurement of disease state

Diagnosis of T2DM is based on criteria published by the World Health Organization (WHO). These include diabetes symptoms, in addition to:

- A random venous plasma glucose concentration of ≥ 11.1 mmol/L, or
- A fasting plasma glucose concentration of ≥ 7.0 mmol/L (whole blood ≥ 6.1 mmol/L), or
- Two hour plasma glucose concentration ≥11.1 mmol/L two hours after 75 g anhydrous glucose in an oral glucose tolerance test (29).

When no symptoms are present, diagnosis should be confirmed by at least one additional glucose test taken on a different day.

HbA_{1c} testing can also be used to diagnose diabetes, with a cut-off of 48mmol/mol (6.5%) recommended for diagnosis. HbA_{1c} is also used to set therapy targets for patients throughout their treatment (30).

1.4.2 Current therapies with a monotherapy indication

1.4.2.1 Metformin (31)

Indication:

Metformin is indicated for the treatment of T2DM, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. In adults, metformin may be used as monotherapy or in combination with other OADs or with insulin. In children (from 10 years of age), metformin may be used as monotherapy or in combination with insulin.

Administration:

The usual starting dose of metformin is 500 mg or 850 mg given orally two or three times daily (during or after meals), whether metformin is used as monotherapy or in combination with OADs or insulin. The dose should be adjusted on the basis of blood glucose measurements after 10 to 15 days. The maximum recommended dose of metformin in adults is 3 g daily, taken as 3 divided doses. The maximum recommended dose in children is 2 g daily, taken as 2 or 3 divided doses.

When administered to elderly patients, the dosage should be adjusted based on renal function.

Metformin is contraindicated in the presence of any of the following:

- Hypersensitivity to metformin hydrochloride or to any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma
- Moderate (stage 3b) or severe renal failure or renal dysfunction (creatinine clearance <45 mL/min)
- Acute conditions with the potential to alter renal function
- Acute or chronic disease which may cause tissue hypoxia
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation.

1.4.2.2 SUs (glibenclamide) (32)

Indication:

Glibenclamide is indicated for the treatment of T2DM in patients who do not respond adequately to dietary measures alone.

Administration:

The starting dose of glibenclamide is 5 mg daily, administered as oral tablets. If glycaemic control is satisfactory the dose may be continued as the maintenance dose. If glycaemic control is unsatisfactory, the dose can be adjusted by increments of 2.5 mg or 5 mg at weekly intervals. The total daily dose of glibenclamide rarely exceeds 15 mg. Elderly patients should start treatment at a dose of 2.5 mg daily.

1.4.2.3 SUs (gliclazide) (33)

Indication:

Gliclazide is indicated for the treatment of T2DM.

Administration:

The total daily dose may vary from 40 to 320 mg, administered orally. The dose should be adjusted according to the individual patient's response, starting with 40-80mg daily (1/2 – 1 tablet) and increasing until adequate control is achieved. A single dose should not exceed 160mg (two tablets). When higher doses are required, gliclazide tablets should be taken twice daily according to the main meals of the day.

In obese patients or those not showing adequate response to gliclazide alone, additional therapy may be required.

1.4.2.4 SUs (glimepiride) (34)

Indication:

Glimepiride is indicated for the treatment of T2DM when diet, physical exercise and weight reduction alone are not adequate.

Administration:

The starting dose of glimepiride is 1 mg per day, given as oral tablets. If good control is achieved, this dosage should be used for maintenance. If control is unsatisfactory the dosage should be increased in a stepwise manner to 2 mg, 3 mg or 4 mg per day based on glycaemic control, with 1 to 2 weeks between each step. The maximum recommended dose is 6 mg per day, although a dosage of >4 mg per day only gives better results in exceptional cases.

1.4.2.5 SUs (glipizide) (35)

Indication:

Glipizide is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

Administration:

The recommended starting dose of glipizide is 5 mg, given orally before breakfast or the midday meal. Elderly patients, those with mild diabetes or those with liver disease may be started on a dose of 2.5 mg. The dose should then be adjusted, normally in increments of 2.5 mg to 5 mg, based on glycaemic control. The maximum recommended single dose is 15 mg; if this does not provide adequate control the dosage may be split up to a maximum daily dose of 20 mg.

1.4.2.6 SUs (tolbutamide) (36)

Indication:

Tolbutamide is indicated for the oral treatment of patients with T2DM who do not respond adequately to dietary treatment alone.

Administration:

The starting dose of tolbutamide is 500 mg twice daily (i.e. two tablets twice daily), given orally. The dose should be adjusted according to each individual's response. The average daily dose is 500 mg to 1,500 mg (one to three tablets); patients who do not respond to 4 tablets daily are not likely to respond to higher doses.

1.4.2.7 Canagliflozin (Invokana) (37)

Indication:

Canagliflozin (Invokana) is indicated for the treatment of adults aged ≥18 years with T2DM to improve glycaemic control as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- Combination therapy: add-on to other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Administration:

The recommended starting dose of canagliflozin is 100 mg OD, given as oral tablets. This dose can be increased to 300 mg OD in patients who tolerate canagliflozin 100 mg OD, who have an eGFR ≥60 mL/min/1.72m^2 or creatinine clearance (CrCl) ≥60 mL/min and need tighter glycaemic control.

Care should be taken when increasing the dose in certain groups, including patients ≥ 75 years of age, patients with known cardiovascular disease (CVD) or patients in whom canagliflozin-induced diuresis poses a risk. When canagliflozin is used in combination with insulin, a lower dose of insulin may be considered to reduce the risk of hypoglycaemia.

1.4.2.8 Dapagliflozin (Forxiga) (38)

Indication:

Dapagliflozin (Forxiga) is indicated in adults aged ≥18 years with T2DM to improve glycaemic control as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin is considered inappropriate due to intolerance.
- Combination therapy: add-on to other glucose-lowering medicinal products, including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Administration:

The recommended dose of dapagliflozin is 10 mg OD for both monotherapy and combination therapy. Dapagliflozin is administered as oral tablets. When dapagliflozin is given in combination with insulin, a lower dose of insulin may be considered to reduce the risk of hypoglycaemia.

1.4.2.9 Sitagliptin (Januvia) (39)

Indication:

Sitagliptin (Januvia) is indicated for the treatment of adult patients with T2DM to improve glycaemic control as:

- Monotherapy: in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
- Dual therapy: in combination with metformin when diet and exercise alone do not provide adequate glycaemic control. Sitagliptin can also be used in combination with a SU (when metformin is contraindicated or not tolerated) or a thiazolidinedione (when use of thiazolidinedione is appropriate).
- Triple therapy: in combination with a SU and metformin when diet and exercise plus dual therapy does not provide adequate glycaemic control. Sitagliptin can also be used in combination with metformin and a thiazolidinedione when use of the latter is appropriate, and diet and exercise plus dual therapy does not provide adequate glycaemic control.

- Combination with insulin: with or without metformin when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control

Administration:

The recommended dose of sitagliptin is 100 mg OD, given as oral tablets. When sitagliptin is used in combination with a SU or insulin, a lower dose of the SU or insulin may be considered to reduce the risk of hypoglycaemia. Dose adjustments are required for patients with moderate or severe renal impairment.

1.4.2.10 Saxagliptin (Onglyza) (40)

Indication:

Saxagliptin (Onglyza) is indicated for the treatment of adult patients with T2DM to improve glycaemic control as:

- Monotherapy: in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
- Dual therapy: in combination with metformin when metformin alone, with diet and exercise, does not provide adequate glycaemic control. Saxagliptin can also be used in combination with a SU (when metformin is considered inappropriate) or a thiazolidinedione (when use of thiazolidinedione is appropriate).
- Triple therapy: in combination with metformin and a SU when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.
- Combination with insulin: with or without metformin when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

Administration:

The recommended dose of saxagliptin is 5 mg OD, administered as oral tablets. When saxagliptin is given in combination with insulin or a SU, a lower dose of the insulin or SU may be required to reduce the risk of hypoglycaemia. Dose adjustments are required for patients with moderate or severe renal impairment.

1.4.2.11 Linagliptin (Trajenta) (41)

Indication:

Linagliptin (Trajenta) is indicated for the treatment of T2DM in adults to improve glycaemic control as:

- Monotherapy: in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment.
- Combination therapy: add-on to metformin (with or without a SU) when diet and exercise plus metformin (with or without a SU) do not provide adequate glycaemic control.
- Combination with insulin: with or without metformin when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

Administration:

The recommended dose of linagliptin is 5 mg OD, given as oral tablets. When linagliptin is used in combination with a SU or insulin, a lower dose of the SU or insulin may be required to reduce the risk of hypoglycaemia.

1.4.2.12 Vildagliptin (Galvus) (42)

Indication:

Vildagliptin (Galvus) is indicated for the treatment of T2DM in adults as:

- Monotherapy: in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance
- Dual therapy: in combination with metformin in patients with insufficient glycaemic control despite maximal tolerate dose of monotherapy with metformin. Vildagliptin can also be used in combination with a SU (when metformin is inappropriate due to contraindications or intolerance) or a thiazolidinedione (when use of thiazolidinedione is appropriate).
- Triple therapy: in combination with a SU and metformin when diet and exercise plus dual therapy does not provide adequate glycaemic control.
- Combination with insulin: with or without metformin when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

Administration

The recommended dose of vildagliptin (when used as monotherapy and in combination with metformin, thiazolidinedione, metformin plus a SU or insulin) is 50 mg twice daily, administered orally as two 50 mg tablets. When used in dual therapy with a SU, the recommended daily dose is 50 mg.

1.4.2.13 Acarbose (43)

Indication:

Acarbose is recommended for the treatment of T2DM in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

Administration:

The recommended starting dose of acarbose is 50 mg three times daily, administered as oral tablets. In some patients the dose may be increased gradually to minimise GI side effects. In this case the initial dose may be 50 mg once or twice a day, with a subsequent titration to three times a day. If the clinical response is still inadequate after six to eight weeks, the dosage may be increased to 100 mg three times a day. This may be further increased to the maximum dose of 200 mg three times a day, if necessary.

1.4.2.14 Thiazolidinediones (pioglitazone) (44)

Indication:

Pioglitazone is indicated for the treatment of T2DM as:

- Monotherapy: in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate due to contraindications or intolerance.
- Dual therapy: in combination with metformin in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of metformin monotherapy. Pioglitazone can also be used in combination with a SU in adult patients who show intolerance to metformin, or for whom metformin is contraindicated.
- Triple therapy: in combination with metformin and a SU in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
- Combination with insulin in patients with insufficient glycaemic control on insulin for whom metformin is inappropriate due to intolerance or contraindications.

Patients treated with pioglitazone should be reviewed after three to six months of treatment; if glycaemic response is not adequate treatment should be discontinued.

Administration:

The initial dose of pioglitazone is 15 mg or 30 mg OD, administered as oral tablets. The dose may be increased in increments up to 45 mg OD. If patients experience hypoglycaemia during treatment with pioglitazone and insulin, the dose of insulin should be decreased.

1.4.2.15 Repaglinide (45)

Indication:

Repaglinide is indicated for the treatment of adults with T2DM whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in adults with T2DM who are not satisfactorily controlled on metformin alone.

Administration:

The recommended starting dose of repaglinide is 0.5 mg, with one or two weeks between titration steps (as determined by blood glucose response). The maximum recommended single dose is 4 mg taken with main meals, and the total maximum daily dose should not exceed 16 mg. Repaglinide is administered as oral tablets.

1.4.3 Treatment pathway

Current treatment of T2DM in the UK broadly follows NICE guidelines (published in 2009). Figure 1 shows the current care pathway for patients with T2DM, which was updated in 2015 (4).

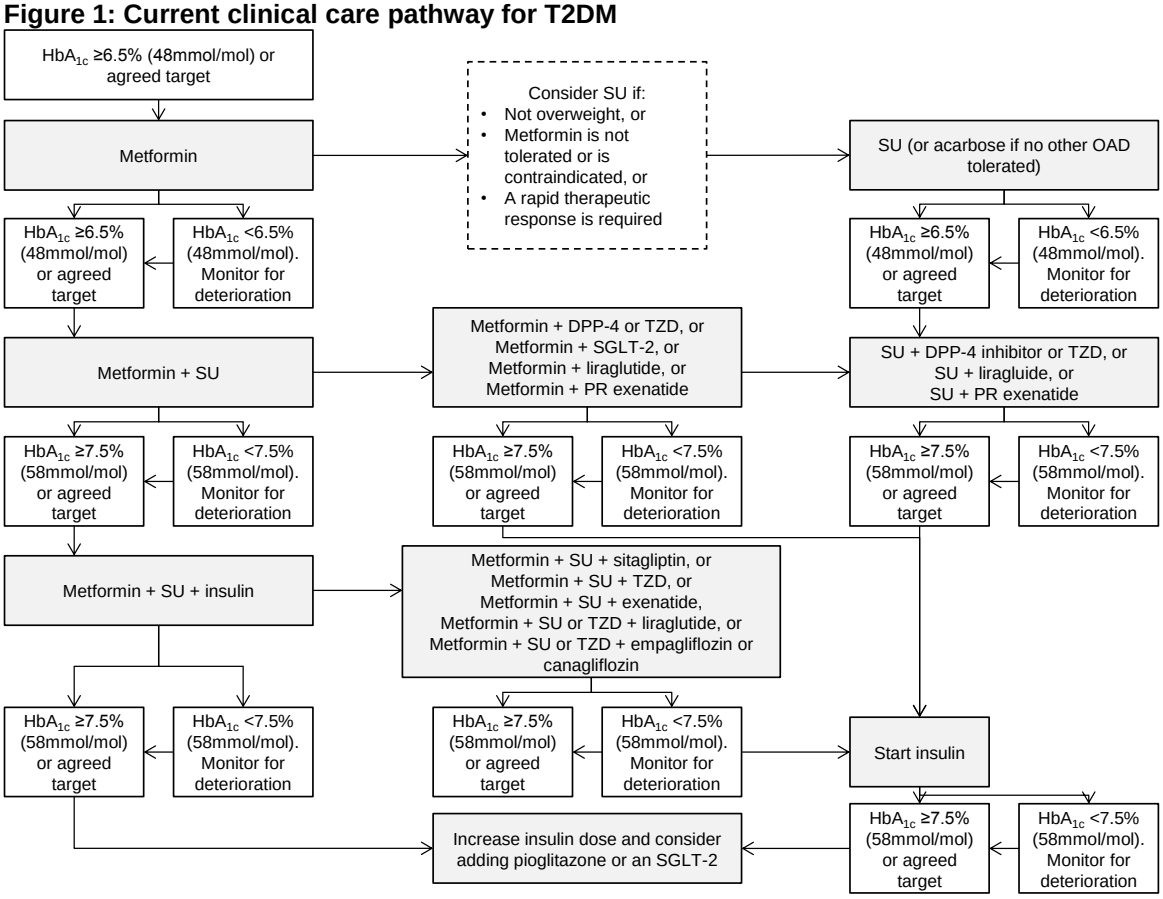
Patients with inadequate glycaemic control (HbA_{1c} ≥6.5% or 48 mmol/mol) despite a diet and exercise programme are initially treated with metformin monotherapy. SUs can be used as an alternative to metformin if the patient is not overweight, if metformin is not tolerated or is contraindicated or a rapid therapeutic response is required due to hyperglycaemic symptoms. Patients' HbA_{1c} levels are monitored during treatment, and dual therapy is considered once they exceed the agreed HbA_{1c} target. Acarbose

monotherapy may be considered if the patient is unable to use other oral glucose-lowering mediations.

NICE is currently assessing the use of SGLT-2 inhibitors (canagliflozin and dapagliflozin in addition to empagliflozin) as monotherapy for the treatment of T2DM patients who cannot take metformin (due to intolerance or contraindication).

DPP-4 inhibitors and thiazolidinedione (pioglitazone) are not included as monotherapy in the current pathway; these are only included as dual or triple therapy.

Figure 1: Current clinical care pathway for T2DM



Abbreviations: DPP-4, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated haemoglobin; OAD, oral antidiabetic; PR, prolonged release; SGLT-2, sodium dependent glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione
Source: NICE diabetes pathway (4)

1.4.3.1 Treatment guidelines

NICE guideline [CG87]

As presented above, metformin is considered first-line therapy following lifestyle interventions, for people who are not overweight or contra-indicated. SUs are an alternative if metformin cannot be used (30).

American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD)

In addition to the NICE guidance (represented by the pathway above), guidelines are also available from the ADA and EASD (“Management of hyperglycaemia in type 2

diabetes: a patient-centred approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)", June 2012); an update was also published in January 2015). These guidelines recommend metformin as first-line pharmacological therapy, after diet exercise and education, unless contraindicated. Specific recommendations for the choice of therapy in patients who cannot take metformin are not given (46, 47).

1.5 Factors for consideration in therapy

1.5.1 Adherence to therapy

Poor adherence to diabetes medication is thought to predict long-term glycaemic control, based on several studies in T2DM patients (13). In spite of this, suboptimal adherence to OADs has been reported globally, based on a review conducted by Cramer et al (14). There is therefore an unmet need to increase adherence and compliance to therapy, in order to improve outcomes in T2DM.

1.5.2 Mortality from disease

T2DM causes considerable mortality globally; life expectancy is reduced by up to 10 years compared with those without diabetes (11). In England and Wales, people with T2DM are at a 34.5% increased risk of death than age-matched individuals without diabetes (48). Data from the National Diabetes Audit suggest that more than 20,000 people with diabetes in England and Wales die prematurely every year (48).

1.5.3 Morbidity from disease

T2DM is associated with a number of co-morbidities when not adequately managed, and around half of patients have co-morbidities at the time of diagnosis (49). These include CVD, kidney disease, blindness, limb amputation neuropathy and depression, all of which can lead to increased patient disability (10). CVD in particular is a common complication; people with T2DM have at least a 2 times increased risk of CVD compared with those without diabetes (21-24). In addition, it is a major cause of death and disability in people with diabetes, accounting for 52% of deaths in those with T2DM (50). Kidney disease is another common co-morbidity, with around 25% of diabetes patients developing some stage of renal disease during their lifetime (10).

1.5.4 AEs with therapy

Current therapies are generally well tolerated, however a number of side effects are seen. Metformin is associated with an increased risk of gastrointestinal (GI) side effects, such as nausea, vomiting, diarrhoea and abdominal pain, resulting in the need to step up the dosage of metformin over several weeks (31). Lactic acidosis, a rare but serious metabolic condition, can also occur during treatment with metformin, leading to high mortality in the absence of prompt treatment (31). SUs are associated with a risk of hypoglycaemia and weight gain (4, 34). Whilst mild/moderate hypoglycaemia can be treated with dietary measures, severe or prolonged hypoglycaemia requires immediate medical treatment and occasionally hospitalisation. There is therefore a need for alternative therapies with a reduced risk of these AEs, in particular reduced risk of hypoglycaemia.

1.6 Empagliflozin (Jardiance®)

Please see Appendix A (provided separately) for the summary of product characteristics for empagliflozin.

Indication

Empagliflozin was granted EU marketing authorisation in May 2014, and is licensed in the UK for the treatment of T2DM to improve glycaemic control in adults as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin is considered inappropriate due to intolerance.
- Combination therapy: in combination with other glucose lowering medicinal products, including insulin, when these together with diet and exercise do not provide adequate control.

This submission relates to the use of empagliflozin as monotherapy for treatment-naïve or metformin intolerant/contraindicated patients.

Administration

Empagliflozin is administered as oral, film-coated tablets. The recommended starting dose is 10 mg OD; this dose can be increased to a maximum of 25 mg daily for patients who tolerate empagliflozin well and are in need of tighter glycaemic control (i.e. eGFR ≥60 mL/min/1.73m^2).

1.6.1 Advantages of empagliflozin

Empagliflozin (10 mg and 20 mg) has demonstrated clinically significant improvements in glycaemic control (see Section 3 for further details). This is achieved with a generally low incidence of hypoglycaemia and a reduction in SBP and weight compared with placebo.

Empagliflozin monotherapy is indicated for use as an alternative to metformin monotherapy for metformin intolerant/contraindicated patients. SUs, recommended by NICE as an alternative to metformin monotherapy, should not be used in patients who are overweight (see Section 1.4.3); thus empagliflozin provides an additional treatment option for overweight patients who cannot take metformin. Empagliflozin also represents an alternative with a lower risk of hypoglycaemia compared with SUs.

In addition, empagliflozin monotherapy has comparable improvements in glycaemic control compared with other SGLT-2 inhibitors (canagliflozin and dapagliflozin), with empagliflozin 25 mg demonstrating a greater reduction in weight compared with DPP-4 inhibitors at 24 weeks (see Section 4.1.5). Similarly, empagliflozin and the other SGLT-2 inhibitors demonstrated a greater reduction in weight vs. placebo in comparison with all the comparators at 24 weeks. Empagliflozin (which was the only SGLT-2 inhibitor for which data were available) also demonstrated greater reductions in weight vs. placebo in comparison with all comparators at 52 weeks.

2. Systematic review of the literature

2.1 Identification of studies

A systematic review was conducted to identify relevant clinical data from the published literature regarding the clinical effectiveness of empagliflozin monotherapy for the treatment of T2DM in treatment naïve or metformin intolerant/contraindicated patients.

The objectives of the review were:

- To provide clinical evidence for the efficacy and safety outcomes of empagliflozin monotherapy in treatment naïve or metformin intolerant/contraindicated patients with T2DM
- To compare the efficacy and safety of SGLT-2 inhibitors with other relevant licensed monotherapies for treatment of T2DM.

Searches were conducted on 15th October 2014 in The Cochrane Library, OVID MEDLINE (including MEDLINE In-process) and OVID Embase, with no restrictions on date. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for the condition, the treatments and the outcomes of interest. The full search strategy can be found in Appendix B (provided separately).

Searches were supplemented by hand searching of conference proceedings for the American Diabetes Association (ADA) – Scientific Sessions and the European Association for the Study of Diabetes (EASD) – EASD Annual Meeting between 2012 and 2014, inclusive. Reference lists of included publications and identified relevant systematic reviews were also hand searched.

Identified publications were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria, and any uncertainties were resolved by discussion with a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer and verified by a second reviewer.

2.2 Study selection

2.2.1 Eligibility criteria

Inclusion and exclusion criteria, based on the population, interventions, comparators, outcomes and study design, are shown in Table 1. Repaglinide was not included in the eligibility criteria, since it is not widely prescribed (51) and was not considered a comparator when the systematic review was initiated. However when the draft NICE T2DM guidelines were published and repaglinide was recommended, papers that reported repaglinide were included in the remainder of the review and extraction.

Table 1: Eligibility criteria used in search strategy

	Description
Inclusion criteria	
Population	Adults (≥18 years) with T2DM: • who are intolerant of or contraindicated for metformin, or • who are treatment naïve, or • who have undergone washout (≥1 week duration) following treatment with metformin, or a SU or other oral anti-diabetic drugs
Interventions	SGLT-2 inhibitor monotherapy: • Canagliflozin • Dapagliflozin • Empagliflozin

Comparators[†]	• SU monotherapy:
	  ○ Carbutamide
	  ○ Acetohexamide
	  ○ Chlorpropamide
	  ○ Tolbutamide
	  ○ Glipizide
	  ○ Gliclazide
	  ○ Glibenclamide (glyburide)
	  ○ Glibornuride
	  ○ Gliquidone
	  ○ Glisoxepide
	  ○ Glyclopyramide
	  ○ Glimepiride
	• DPP-4 inhibitor monotherapy:
	  ○ Sitagliptin
	  ○ Saxagliptin
	  ○ Alogliptin
	  ○ Linagliptin
	  ○ Vildagliptin
	• TZD monotherapy:
	  ○ Pioglitazone
	• Alpha-glucosidase inhibitor monotherapy:
	  ○ Acarbose
	• Placebo

	Description
Outcomes	• Efficacy: ○ HbA_{1c} (including change in HbA_{1c}) ○ Weight (including change in weight) ○ BMI ○ SBP ○ DBP ○ LDL‡ ○ HDL‡ ○ Proportion of patients achieving HbA_{1c} targets as follows: ▪ 6.5% ▪ 7.0% ▪ 7.5% • AEs: ○ Hypoglycaemia (overall, severe, non-severe; with definition) ○ Urinary tract infection ○ Genital tract infection
Study design	RCTs
Language restrictions	English language papers and English language abstracts of non-English language papers
Exclusion criteria	
Population	• Patients receiving continued metformin therapy or tolerating metformin therapy • Patients who discontinued metformin due to lack of efficacy, unless undergone a washout as defined in the inclusion criteria • Patients who received prior treatment for T2DM other than metformin without undergoing a washout as defined in the inclusion criteria • History of diabetic ketoacidosis or type 1 diabetes mellitus • History of pancreas or beta-cell transplantation • Studies in which results are reported for mixed populations only • Unclear whether population meets the listed criteria (due to lack of detailed reporting)
Interventions	NA
Comparators	NA
Outcomes	Quality of life, cost-effectiveness outcomes, resource use
Study design	Observational studies, reviews, editorials/comments, letters/notes
Language restrictions	Non-English abstracts

Abbreviations: AE, adverse event; BMI, body mass index; DBP, diastolic blood pressure; DPP-4, dipeptidyl-peptidase 4; HDL, high density lipoprotein; LDL, low density lipoprotein; NA, not applicable; RCT, randomised controlled trial; SBP, systolic blood pressure; SGLT-2, sodium-glucose co-transporter-2; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.
†Repaglinide was not included in the search strategy since it is not widely prescribed and was not considered a comparator when the systematic review was initiated.
‡Please note that these outcomes were tested as part of the safety evaluation in Study 1275.1 and Study 1245.31.

The search identified 14,809 publications, of which 10,472 were initially assessed based on title and abstract following removal of duplicates (Figure 2). Papers not meeting the inclusion criteria were excluded and allocated an exclusion code, using a hierarchy of codes, to document the rationale. Publications that did not compare at least two monotherapy groups were tagged if they could not be excluded based on any of the other exclusion criteria. This was to enable tracking of these studies in the instance that insufficient evidence on comparative monotherapies alone could be identified and allow expansion of the network diagram to include combination treatments. In addition, relevant systematic reviews were tagged for hand searching of references.

After this stage, 895 publications were included and assessed based on the full text. Further publications were excluded and allocated a code using the same exclusion hierarchy, yielding the 243 publications eligible based on the pre-defined inclusion criteria.

Additional criteria were then applied. These are listed below along with the rationale for applying each of them:

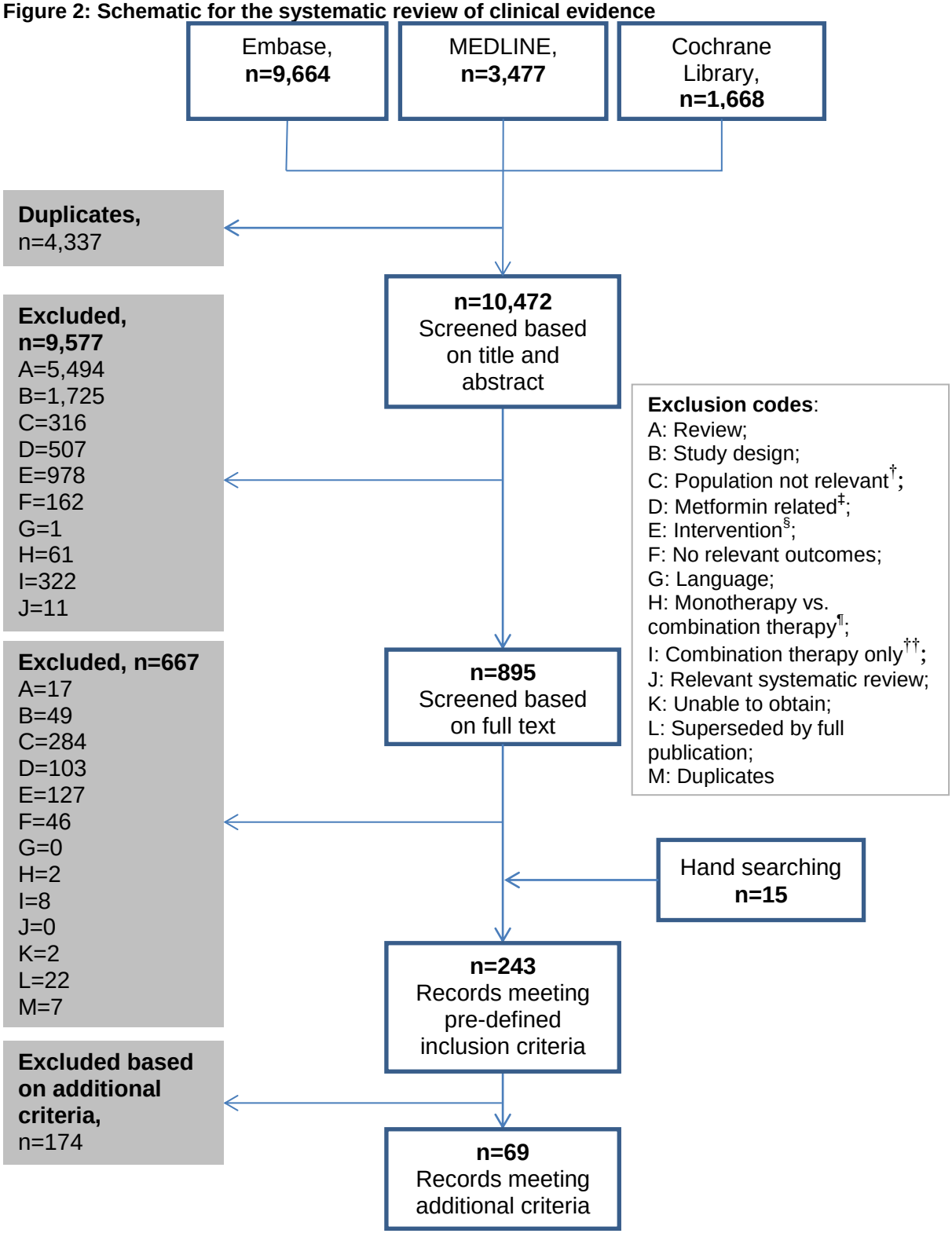
- Size of the analysis population ≥ 50 patient. In order to reduce the likelihood of a small investigative study being included that could introduce significant bias into the results.
- HbA_{1c} data reported at ≥ 18 weeks follow up. In order to drive a model with one-year cycles, it was considered that data of less than 18 weeks duration could not be used, and would not fit within the intended use of broadly 6 month, 12 month or 18 month data.
- At least two relevant monotherapy arms, not including acarbose as it is not included in the NICE scope (52).

Following publication of the NICE draft guidelines which recommended the use of repaglinide it was necessary to allow for a comparison to be made with repaglinide. Therefore any studies examined based on the full publication that compared repaglinide monotherapy with an eligible comparator were subsequently included provided that they met both the pre-defined and additional inclusion criteria.

2.2.2 Included studies

Following assessment and exclusion of studies based on title, abstract and full text, 69 publications of 60 unique RCTs were included based on the additional eligibility criteria, making up the final data set (1, 9, 53-119). Figure 2 shows the systematic review flow.

Figure 2: Schematic for the systematic review of clinical evidence



†Any one of the following apply: not T2DM patients, not treatment naïve or not undergone washout as described in inclusion criteria, aged <18 years, history of ketoacidosis, or received pancreas and/or beta-cell transplantation; ‡Patients in all treatment arms received metformin alone or in combination with any other therapy; § None of the interventions or comparators listed in the inclusion criteria are used; ¶Only one monotherapy arm is reported and it is compared with combination therapy treatment arms only; ††Only combination therapies are reported. Codes H–J were used to tag any publications that did not compare at least two monotherapy groups or required reference searching, and were only applied if the publication was not excluded based on any of the other exclusion criteria.

2.2.3 Details of included RCTs

Details of the 69 publications included in the systematic review are reported in Table 2. Comparator arms that were not relevant are in italics.

Table 2: List of relevant RCTs

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Arjona Ferreira, 2013a (53)	NA	Randomised, double-blind, active-controlled. Preceded by a 6 week diet and exercise period and a 2 week single-blind placebo run-in.	USA†	T2DM; ESRD or peritoneal dialysis therapy for ≥6 months; HbA_{1c} 7−9% at randomisation; Aged >30 years. Treatment naïve to AHAs or undergone at least 8−14 weeks washout, dependent on the AHA.	**Sitagliptin 25 mg, OD**	**59**	54 weeks
					Glipizide 2.5−10 mg, OD−BD Progressively titrated at 2 week intervals	**62**	
Arjona Ferreira, 2013b (54)	NA	Randomised, double-blind, active-controlled. Preceded by a 2 week single-blind placebo run-in.	USA, France†	T2DM; Moderate to severe chronic renal insufficiency (eGFR <50 mL/min/1.73 m^2 based on the MDRD equation); Not on dialysis; HbA_{1c} 7−9%; Aged ≥30 years. Treatment naïve to AHAs or undergone at least a 14 week washout.	**Sitagliptin 25 mg or 50 mg, OD** 25 mg if severe renal insufficiency; 50 mg if moderate renal insufficiency	**135**	54 weeks
					Glipizide 2.5−20 mg, OD Started at 2.5 mg and up-titrated	**142**	
Aronoff, 2000 (55)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 6–8 week single-blind placebo run-in.	USA	T2DM; HbA_{1c} ≥7.0%; FPG ≥140 mg/dL; Fasting C-peptide >1 ng/mL. Treatment naïve to AHAs, or undergone at least 8 weeks washout prior to randomisation.	**Placebo**	**79**	26 weeks
					Pioglitazone 7.5 mg	**80**	
					Pioglitazone 15 mg	**79**	
					Pioglitazone 30 mg	**85**	
					Pioglitazone 45 mg	**76**	
Aschner, 2006 (56)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 2 week single-blind placebo run-in.	Multinational	T2DM; HbA_{1c} 7−10% at screening; FPG ≤260 mg/dL; Aged 18−75 years. Treatment naïve to AHAs or undergone at least 6−12 weeks washout, dependent on the AHA.	**Placebo, OD**	**244**	24 weeks
					Sitagliptin 100 mg, OD	**229**	
					Sitagliptin 200 mg, OD	**238**	
Bailey, 2012 (57)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 2 week single-blind placebo run-in.	USA, India, Canada, Mexico, Russia, South Africa, Puerto Rico	T2DM; HbA_{1c} 7−10%; BMI ≤45 kg/m^2; C-peptide ≥0.34 nmol/L; Aged 18−77 years. Treatment naïve to AHAs, or received anti-diabetic medication for <24 weeks, not in the 4 weeks prior to enrolment, and never for >14 days in the 12 weeks prior	**Placebo, OD in the morning**	**68**	24 weeks
					Dapagliflozin 1 mg, OD in the morning	**72**	
					Dapagliflozin 2.5 mg, OD in the morning	**72**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
				to enrolment.	**Dapagliflozin 5 mg, OD in the morning**	**66**	
Barnett, 2012 (58)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 2 week single-blind placebo run-in.	Canada, Mexico, Philippines, Romania, Russia, Ukraine, USA	T2DM; HbA_{1c} 7−10% (7−9% in Canada) if treatment naïve (6.5−9% if on 1 AHA); BMI ≤40 kg/m^2. Intolerant or contraindicated for metformin; Treatment naïve to AHAs or undergone at least 10 weeks washout from previous anti-diabetic therapy.	**Placebo**	**73**	18 weeks (A 34 week extension was also carried out, but placebo arm was switched to sitagliptin).
					Linagliptin 5 mg, OD	**147**	
Barzilai, 2011 (59)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 2 week single-blind placebo run-in.	USA	T2DM; HbA_{1c} 7−10%; Aged ≥ 65 years. Treatment naïve to AHAs, or undergone at least 8−10 weeks washout.	**Placebo, OD**	**91**	24 weeks
					Sitagliptin 50 or 100 mg, OD 100 mg OD if eCrCl ≥ 50 mL/min. 50 mg OD if eCrCl <50 and ≥ 30 mL/min**.**	**101**	
Boardman, 2011 (60) (abstract)	Russell-Jones, 2012 (106); Cuddihy, 2011 (65) (abstract)	Subgroup analysis of a randomised, double-blind trial (106).	Multinational (Europe, USA, Brazil, Argentina, Canada, India, Israel, Korea, Mexico, South Africa, Taiwan)	T2DM; HbA_{1c} 7.1–11%; BMI 23-45 kg/m^2; History of stable weight. Treatment naïve to AHAs, or received AHAs for <7 days in the 3 months prior to screening.	**Sitagliptin 100 mg, per day**	**163**	26 weeks
					Pioglitazone 45 mg, per day Titrated in weekly increments to reach this dose.	**163**	
					Metformin 2,000–2,500 mg, per day¶	***246***	
					Exenatide 2 mg, qw¶	***248***	
Charbonnel, 2005 (61)	Tan, 2005 (116)	Randomised, double-blind. Consisted of a 16 week titration period and a 36	Europe, Australia, Canada, South Africa,	T2DM; HbA_{1c} 7.5–11%, stable or worsening over the previous 3 months; Aged 35–75 years. Treatment naïve to AHAs, and treated	**Gliclazide 40–160 mg, BD** Increased in 80 mg/day intervals every 4 weeks, to maximum tolerated dose at 16 weeks.	1270§	52 weeks

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
		week maintenance period at maximum tolerated dose.	Israel	with diet only.	**Pioglitazone 15–45 mg, OD** Increased in 15 mg intervals every 4 weeks, to maximum tolerated dose at 16 weeks.		
Chen, 2013 (62) (abstract)	NA	Randomised, double-blind, placebo-controlled, Phase III.	China, Malaysia, Philippines	T2DM. Treatment naïve to AHAs, or at least 4 weeks washout following AHA monotherapy.	**Placebo, OD**	**99**	24 weeks
					Linagliptin 5 mg, OD	**201**	
Chou, 2012 (63)	NA	Randomised, double-blind, placebo- and active-controlled, Phase III. Preceded by a 2 week single-blind placebo run-in and followed by a 2 week safety period.	USA, India, Europe, South America, South Africa	T2DM; HbA_{1c} >7% to ≤ 8.5%; Non-fasting C-peptide >0.5 ng/mL; Aged ≥ 18 years. Treatment naïve to AHAs, or not taken any AHA in the previous 2 months, or discontinued AHAs at the start of 2 week placebo run-in.	**Placebo, OD in the morning**	**134**	26 weeks
					Pioglitazone 45 mg, OD in the morning	**728**	
					Rivoglitazone 1 mg, OD in the morning¶	***266***	
					Rivoglitazone 1.5 mg, OD in the morning¶	***733***	
Coniff, 1995 (64)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 6 week diet-only run-in and ended with a 6 week follow-up on diet and exercise only.	USA	T2DM for ≥ 6 months; Body weight stable ±5 kg in the previous 3 months; FPG ≥ 140 mg/dL at enrolment; Aged ≥18 years. Treatment naïve to AHAs, or undergone at least 4 weeks washout prior to enrolment.	**Placebo**	**62**	24 weeks
					Tolbutamide 250 mg, tid Titrated in 250 mg intervals if 1 hour PPG ≥ 200 mg/dL after 6, 12 or 18 weeks	**66**	
					Acarbose 200 mg, tid¶	***67***	
					Acarbose 200 mg, tid + Tolbutamide 250 mg, tid¶	***60***	
Cuddihy, 2011 (65) (abstract)	Russell-Jones, 2012 (106); Boardman, 2011 (60) (abstract)	Additional HbA_{1c} data from a randomised, double-blind trial (106).	Multinational (Europe, USA, Brazil, Argentina, Canada, India, Israel,	T2DM; HbA_{1c} 7.1–11%; BMI 23-45 kg/m^2; History of stable weight. Treatment naïve to AHAs, or received AHAs for <7 days in the 3 months prior to screening.	**Sitagliptin 100 mg, per day**	**163**	26 weeks
					Pioglitazone 45 mg, per day Titrated in weekly increments to reach this dose.	**163**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
			Korea, Mexico, South Africa, Taiwan)		***Metformin 2,000–2,500 mg, per day***¶	***246***	
					Exenatide 2 mg, qw¶	***248***	
DeFronzo, 2008 (66)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 4 week single-blind placebo run-in.	South America, Australia, New Zealand, Central America, USA, India, South Africa, Europe	T2DM, on diet and exercise treatment for >1 month; HbA_{1c} 7–10%; BMI 23-45 kg/m^2; SBP ≤ 180 mmHg; DBP ≤110 mmHg; FPG <275 mg/mL; Aged 18–80 years. Treatment naïve to AHAs, or not currently on AHA therapy and not for ≥7 days within the previous 3 months.	**Placebo, OD before first meal**	**64**	26 weeks
					Alogliptin 12.5 mg, OD before first meal	**133**	
					Alogliptin 25 mg, OD before first meal	**131**	
Dejager, 2007 (67)	NA	Randomised, double-blind, placebo-controlled.	USA, Russia, Tunisia	T2DM; HbA_{1c} 7.5−10%; FPG <15 mmol/L; BMI 22−45 kg/m^2; Aged 18−80 years. Treatment naïve to AHAs, or not taken AHAs in the 12 months prior to enrolment and never for >3 consecutive months.	**Placebo**	**94**	24 weeks
					Vildagliptin 50 mg, OD	**104**	
					Vildagliptin 50 mg, BD	**90**	
					Vildagliptin 100 mg, OD	**92**	
Del Prato, 2011 (68)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 2 week placebo run-in.	Multinational (Europe and Asia)	T2DM; HbA_{1c} 7−10% at end of run-in; BMI ≤ 40 kg/m^2; Aged 18−80 years. Treatment naïve to AHAs, or undergone at least 6 weeks washout.	**Placebo**	**163**	24 weeks
					Linagliptin 5 mg, OD	**333**	
Derosa, 2003 (69)	NA	Randomised, double-blind, placebo-controlled.	Italy	T2DM for ≥6 months; HbA_{1c} >7%; SBP <130 mmHg; DBP <85 mmHg; Serum creatinine <1.5 mg/dL; LDL ≥100 mg/dL; Non-smokers. Treatment naïve to AHAs, or undergone at least 4 weeks washout.	**Glimepiride 1 mg, OD**	**62**	26 weeks and 52 weeks
					Repaglinide 1 mg, OD	**62**	
Dills, 1996 (70)	NA	Randomised, double-blind, active-controlled. Preceded by a 4 week single-blind placebo	USA	T2DM; Body weight 90−150% of ideal; FPG <200 mg/dL (patients on AHAs) or 160−300 mg/dL (diet treated patients only); Aged 30−80 years.	**Glimepiride 1−16 mg, OD–BD** Once 12 mg reached, dosage was split and a BD regimen used.	**261**	52 weeks

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
		run-in. Consisted of a 12 week titration phase, during which dose was increased at 2-week intervals, and 40 week maintenance period.		Treatment naïve to AHAs, or undergone at least 4 weeks of washout.	**Glibenclamide 1.25−20 mg, OD–BD** Once 15 mg reached, dosage was split and a BD regimen used.	**259**	
Drouin, 2000 (71)	NA	Randomised, double-blind. Preceded by a 2 week single-blind placebo run-in. Consisted of a 4 month titration phase and a 6 month maintenance phase.	Czech Republic, France, Greece, Germany, Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain	T2DM for ≥6 months; HbA_{1c} 6–9%; BMI 22–35 kg/m^2; FPG 7.8–13.9 mmol/L. Treatment naïve to AHAs or undergone at least 2 weeks washout. Treated for ≥3 months with diet.	**Gliclazide 80–320 mg, per day** Titrated in 80 mg intervals every 4 weeks for first 16 weeks, as necessary. 80 mg taken OD; Doses >80 mg split and taken as a BD regimen.	**378**	43 weeks
					Gliclazide MR 30–120 mg, OD in the morning Titrated in 30 mg intervals every 4 weeks for first 16 weeks, as necessary.	**378**	
Erem, 2014 (72)	NA	Randomised. Included a 4–8 week titration period.	Turkey	T2DM newly diagnosed; FPG ≥140 mg/dL or HbA_{1c} ≥8%; or, FPG 126–139 mg/dL or HbA_{1c} 7–8% and HOMA-IR >3; Aged 30–70 years. Treatment naïve to AHAs.	**Gliclazide MR 30–120 mg, OD** Titrated at 2–4 week intervals for first 4–8 weeks as necessary.	**19**	26 weeks and 52 weeks
					Pioglitazone 15–45 mg, per day Titrated at 2–4 week intervals for first 4–8 weeks as necessary.	**19**	
					Metformin 500 mg, OD to 1000 mg BD¶ *Titrated at 1–2 week intervals.*	***19***	
Ferrannini, 2010 (73)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 2 week diet and exercise placebo run-in (1 week for patients with HbA_{1c} 10.1−12%).	USA, Canada, Mexico, Russia	T2DM; HbA_{1c} 7−10%; Fasting C-peptide ≥1 ng/mL; BMI ≤45 kg/m^2; Aged 18−77 years. Treatment naïve to AHAs and inadequately controlled on diet and exercise alone.	**Placebo**	**75**	24 weeks
					Dapagliflozin 2.5 mg, OD in the morning	**65**	
					Dapagliflozin 5 mg, OD in the morning	**64**	
					Dapagliflozin 10 mg, OD in the morning	**70**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
					Dapagliflozin 2.5 mg, OD in the evening	**67**	
					Dapagliflozin 5 mg, OD in the evening	**68**	
					Dapagliflozin 10 mg, OD in the evening	**76**	
				As above, except HbA_{1c} 10.1−12%.	**Dapagliflozin 5 mg, OD in the morning**	**34**	
					Dapagliflozin 10 mg, OD in the morning	**39**	
Foley, 2009 (75)	NA	Randomised, double-blind, active-controlled.	Multinational (Europe, Latin America, South Africa)	T2DM; HbA_{1c} 7.5−11%; BMI 22-45 kg/m^2; FPG <15 mmol/L (270 mg/dL); Aged ≥18 years. Treatment naïve to AHAs or not received any AHA in the 12 weeks prior to screening and not for >3 consecutive months at any point.	**Vildagliptin 50 mg, BD**	**546**§	104 weeks
					Gliclazide 80−320 mg, OD Titrated every 4 weeks, in 80 mg intervals, if FPG >7 mmol/L (126 mg/dL).		
Foley, 2011 (74)	NA	Randomised, double-blind.	Switzerland	T2DM; HbA_{1c} ≤7.5%; BMI 22–45 kg/m^2; Aged ≥30 years. Treatment naïve to AHAs, or not received any AHA in the 12 weeks prior to randomisation and not for >3 consecutive months at any time.	**Placebo**	**30**	52 weeks
					Vildagliptin 100 mg, OD	**29**	
Frederich, 2012 (76)	NA	Randomised, double-blind, placebo-controlled, Phase III.	USA, India, Russia, Taiwan	T2DM; HbA_{1c} 7−10% after diet and exercise treatment only; BMI ≤40 kg/m^2; C-peptide ≥1 ng/mL. Treatment naïve to AHAs or received an AHA for <6 months since diagnosis.	**Placebo**	**68**	24 weeks and 76 weeks (placebo group on metformin after week 24)
					Saxagliptin 2.5 mg, OD in the morning	**67**	
					Saxagliptin 5 mg, OD in the morning	**69**	
					Saxagliptin 2.5−5 mg, OD in the morning	**69**	
					Saxagliptin 5 mg, OD in the evening	**70**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Gantz, 2014 (77) (abstract)	NA	Randomised, double-blind, placebo and active-controlled. Preceded by a diet and exercise only placebo run in period.	Japan	T2DM; HbA_{1c} 7−10% at start of run-in. Treatment naïve to AHAs, or undergone at least 6 months washout.	**Placebo**	**82**	24 weeks
					Sitagliptin 50 mg, OD	**164**	
					Omarigliptin 25 mg, qw¶	***166***	
Goldstein, 2007 (78)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 2−6 week single-blind placebo run-in, dependent on previous AHA treatment and HbA_{1c} level.	Australia, USA, New Zealand, Malaysia, Philippines, Central America, South America, Europe, South Africa	T2DM; HbA_{1c} 7.5−11% at the start of run-in period; FPG ≤280 mg/dL after the run-in; Aged 18−78 years. Treatment naïve to AHAs or undergone at least 6−12 weeks washout, dependent on AHA.	**Placebo**	**165**	24 weeks
					Sitagliptin 10 mg, OD	**175**	
					Metformin 500 mg, BD¶	***178***	
					Metformin 1000 mg, BD¶	***177***	
					Sitagliptin 50 mg +Metformin 500 mg, BD¶	***183***	
					Sitagliptin 50 mg +Metformin 1000 mg, BD¶	***178***	
Gonzalez-Galvez, 2014 (79) (abstract)	Stenlof, 2013 (114); Stenlof, 2014 (115)	Subgroup analysis of randomised, double-blind, placebo-controlled, Phase III trial (114): Patients on AHAs at screening vs. not on AHAs at screening.	Multinational (USA, South and Central America, Europe, India, South Korea)	T2DM; HbA_{1c} 6.5−9.5% (patients on AHAs) or 7−10% (patients not on AHAs) at screening, and 7−10% 2 weeks prior to randomisation; FPG <15 mmol/L at randomisation; Aged 18−80 years. Treatment naïve to AHAs, or undergone at least 8 weeks washout.	**Placebo, OD**	**90 and 99**	26 weeks
					Canagliflozin 100 mg, OD	**92 and 99**	
					Canagliflozin 300 mg, OD	**93 and 101**	
Gupta, 2013†† (80) (abstract)	NA	Randomised, active-controlled.	NR	T2DM, newly diagnosed; Inadequate glycaemic control. Treatment naïve to AHAs; Diet treated only.	**Sitagliptin 50−200 mg, per day** Adjusted after 4 weeks if glycaemic control not achieved	**167**§	24 weeks
					Glimepiride 1−4 mg, per day Adjusted after 4 weeks if glycaemic control not achieved		
Henry, 2014 (81)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 3–11 week run-in, including a 2 week single-blind placebo	USA, France†	T2DM; HbA_{1c} 7.5–11%; FPG 130-270 mg/dL. Treatment naïve to AHAs, or undergone at least 8 weeks washout.	**Sitagliptin 100 mg, OD**	**172**	24 and 54 weeks
					Pioglitazone 15 mg, OD	**163**	
					Pioglitazone 30 mg, OD	**181**	
					Pioglitazone 45 mg, OD 30 mg for first 4 weeks	**171**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
		run-in period.			***Sitagliptin 100 mg OD + Pioglitazone 15 mg OD***¶	***179***	
					Sitagliptin 100 mg OD + Pioglitazone 30 mg OD¶	***173***	
					Sitagliptin 100 mg OD + Pioglitazone 45 mg OD¶	***188***	
Inagaki, 2014a (83)	Inagaki, 2014b (82) (abstract)	Randomised, double-blind, placebo-controlled. Preceded by a 4 week single-blind placebo run-in. (Abstract (82) contains additional data).	Japan	T2DM, diagnosed ≥3 months prior to run-in; HbA_{1c} 7−10%; Diet and exercise therapy for ≥55 days; Aged ≥20 years. Treatment naïve to AHAs, or undergone at least 55 days of washout.	**Placebo, OD before breakfast**	**93**	24 weeks
Inagaki, 2014b (82) (abstract)	Inagaki, 2014a (83)				**Canagliflozin 100 mg, OD before breakfast**	**90**	
					Canagliflozin 200 mg, OD before breakfast	**88**	
Jain, 2006 (84)	NR	Randomised, double-blind, active-controlled. Consisted of a 16 week titration phase and a 40 week maintenance phase.	Puerto Rico, USA	T2DM for ≤2 years; HbA_{1c} 7.5–11% at screening; FPG >120 mg/dL; Fasting C-peptide ≥1 ng/mL; Aged 18–80 years. Treatment naïve to AHAs, or not treated with a TZD in the previous 3 months and not received a meglitinide analogue, α-glucosidase inhibitor, metformin, insulin or a SU for ≥3 months at any time.	**Glibenclamide 15–45 mg, per day** Started on 15 mg and titrated in 5mg increments every 4 weeks for 16 weeks.	**251**	16, 24, 32, 40, 48 and 56 weeks.
					Pioglitazone 5–15 mg, per day Started on 15 mg and titrated in 15 mg increments every 4 weeks for 16 weeks.	**251**	
Ji, 2014 (85)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 6 week single-blind placebo run-in.	China, Korea, Taiwan, India	T2DM; HbA_{1c} 7.5−10.5%; C-peptide ≥1 nmol/L; BMI ≤45 kg/m^2; Aged ≥18 years. Treatment naïve to AHAs, or received AHAs for <24 weeks since diagnosis.	**Placebo, OD before first meal**	**127**	24 weeks
					Dapagliflozin 5 mg, OD before first meal	**122**	
					Dapagliflozin 10 mg, 1d before first meal	**127**	
Jibran, 2006 (86)	NA	Randomised.	Pakistan	T2DM, newly diagnosed; Aged 30-70 years. Treatment naïve to AHAs; Inadequate glycaemic control after diet and exercise only.	**Glibenclamide 5–15 mg, per day**	**50**	26 and 52 weeks
					Repaglinide 0.5–2 mg, tid	**50**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Jovanovich, 2004 (87)	NA	Randomised, open-label. Consisted of a 12 week dose optimisation phase and a 12 week maintenance phase.	USA†	T2DM for ≥12 months; HbA_{1c} >7% and <12%; BMI <45 kg/m^2; Aged ≥18 years. Undergone at least 2 weeks washout from metformin (at ≥50 of maximum dose) or a SU, following treatment for ≥3 months.	**Repaglinide 0.5–4 mg, tid** Started on 0.5 mg if HbA_{1c} ≤8%, or 1 mg if>8%. Adjusted every 4 weeks for 12 weeks, to target FPG 80-120 mg/dL.	**54**	24 weeks
					Pioglitazone 30 mg, OD	**57**	
					Repaglinide 0.5–4 mg, tid + Pioglitazone 30 mg, OD¶	***123***	
Kaku, 2013 (89) (abstract)	NA	Randomised, double-blind, placebo-controlled, Phase III.	Japan	T2DM; HbA_{1c} 6.5−10% at 1 week prior to randomisation; Aged ≥20 years. Inadequate glycaemic control by diet and exercise alone.	**Placebo, OD**	**87**	24 weeks
					Dapagliflozin 5 mg, OD	**86**	
					Dapagliflozin 10 mg, OD	**88**	
Kaku, 2014(88) (abstract)	NA	Randomised, double-blind, placebo-controlled, non-inferiority trial.	Japan	T2DM. Inadequate glycaemic control with diet and exercise therapy alone.	**Placebo**	**50**	24 weeks
					Alogliptin 25 mg, per day	**92**	
					Trelagliptin 100 mg, qw¶	***101***	
Kikuchi, 2012 (90)	NA	Randomised, double-blind, placebo-controlled.	Japan	T2DM; HbA_{1c} ≥7.4%; Aged 20–75 years. Treatment naïve to AHAs.	**Placebo**	**54**	16 and 28 weeks
					Pioglitazone 15–45 mg, OD Titrated to 30 mg at week 4, and to 45 mg at week 17 if HbA_{1c} ≥6.5% at week 16.	**159**	
					Rosiglitazone 4–8 mg, OD¶ *Titrated to 8 mg at week 17 if HbA_{1c} ≥6.5% at week 16.*	***159***	
Lawrence, 2004 (91)	NA	Randomised, open-label. Preceded by a 3 month run-in on diet treatment only.	UK†	T2DM; HbA_{1c} >7% (patients diet-treated only) or <7.5% (patients on low dose AHA) at screening; BMI >27 kg/m^2; Aged 45–80 years. Treatment naïve to AHAs or undergone at least 3 months washout prior to randomisation.	**Gliclazide 80–160 mg, OD–BD** Started at 80 mg OD, uptitrated to 160 BD if FPG >7 mmol/L at in first 12 weeks.	**20**	24 weeks
					Pioglitazone 30–45 mg, OD Uptitrated to 45 mg if FPG >7 mmol/L in first 12 weeks.	**20**	
					Metformin 500 mg, BD – 1000 mg, tid¶	***20***	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Lewin, 2014a (92) (abstract)	Lewin, 2014b (93)	Randomised, Phase III.	USA, UK, Germany†	T2DM. Treatment naïve to AHAs.	**Linagliptin 5 mg**	**133**	24 weeks
					Empagliflozin 10 mg	**132**	
					Empagliflozin 25 mg	**133**	
					Empagliflozin 25 mg + Linagliptin 5 mg	***135***	
					Empagliflozin 10 mg + Linagliptin 5 mg	***134***	
Lewin, 2014b (93) (abstract)	Lewin, 2014a (92)	Extension			**Linagliptin 5 mg**	***133***	52 weeks
					Empagliflozin 10 mg	***131***	
					Empagliflozin 25 mg	***133***	
					Empagliflozin 25 mg + Linagliptin 5 mg	***134***	
					Empagliflozin 10 mg + Linagliptin 5 mg	***134***	
Majima, 2006 (94)	NA	Randomised.	Japan	T2DM; Newly diagnosed; Female. Treatment naïve to AHAs.	**Pioglitazone 7.5 mg, per day**	**53**	26 weeks
					Pioglitazone 15 mg, per day	**31**	
Marbury, 1999 (95)	NA	Randomised, double-blind. Consisted of an 8 week titration phase and a 52 week maintenance phase.	USA†	T2DM for ≥6 months; HbA_{1c} 6.5–14.6%; BMI 20–40 kg/m^2; Aged 37–75 years. Treated with diet and exercise only. *(Patients on AHAs at screening only discontinued the AHA at randomisation, so their data are not included in the systematic review; total patient numbers in italics).*	**Repaglinide 0.5–12 mg, per day** Adjusted in 1, 2 or 4 mg increments up to 12 mg maximum daily dose.	**45** ***(338)*** ¶	60 weeks
					Glibenclamide 2.5–15 mg, per day Increased to 5, 10 or 15 mg daily. (15 mg administered in 2 doses, 10 mg + 5 mg).	**21** ***(171)*** ¶	
Miyazaki, 2002 (96)	NA	Randomised, double-blind, placebo-controlled.	USA†	T2DM; HbA_{1c} ≥7%; FPG ≥140 mg/dL; Fasting C-peptide >1 ng/mL. Treatment naïve to AHAs, or undergone at least 6–8 weeks washout.	**Placebo**	**11**	26 weeks
					Pioglitazone 7.5 mg	**13**	
					Pioglitazone 15 mg	**12**	
					Pioglitazone 30 mg	**11**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
					Pioglitazone 45 mg	**11**	
Mohan, 2009 (97)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 3 or 6 week diet and exercise run-in and a 2 week single-blind placebo run-in.	India, China, Korea	T2DM for ≤5 years; HbA_{1c} 7.5−11% (patients not on AHAs) or 7−10% (patients on AHAs); Aged ≥18 years. Treatment naïve to AHAs, or discontinued AHAs at start of diet and exercise run-in at the latest.	**Placebo, OD**	**169**	18 weeks
					Sitagliptin 100 mg, OD	**339**	
Pan, 2012 (98)	NA	Double-blind, placebo-controlled, Phase III. Preceded by a 4 week single-blind placebo run-in.	China, India, Philippines, South Korea	T2DM, HbA_{1c}, 7−10% at randomisation; Fasting C-peptide ≥0.33 nmol/L; Aged ≥18 years. Treatment naïve to AHAs, or received AHAs for <6 months since diagnosis and not for >3 consecutive days or >7 days in the previous 8 weeks.	**Placebo**	**274**	24 weeks
					Saxagliptin 5 mg, OD	**277**	
Papanas, 2006 (99)	NA	Randomised, active-controlled.	Greece	T2DM; HbA_{1c} >7%. Not treated with AHAs for at least 3 weeks prior to randomisation (patients underwent washout if necessary).	**Gliclazide, dose NR**	**53**	26 weeks
					Glibenclamide, dose NR	**51**	
Pi-Sunyer, 2007 (100)	NA	Randomised, double-blind, placebo-controlled.	USA, India, Slovakia	T2DM; HbA_{1c} 7.5−10%; BMI 22−45 kg/m^2; FPG <15 mmol/L; Aged 18−80 years. Treatment naïve to AHAs, or not received AHAs for ≥12 weeks prior to screening or for >3 consecutive months at any point.	**Placebo**	**88**	24 weeks
					Vildagliptin 50 mg, OD	**84**	
					Vildagliptin 50 mg, BD	**79**	
					Vildagliptin 100 mg OD	**89**	
Pratley, 2014 (101)	NA	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 4 week placebo run-in.	Multinational (Europe, USA, Israel, Mexico, Puerto Rico, South Africa)	T2DM; HbA_{1c} 7.5−10%; BMI 23−45 kg/m^2; FPG ≥0.5 ng/mL; Aged 18−80 years. Treatment naïve to AHAs, or received <7 days of AHA therapy in the 2 months prior to screening. On diet and exercise therapy for >2 months prior to screening.	**Placebo, OD**	**109**	26 weeks
					Alogliptin 25 mg, OD	**112**	
					Alogliptin 12.5 mg, BD	**113**	
					Metformin 500 mg, BD¶	***114***	
					Metformin 1000 mg, BD¶	***111***	
					Alogliptin 12.5 mg + metformin 500 mg, BD¶	***111***	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
					Alogliptin 12.5 mg + metformin 1000 mg, BD¶	***114***	
Raz, 2006 (102)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 2 week single-blind placebo run-in.	USA, Germany, Israel†	T2DM; HbA_{1c} 7−10%; Aged 18−75 years. Treatment naïve to AHAs, or undergone at least 12 weeks washout.	**Placebo, OD**	**103**	18 weeks
					Sitagliptin 100 mg, OD	**193**	
					Sitagliptin 200 mg, OD	**199**	
Roden, 2013 (1)	Roden, 2014 (9) (abstract)	Randomised, double-blind, placebo-controlled, Phase III. Preceded by a 2 week open-label placebo run-in.	USA, China, Canada, India, Japan, Belgium, Ireland, Switzerland	T2DM; HbA_{1c} 7−10% (7−9.5% Germany); BMI 45 kg/m^2; Aged ≥18 years (≥20 years Japan, 18-65 years India). Treatment naïve to AHAs, or no AHAs in the 12 weeks prior to randomisation. 68.4% of patients continued in the extension study.	**Placebo**	**228**	24 weeks
					Empagliflozin 10 mg, OD	**224**	
					Empagliflozin 25 mg, OD	**224**	
					Sitagliptin 100 mg, OD	**223**	
Roden, 2014 (9) (abstract)	Roden, 2013 (1)	Randomised, double-blind, 52 week extension.			**Placebo**	**228**	≥76 weeks
					Empagliflozin 10 mg, OD	**224**	
					Empagliflozin 25 mg, OD	**224**	
					Sitagliptin 100 mg, OD	**223**	
Rosenstock, 2007 (104)	NA	Randomised, double-blind, active-controlled.	USA, Asia, Europe	T2DM; HbA_{1c} 7.5–11% at screening; FPG <15 mmol/L; BMI 22–45 kg/m^2; Aged 18–80 years. Treatment naïve to AHAs, or undergone at least 12 weeks washout prior to screening and never received an AHA for >3 consecutive months.	**Vildagliptin 100mg, OD**	**150**	24 weeks
					Pioglitazone 30 mg, OD	**157**	
					Vildagliptin 50 mg, OD + Pioglitazone 15 mg, OD¶	***139***	
					Vildagliptin 100 mg, OD + Pioglitazone 30 mg, OD¶	***146***	
Rosenstock, 2010 (103)	NA	Randomised, double-blind, Phase III. Preceded by a 4 week placebo run-in.	USA, Germany†	T2DM; HbA_{1c} 7.5–11%; BMI 23-45 kg/m^2; Aged 18–80 years. Treatment naïve to AHAs, or ≤6 days of AHA treatment in the 6 months prior to screening, and treated with diet and exercise alone for ≥2 months prior to screening.	**Alogliptin 25 mg, OD**	**164**	26 weeks
					Pioglitazone 30 mg, OD	**163**	
					Alogliptin 12.5 mg, OD + Pioglitazone 30 mg, OD¶	***163***	
					Alogliptin 25 mg, OD + Pioglitazone 30 mg, OD¶	***164***	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Rosenstock, 2013 (105)	NA	Randomised, double-blind, active-controlled.	Multinational (USA, Israel, India, Peru, Mexico, South Africa, Europe)	T2DM; HbA_{1c} 6.5−9% at screening (patients not on AHA) or 6.5−8.5% (patients on AHAs); Aged 65−90 years. Treatment naïve to AHAs, or undergone at least 4 weeks washout. Treated with diet and exercise for the 2 months prior to screening.	**Glipizide 5−10 mg, OD** Titrated as necessary.	**162 PP;** **219 FAS**	52 weeks
					Alogliptin 25 mg, OD	**180 PP;** **222 FAS**	
Russell-Jones, 2012 (106) (DURATION-4)	Boardman, 2011 (60); Cuddihy, 2011 (65)	Randomised, double-blind.	Multinational (Europe, USA, Brazil, Argentina, Canada, India, Israel, Korea, Mexico, South Africa, Taiwan)	T2DM; HbA_{1c} 7.1–11%; BMI 23-45 kg/m^2; History of stable weight. Treatment naïve to AHAs, or received AHAs for <7 days in the 3 months prior to screening.	**Sitagliptin 100 mg, per day**	**163**	26 week
					Pioglitazone 45 mg, per day Titrated in weekly increments to reach this dose.	**163**	
					Metformin 2,000–2,500 mg, per day¶	***246***	
					Exenatide 2 mg, qw¶	***248***	
Saleem, 2011 (107)	NA	Randomised.	Pakistan	T2DM newly diagnosed; Aged 30-70 years. Treatment naïve to AHAs and inadequate glycaemic control on diet and exercise alone.	**Glibenclamide 8.8 mg (mean), per day**	**50**	26 and 52 weeks
					Repaglinide 4.27 mg (mean), per day	**50**	
Schade, 1998 (108)	NA	Randomised, double-blind, placebo-controlled, dose titration trial. Consisted of a 10 week titration phase and a 12 week maintenance phase.	USA	T2DM; Body weight 90−150% of ideal (by Metropolitan Life Insurance tables); FPG 151−300 mg/dL; Aged 30−75 years. Treatment naïve to AHAs, or no AHAs received in the 6 months prior to randomisation.	**Placebo**	**97**	22 weeks
					Glimepiride 1−8 mg, OD Titrated at 2-week intervals as necessary	**106**	
Scherbaum, 2002 (109)	NA	Randomised, double-blind, placebo-controlled, Phase II.	Germany†	T2DM; HbA_{1c} 7.5–12%; FPG 140-300 mg/dL (≤250 mg/dL at randomisation); BMI 25–35 kg/m^2. Treatment naïve to AHAs, or undergone at least 10 weeks washout on placebo.	**Placebo**	**76**	26 weeks
					Pioglitazone 15 mg, OD	**83**	
					Pioglitazone 30 mg, OD	**76**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Scherbaum, 2008a (110)	Scherbaum, 2008b (111)	Randomised, double-blind, placebo-controlled. Preceded by a 4 week single-blind washout period.	Finland, France, Germany, Romania, Spain Sweden	T2DM for ≥8 weeks; HbA_{1c} 6.2−7.5% at screening (upper limit 7% in Finland and Spain); BMI 22−45 kg/m^2; Aged ≥18 years. Treatment naïve to AHAs, or received no AHA for at least 12 weeks prior to screening and not for >3 consecutive months at any time.	**Placebo**	**150**	52 weeks
					Vildagliptin 50 mg, OD	**156**	
Scherbaum, 2008b (111)	Scherbaum, 2008a (110)	Double-blind extension. Preceded by a 4 week placebo washout following the core study.			**Placebo**	**63**	104 weeks
					Vildagliptin 50 mg, OD	**68**	
Segal, 1997 (112)	NA	Randomised, double-blind, placebo-controlled. Preceded by a 4 week single-blind placebo run-in.	Austria, Germany, Israel, Czech Republic	T2DM for ≥3 months; HbA_{1c} 7.5−9.5%; Stable body weight on diet alone; Aged 30−70 years. Treatment naïve to AHAs, or not treated with AHAs in the previous 3 months.	**Placebo**	**42**	24 weeks
					Glibenclamide 3.5 mg, OD Dose doubled after 4 weeks if necessary.	**37**	
					Miglitol 50–100 mg, tid¶ Increased to 100 mg after 4 weeks	***40***	
Shihara, 2011 (113)	NA	Randomised, non-blinded.	Japan	T2DM; HbA_{1c} 6.9 to <10.4% at both 1 month before and at randomisation; Aged 30–75 years.	**Glimepiride 0.5–6 mg, per day** Started at 0.5 mg if HbA_{1c} <7.4%; 1 mg if HbA_{1c} ≥7.4%. Increased as needed to achieve FPG <120 mg/dL.	**86**	12 and 26 weeks
					Pioglitazone 15–45 mg, per day Started at 15 mg. Increased to 30 mg (women) or 45 mg (men) as needed to achieve FPG <120mg/dL.	**91**	
Stenlof, 2013 (114)	Gonzalez-Galvez, 2014	Randomised, double-blind, placebo-	Multinational (USA, South	T2DM; HbA_{1c} 6.5−9.5% (patients on AHAs) or 7−10% (patients not on AHAs)	**Placebo, OD**	**192**	26 weeks

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
CANTATA-M)	(79) (abstract); Stenlof, 2014 (115)	controlled, Phase III. Preceded by a 2 week single-blind placebo-run-in.	and Central America, Europe, India, South Korea)	at screening, and 7−10% 2 weeks prior to randomisation; FPG <15 mmol/L at randomisation; Aged 18−80 years. Treatment naïve to AHAs, or undergone at least 8 weeks washout.	**Canagliflozin 100 mg, OD**	**195**	
					Canagliflozin 300 mg, OD	**197**	
Stenlof, 2014 (115)	Stenlof, 2013 (114); Gonzalez-Galvez, 2014 (79) (abstract);	Double-blind, active-controlled extension. Placebo patients switched to sitagliptin to maintain blinding and prevent prolonged exposure to placebo.			**Sitagliptin 100 mg**	**155**	26 weeks‡‡
					Canagliflozin 100 mg, OD	**195**§§	52 weeks
					Canagliflozin 300 mg, OD	**197**§§	
Tan, 2004 (117)	NA	Randomised trial. Consisted of a 12 week titration phase and a 40 week treatment period.	Denmark, Finland, Norway, Sweden	T2DM; HbA_{1c} >7.5% to ≤11% (if not on AHA at screening, or >7.5% to ≤9.5% (if on AHA at screening); Fasting C-peptide 1.0 ng/mL. Treatment naïve to AHAs, or undergone at least 1–3 weeks washout. Inadequate glycaemic control with diet and exercise alone.	**Glibenclamide 1.75–10.5 mg, OD** Increased at weeks 4, 8 and 12 to reach maximum at week 12.	**96**	36 and 52 weeks
					Pioglitazone 30–45 mg, OD Started at 30 mg, increased to 45 mg at week 4.	**83**	
Tan, 2005 (116)	Charbonnel, 2005 (61)	Double-blind, 52 week extension. All patients from 98 centres, selected from the core study for the extension, were enrolled if they had completed the initial 52 weeks.	Australia, Canada, Finland, Poland, Slovakia, South Africa, UK	T2DM; HbA_{1c} 7.5–11%, stable or worsening over the previous 3 months; Aged 35–75 years. Treatment naïve to AHAs, and treated with diet.	**Gliclazide 40–160 mg, BD** Increased in 80 mg/day intervals every 4 weeks, to maximum tolerated dose at 16 weeks.	**297**	104 weeks
					Pioglitazone 15–45 mg, OD Increased in 15 mg intervals every 4 weeks, to maximum tolerated dose at 16 weeks.	**270**	
Teramoto, 2007 (118)	NA	Randomised, non-blinded.	Japan	T2DM; FPG ≥140 mg/dL; HDL ≤80 mg/dL; Triglycerides 150–500 mg/dL; Japanese; Aged 20–79 years. Treated with diet and exercise therapy only, without AHAs or lipid lowering drugs.	**Glibenclamide 1.25–2.5 mg, OD** 1.25 mg for weeks 0–8. Increased to 2.5 mg for weeks 9–24 if FPG ≥126 mg/dL at 8 weeks.	**45**	24 weeks
					Pioglitazone 15–30 mg, OD Increased to 30 mg at 8 weeks if FPG ≥126 mg/dL.	**46**	

Reference	Linked publications	Study design	Country	Population	Interventions	Patient numbers‡	Follow up times
Yamanouchi, 2005 (119)	NA	Randomised trial. Preceded by a 1 month observation period for taking baseline measurements.	Japan	T2DM; HbA_{1c} ≥7%; FPG ≥7.78 mmol/L; BMI 22–35 kg/m^2. Treatment naïve to AHAs and treated with diet and exercise for ≥3 months.	**Glimepiride 1–2 mg, per day** Increased to 2 mg/day after 1 month if HbA_{1c} decreased by ≤0.3%.	**37**	52 weeks
					Pioglitazone 30 or 45 mg, per day 30 mg women; 45 mg men	**38**	
					Metformin 750 mg, per day¶	***39***	

Abbreviations: AHA, anti-hyperglycaemic agent; BD, twice daily; BMI, body mass index; DBP, diastolic blood pressure; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FAS, full analysis set; FPG, fasting plasma glucose; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL, low density lipoprotein; MDRD, modification of diet in renal disease; MR, modified release; NA, not applicable; NR, not reported; OD, once daily; PP, per protocol; PPG, postprandial plasma glucose; qw, once weekly; SBP, systolic blood pressure; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; tid, three times daily; TZD, thiazolidinedione. †Authors' country(ies); ‡Based on patient numbers in the HbA_{1c} analysis; §Total across all treatment groups; ¶Non-relevant comparator arm or patient population (in italics); ††The full paper of this publication has been withdrawn by the authors; ‡‡Placebo group was switched to sitagliptin, so these results represent 26 weeks of active treatment only; §§Data are reported for all patients analysed in the core study (as in table) and in the extension study alone (sitagliptin, n=155; canagliflozin 100 mg, n=170; canagliflozin 300 mg, n=170).

3. Efficacy and safety of therapy

3.1 Introduction

Empagliflozin is a member of the SGLT-2 inhibitor class of glucose lowering therapies. Under normal physiological conditions, nearly all filtered glucose is reabsorbed in the proximal tubule of the nephron in the kidney, principally via SGLT-2. SGLT-2 inhibitors are a relatively new class of OADs, which reduce hyperglycaemia by blocking reabsorption of filtered glucose through inhibiting SGLT-2, the primary glucose transporter in the proximal tubular cell, leading to increased urinary glucose excretion and a lowering of serum glucose, independently of insulin secretion or action (1, 6). Furthermore, urinary glucose excretion results in weight loss and a reduction in blood pressure from osmotic diuresis (1, 15).

Empagliflozin is an oral, potent and selective inhibitor of SGLT-2, with a 5,000 times higher selectivity for SGLT-2 than SGLT-1 (15). It provides an additional treatment option for patients who experience poor glycaemic control with glucose lowering therapies as a result of inadequate response to treatment or as a result of disease progression (1).

The efficacy and safety of empagliflozin has been investigated in clinical trial programmes as monotherapy and combination therapy for T2DM involving over 5,000 patients to date. A number of studies are also ongoing.

Empagliflozin has demonstrated efficacy and safety across two main phase III RCTs involving 2,327 patients with T2DM, of who 1,077 received empagliflozin 25 mg or 10 mg monotherapy (1, 5). An extension study over a total of 76 weeks (52 weeks in addition to the 24 weeks covered by Study 1245.20) also demonstrated that empagliflozin is both well tolerated and clinically effective with continued use (8, 9). Overall, empagliflozin (10 mg and 25mg) OD produced clinically significant improvements in glycaemic control, with a generally low incidence of hypoglycaemia, and reduction in SBP and weight compared with placebo.

The two main phase III studies were 1245.20 and 1275.1. The extension study (1245.31) was an extension to study 1245.20. The following section will describe in detail these three studies, providing the key direct clinical evidence for empagliflozin. In addition, study 1245.20 also included an open label extension (Table 3).

Together, the two phase III RCTs and the 76 week extension study form the basis of this submission covering all the current and pending licensed indications for empagliflozin monotherapy, which provides NICE with the first opportunity to consider an SGLT-2 inhibitor for such a widely defined population of patients in England.

In this section, the three studies comparing empagliflozin with a relevant comparator are presented in the following order:

- Fixed dose combination (FDC) of empagliflozin/linagliptin compared to empagliflozin monotherapy and linagliptin monotherapy over 52 weeks (n=1,363, Section 3.4)
- Empagliflozin monotherapy compared to placebo and sitagliptin over 24 weeks (n=986, Section 3.3)
- Empagliflozin monotherapy compared to placebo and sitagliptin over 76 weeks (n = 615, Section 3.3)

Safety evidence is presented in Section 3.5 with detailed discussion provided on the occurrence of specific AEs.

3.2 Summary of efficacy and safety evidence

Overall summary of efficacy

Empagliflozin is administered once daily as a 25 mg or 10 mg oral tablet and has demonstrated efficacy and safety across two main phase III RCTs (including an open-label arm extension and a 76 week extension study) involving 2,327 patients with T2DM, of whom 1,077 received empagliflozin (Jardiance®) monotherapy (excluding FDC). Overall, empagliflozin 25 mg and 10 mg OD produced clinically significant improvements in glycaemic control, with a lower incidence of hypoglycaemia, and a reduction in body weight that was maintained at 52 and 76 weeks. This submission is made to support the use of empagliflozin as monotherapy in a wide patient population. Two pivotal phase III empagliflozin 25 and 10 mg randomised studies and a 76-week monotherapy extension study are relevant here.

Study 1275.1, Lewin et al, 2015 (6, 7)

- A 52 week study of empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg FDC tablets vs. empagliflozin 25 mg and 10 mg monotherapy and linagliptin.
- The FDC of empagliflozin 25 mg/linagliptin 5 mg was shown to be superior to linagliptin 5 mg treatment ($p<0.0001$), but did not show statistically significant difference vs. empagliflozin 25 mg monotherapy. According to the pre-defined hierarchical testing procedure, all subsequent analyses were considered exploratory. However, statistically significant differences were noted ($p<0.0001$) between empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 10 mg and linagliptin 5 mg.
- In the treatment naïve patient group, reductions in HbA_{1c} from baseline were clinically meaningful in all treatment groups, and were greater in the empagliflozin 25 mg and 10 mg groups (-0.94 % and -0.84%, respectively) than in the linagliptin 5 mg group (-0.69%) (7).

Study 1245.20, Roden et al, 2013 (1, 5)

- A 24 week study of empagliflozin monotherapy vs. placebo, with an exploratory comparison vs. sitagliptin.
- At Week 24, a mean HbA_{1c} treatment difference of -0.74% ($p<0.0001$) was reported for empagliflozin 10 mg and -0.85% for empagliflozin 25 mg compared with placebo.
- The sustained safety and efficacy of empagliflozin as monotherapy in patients with very poor glycaemic control has also been established in an open-label extension study (study 1245.20).
- In the open label arm, the mean change in HbA_{1c} from baseline at Week 24 was -3.10%.

Study 1245.31, Roden et al, 2014 (8, 9)

- A 76 week extension study (52 weeks in addition to the 24 weeks covered in Study 1245.20) of empagliflozin monotherapy vs. sitagliptin and placebo.
- At Week 76, treatment with empagliflozin 10 mg and 25 mg resulted in a mean HbA_{1c} difference from placebo of –0.78 and -0.89 respectively. Compared to sitagliptin, treatment with empagliflozin 10 mg and 25mg resulted in a mean HbA_{1c} difference of -0.12 and -0.22 respectively.

Overall summary of safety

- The adverse effect profile of empagliflozin is typical of an SGLT-2 inhibitor.
- Overall, empagliflozin was well tolerated, and the safety assessment revealed no trends of clinical relevance. AEs were generally of mild or moderate intensity across both studies.

Study 1275.1, Lewin et al, 2015 (6, 7)

- In active controlled trials comparing FDCs to empagliflozin and linagliptin monotherapies, the overall safety profile of the empagliflozin/linagliptin FDCs after 52 weeks of treatment was similar to the known safety profiles of the individual components, both in treatment naïve patients with T2DM and in patients with metformin background therapy.
- The frequency of patients reported with at least one AE on treatment at Week 52 was 75.7% of patients in the empagliflozin 25 mg/linagliptin 5 mg FDC group, 72.8% of patients in the empagliflozin 10 mg/linagliptin 5 mg FDC group, 68.9% of patients in the empagliflozin 25 mg group, 81.5% of patients in the empagliflozin 10 mg group, and 71.9% of patients in the linagliptin 5 mg group (values for treatment-naïve patients).
- AEs assessed as drug related at Week 52 were reported in 16.9% of patients in the higher dose FDC group, 10.3% in the lower dose FDC group, 16.3% in the empagliflozin 25 mg group, 11.9% in the empagliflozin 10 mg group, and 12.6% in the linagliptin 5 mg group.
- The most common AEs that were reported in ≥ 5% of patients include UTI, nasopharyngitis, upper respiratory tract infection, hyperglycaemia, headache and arthralgia.

Study 1245.20, Roden et al, 2013 (1, 5)

- The number of patients with AEs in treatment groups was comparable to placebo (61%) and sitagliptin 100 mg (53%), reported at 55% for empagliflozin 10 mg and 61% for empagliflozin 25 mg (64% in the open label empagliflozin 25 mg group). More patients in the placebo group (3%) than in the empagliflozin 25 mg group (2%) and the empagliflozin 10 mg group (1%) discontinued due to AEs.(1) Drug-related AEs were higher in the Empagliflozin 10 mg and 25 mg groups (12% and 17%, respectively), compared to placebo (7%) and sitagliptin (9%).
- The most common AEs that were reported in ≥ 5% of patients include nasopharyngitis, UTI, hyperglycaemia and dyslipidaemia.

Study 1245.31, Roden et al, 2014 (8, 9)

- The number of patients with at least one treatment emergent AE was similar across treatment groups: placebo 76.4%, empagliflozin 10 mg 76.8%, empagliflozin 25 mg 78.0% and sitagliptin 72.2%.
- Few patients experienced AEs leading to premature discontinuation of trial medication. More patients in the placebo group (6.6%) discontinued due to AEs than patients in the empagliflozin 10 mg and 25 mg groups (4.9% and 4.0%, respectively) and sitagliptin group (4.9%).
- The most common AE group reported was ‘infections and infestations’, but this was similar across all treatment groups (37.1% for placebo, 42.0% for empagliflozin 10 mg, 40.8% for empagliflozin 25 mg and 37.2% for sitagliptin).

Table 3: Overview of empagliflozin Phase III/II studies (pivotal evidence of relevance to this submission) in the treatment of T2DM mellitus

ID and publication	Study design	Number of patients (FAS)	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary end-points (x vs. y)
Monotherapy and FDC with linagliptin						
1275.1, Lewin et al. 2015 (6, 7)	Phase III, randomised, double-blind, parallel group, multicentre, 52 week study.	1363	Patients aged ≥ 18 years of age with a BMI of ≤45 kg/m^2. HbA_{1c} ≥ 7.0% and ≤10.5%. Treatment-naïve or pre-treated with Met, unchanged for 12 weeks prior.	Male patients: 54% Age (years, mean): 55	Empagliflozin/linagliptin 25 mg/5 mg FDC /day 10 mg/5 mg/day, empagliflozin 25 mg/day, 10 mg/day and linagliptin 5 mg/day for 52 weeks.	Change from baseline HbA_{1c} after 24 weeks.
Monotherapy						
1245.20, Roden et al. 2013 (1, 5)	Phase III, randomised, double-blind, placebo-controlled, multicentre, 24 week study. Plus an open-label arm. Followed by a double-blind, extension trial BI 1245.31.	986	Drug-naïve patients ≥18 years of age (Japan: ≥ 20 years; India ≥18 years and ≤65 years) with a BMI of ≤45 kg/m^2. HbA_{1c} ≥ 7.0% and ≤10.0% (Germany: ≥ 7.0 to ≤9.0%). Patients with HbA_{1c} >10% enrolled in empagliflozin 25 mg open-label arm.	Male patients: 61% Age (years, mean): 55	Empagliflozin 25 mg/day,10 mg/day, and sitagliptin 100 mg/day for 24 weeks.	Change from baseline HbA_{1c} after 24 weeks.
1245.31, Roden et al. 2014 (8, 9)	Phase III, double-blind, extension, placebo-controlled parallel group safety and efficacy trial, 76 week extension trial (including 24 weeks of preceding trial)	615	Patients with T2DM mellitus, patients who have successfully completed the preceding blinded study1245.20	1245.20 Male patients: 61.3% Age(years, mean): 55	Empagliflozin 25 mg/day, 10 mg/day, and sitagliptin 100 mg/day for 24 weeks.	No primary efficacy endpoint was defined (primary endpoint was analysed at Week 24 of preceding trial).

Abbreviations: BI, Boehringer Ingelheim; BMI, body mass index; FDC, fixed dose combination; HbA_{1c}, glycosylated haemoglobin; ITT, intention-to-treat; Met, metformin; SU, sulfonylureas; T2DM, type 2 diabetes mellitus.

3.3 Empagliflozin in combination with linagliptin plus empagliflozin monotherapy (active control)

3.3.1 Study 1275.1 (Lewin et al., 2015: FDC empagliflozin/linagliptin compared to empagliflozin and linagliptin

3.3.1.1 Methodology: Study 1275.1

A summary of the methodology for Study 1275.1 is provided in Table 4.

Table 4: Study methodology

Study	Study 1275.1 (Lewin et al., 2015) (6)
Summary	To evaluate the efficacy and safety of empagliflozin/linagliptin in subjects with T2DM, subjects not receiving antidiabetic therapy for at least 12 weeks were randomized to empagliflozin 25 mg/linagliptin 5 mg (n = 137), empagliflozin 10 mg/linagliptin 5 mg (n = 136), empagliflozin 25 mg (n = 135), empagliflozin 10 mg (n = 134), or linagliptin 5 mg (n = 135) for 52 weeks. The primary end point was change from baseline in HbA_{1c} at Week 24. This study is completed and registered with ClinicalTrials.gov, number NCT01422876.
Objectives	To assess the safety, efficacy and tolerability of the FDC of empagliflozin 25 mg/linagliptin 5 mg and of the FDC of empagliflozin 10 mg/linagliptin 5 mg compared with the individual components (empagliflozin 25 mg or 10 mg, and linagliptin 5 mg) given OD for 52 weeks in treatment naïve and metformin treated patients with T2DM and insufficient glycaemic control. The primary efficacy evaluation was planned and carried out after 24 weeks of treatment.
Design details	Study 1275.1 was a 52 week, randomised, double blind, parallel group comparison study conducted in 194 trial sites in 22 countries (Malaysia, Philippines, Taiwan, Lebanon, Bulgaria, Denmark, Estonia, Hungary, Italy, Poland, Romania, Russia, Spain, Sweden, Australia, Argentina, Brazil, Colombia, Mexico, Peru, Canada and the USA). Screened patients had to undergo a 2 week single blinded placebo run in period before randomisation. Patients were then randomised to the double blinded 52 week treatment period followed by a 4 week follow up period.
Interventions	Patients who met the eligibility criteria at the end of 2 week placebo run in period were randomly assigned to 1 of the 5 study treatment groups (empagliflozin 25 mg/linagliptin 5 mg FDC, empagliflozin 10 mg/linagliptin 5 mg FDC, empagliflozin 25 mg, empagliflozin10 mg, or linagliptin 5 mg) in a 1:1:1:1:1 ratio. Randomisation was performed at Visit 3, and was stratified separately for treatment-naïve and for metformin treated patients by HbA_{1c} at screening (<8.5% or <69.4 mmol/mol, ≥ 8.5% or ≥69.4 mmol/mol), renal function at screening (eGFR ≥ 90 mL/min/1.73 m2, 60 to 89ml/min/1.73 m2), and geographical region (North America, South America, Asia, and Europe).
Key inclusion criteria	• Previously diagnosed T2DM • Male and female patients aged 18 years • Body Mass Index (BMI) of ≤45 kg/m2 • HbA_{1c} ≥ 7.0 and ≤10.5% (≥ 53.0 mmol/mol and ≤91.3 mmol/mol) • Treatment naïve patients on diet and exercise regimen (defined as absence of any OADs, glucagon like peptide (GLP)-1 analogue or insulin for 12 weeks prior to randomisation) or pre-treated with metformin (≥ 1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation.
Key exclusion criteria	• Uncontrolled hyperglycaemia >240 mg/dL (>13.3 mmol/L) after an overnight fast during placebo run in and confirmed by a second measurement on a following day • Treatment with any other antidiabetic drug within 12 weeks prior to randomisation • Acute coronary syndrome within 3 months prior to informed consent • Indication of liver disease as determined during screening and/or run-in period • Impaired renal function, defined as eGFR <60 mL/min (modification of diet in renal disease [MDRD] formula) as determined during screening and/or run-in period • Bariatric surgery within the past two years and other gastrointestinal (GI) surgeries that induce chronic malabsorption • Treatment with antiobesity drugs within 3 months prior to informed consent or any other treatment at the time of screening (e.g. surgery, aggressive diet regimen) leading to unstable body weight • Current treatment with systemic steroids (other than inhaled steroids) at time of informed consent or any other uncontrolled endocrine disorder except T2DM.

Study	Study 1275.1 (Lewin et al., 2015) (6)
Efficacy outcomes	The primary endpoint in this study was the change from baseline in HbA_{1c} (%) after 24 weeks of treatment. The following key secondary endpoints were also tested: • Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment • Change from baseline in body weight after 24 weeks of treatment • Occurrence of treat to target efficacy response measured as HbA_{1c} <7.0% (<53.0 mmol/mol) after 24 weeks of treatment.
Populations analysed	Screened patients set (SCR) – including all patients screened for the trial, with consent given and who completed at least 1 screening procedure at Visit 1. Randomised set (RS) – including all patients from the screened set who were randomised to a trial medication, regardless of whether any trial medication was taken. Treated set (TS) – including all patients treated with at least 1 dose of randomised trial medication. The TS was the basis for safety analyses. Full analysis set (FAS) – including all randomised patients, treated with at least 1 dose of trial medication and who had a baseline HbA_{1c} value and at least 1 on-treatment HbA_{1c} value. Per-protocol set (PPS) – at 24 weeks, including all randomised patients without important protocol violations until Week 24 leading to exclusion
Statistical analysis	Statistical analyses were performed separately for patients on metformin background and for the treatment naïve patients as these were considered two independent patient populations. A hierarchical testing procedure for superiority at alpha =0.05 (two-sided) was defined for each population separately. The primary endpoint was analysed using an analysis of covariance (ANCOVA) applied on the FAS with randomised treatment, renal function, and geographical region as fixed classification effects and HbA_{1c} baseline as a linear covariate. Missing data was imputed using the last observation carried forward (LOCF) approach. Following a request from health authority, which recommended not using the LOCF approach for primary analysis after completion of the 24-week analysis, a mixed model repeated measures (MMRM) approach was considered as an alternative to LOCF. Both the primary endpoint (HbA_{1c}), and key secondary endpoint of FPG analysed at Week 24 based on the MMRM model using the FAS observed cases (OC), were presented for both patient populations in this trial. The primary endpoint was tested first for the high dose FDC compared with the respective monotherapies, each tested at alpha =0.05. If successful, tests of the low dose FDC compared with its individual components followed. Sensitivity analyses of the primary endpoint were performed by ANCOVA modelling using different analysis sets, with missing data imputed using multiple imputation, and using a restricted maximum likelihood (REML)-based MMRM approach. If analysis of the primary endpoint was successful, the key secondary endpoint FPG was analysed following the same testing procedure as for HbA_{1c} using ANCOVA modelling. Body weight as a key secondary endpoint was then tested for the high dose FDC vs. linagliptin 5 mg followed by the low dose FDC vs. linagliptin 5 mg, using ANCOVA modelling. The treat-to-target endpoint (HbA_{1c} <7%) was the last key secondary endpoint and tested using logistic regression with missing data imputed as failure in the sequence: high dose FDC vs. linagliptin 5 mg, low dose FDC vs. linagliptin 5 mg, high dose FDC vs. empagliflozin 25 mg, and low dose FDC vs. empagliflozin 10 mg. Key categories used for subgroup analyses of primary and key secondary endpoints were age, baseline HbA_{1c}, geographical region, sex, and renal impairment. For further exploratory efficacy endpoints descriptive statistics were generated. Blood pressure and waist circumference were analysed by ANCOVA modelling. Other treat-to-target endpoints and use of rescue medication were analysed using logistic regression. Time to first use of rescue medication was analysed by Kaplan-Meier survival probability estimates and compared using a log rank test. Safety analysis was performed using descriptive statistics. For UTI and genital infection AEs of special interest (AESI), Kaplan-Meier time to event analyses were performed. Lipid parameters were additionally analysed using ANCOVA modelling.

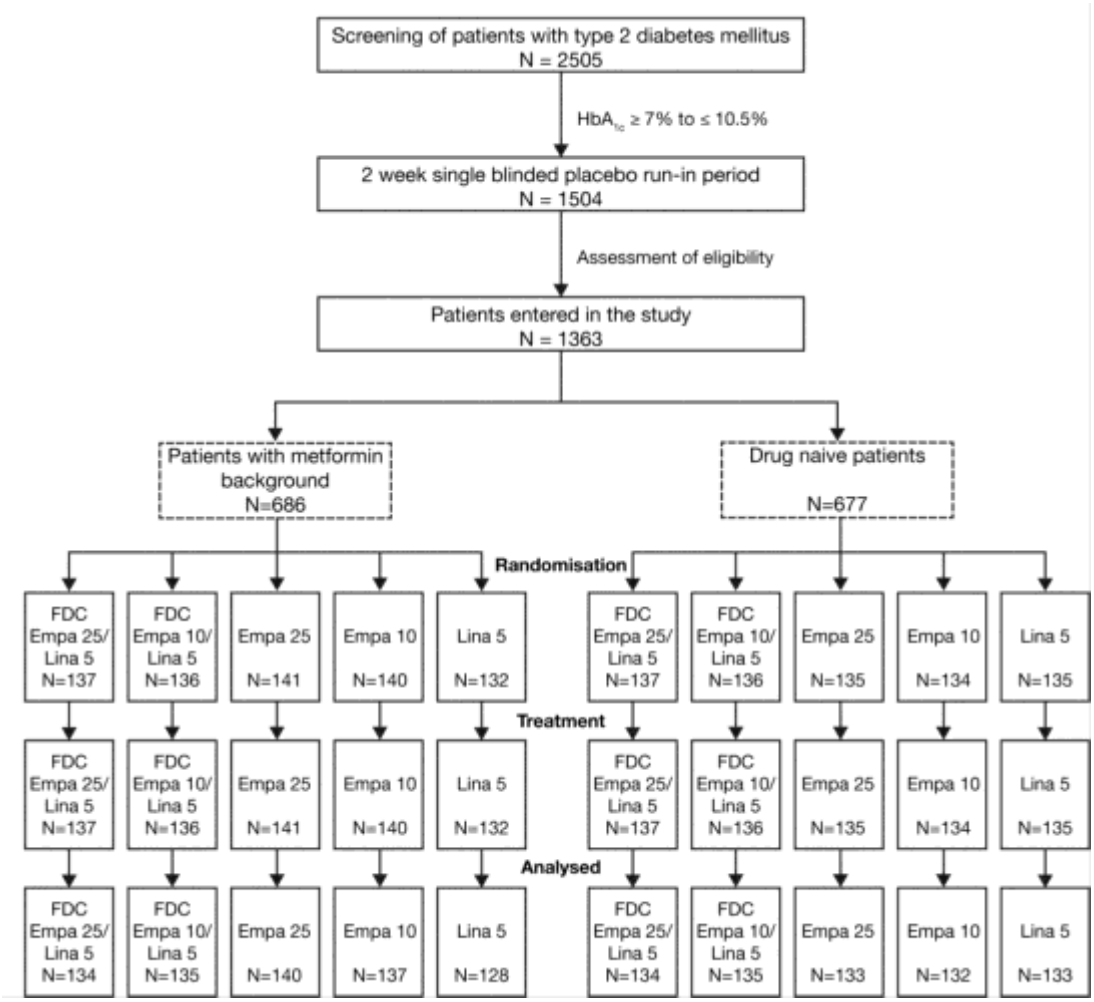
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ANCOVA, analysis of covariance; BMI, body mass index; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FDC, fixed dose combination; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; kg, kilograms; LOCF, last observation carried forward; m, metres; MDRD, modification of diet in renal disease; mg; milligrams; mL/min, millilitres per minute; mmol/L, millimoles per litre; mmol/mol, millimoles per mole; MMRM; mixed effect model repeat measurement; OC, observed cases; OD, once daily; PPS, per-protocol set; REML, restricted maximum likelihood; RS, randomised set; SCR, screened patient set; TD2M, type 2 diabetes mellitus; TS, treated set; UTI, urinary tract infection.

3.3.1.2 Patient population: Study 1275.1

Patient disposition

A total of 1,341 patients were enrolled in the study. In the treatment naïve patient group, 677 patients of 1,341 were enrolled in a 1:1:1:1:1 ratio: empagliflozin 25 mg/linagliptin 5 mg FDC (n=137); empagliflozin 10 mg/linagliptin 5 mg FDC (n=136); empagliflozin 25 mg (n=135); empagliflozin10 mg (n=134); linagliptin 5 mg (n=135). In the previous treatment with metformin patient group, 686 patients of 1,341 were enrolled in a 1:1:1:1:1 ratio: empagliflozin 25 mg/linagliptin 5 mg FDC (n=137); empagliflozin 10 mg/linagliptin 5 mg FDC (n=136); empagliflozin 25 mg (n=141); empagliflozin10 mg (n=140); linagliptin 5 mg (n=132). The proportion of patients completing the study and the subset analysed are shown in Figure 3.

Figure 3: Flow diagram of patient disposition in study 1275.1



Abbreviations: Empa, empagliflozin; FDC, fixed-dose combination; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin.
Source: Study 1275.1 CSR (7)

Patient demographics and baseline characteristics

A summary of patient baseline characteristics (for patients with history of metformin and treatment naïve patients) are provided in Table 5 and Table 6.

Table 5: Baseline characteristics of patients in study 1275.1 (patients with a metformin background)

	Empa 25 mg/Lina 5 mg (n=134)	Empa 10 mg/Lina 5 mg (n=135)	Empa 25 mg (n=140)	Empa 10 mg (n=137)	Lina 5 mg (n=128)	Overall randomised (n=674)
Male (n[%])	72 (53.7)	83 (61.5)	65 (46.4)	78 (56.9)	64 (50.0)	362 (53.7)
Age (years [SD])	57.1 (10.2)	56.2 (10.3)	55.5 (10.0)	56.1 (10.5)	56.2 (10.0)	56.2 (10.2)
FPG (mg/dL)	154.6 (33.3)	156.7 (34.4)	159.9 (37.8)	161.6 (34.8)	156.3 (30.7)	157.9 (34.3)
Body weight (kg)	85.47 (20.36)	86.57 (19.01)	87.68 (17.61)	86.14 (18.19)	85.01 (18.34)	86.20 (18.69)
BMI (kg/m^2)	30.61 (5.69)	30.79 (5.60)	31.80 (5.28)	31.02 (5.27)	30.59 (5.41)	30.98 (5.45)
HbA_{1c} (% [SD])	7.90 (0.79)	7.95 (0.80)	8.02 (0.83)	8.00 (0.93)	8.02 (0.90)	7.98 (0.85)
eGFR (mL/min per 1.73 m^2)*	87.28 (17.15)	89.10 (18.38)`	90.23 (18.31)	91.12 (19.52)	90.03 (20.14)	89.56 (18.71)

Data are n (%) or mean (SD).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Empa, empagliflozin); FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SD, standard deviation.

Table 6: Baseline characteristics of patients in study 1275.1 (treatment naïve patients)

	Empa 25 mg/Lina 5 mg (n=134)	Empa 10 mg/Lina 5 mg (n=135)	Empa 25 mg (n=133)	Empa 10 mg (n=132)	Lina 5 mg (n=133)	Overall randomised (n=667)
Male (n[%])	70 (52.2)	73 (54.1)	77 (57.9)	64 (48.5)	75 (56.4)	359 (53.8)
Age (years [SD])	54.2 (10.0)	55.2 (9.8)	56.0 (9.3)	53.9 (10.5)	53.8 (11.5)	54.6 (10.2)
FPG (mg/dL)	156.1 (35.8)	157.2 (35.4)	152.8 (39.0)	160.3 (41.2)	156.0 (37.1)	156.5 (37.7)
Body weight (kg)	87.92 (18.22)	87.30 (18.44)	86.73 (19.68)	87.82 (23.95)	89.51 (20.12)	87.85 (20.13)
BMI (kg/m^2)	31.83 (5.25)	31.52 (5.56)	31.16 (5.66)	31.52 (5.67)	31.89 (5.92)	31.58 (5.60)
HbA_{1c} (% [SD])	7.99 (0.95)	8.04 (0.96)	7.99 (0.97)	8.05 (1.03)	8.05 (0.89)	8.02 (0.96)
eGFR (mL/min per 1.73 m^2)*	90.09 (19.64)	87.80 (17.65)	88.46 (18.30)	88.38 (18.95)	89.52 (20.29)	88.85 (18.95)

Data are n (%) or mean (SD).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SD, standard deviation.

3.3.1.3 Results: Study 1275.1 (patient population with metformin background)

Results from the metformin treated patient population are not considered relevant to this submission, which describes the efficacy and safety of empagliflozin as monotherapy in

treatment-naïve or metformin intolerant/contraindicated patients. Please see Appendix D (provided separately) for these results.

3.3.1.4 Results: Study 1275.1 (treatment naïve patient population)

Primary efficacy outcome

A summary of primary efficacy outcomes at Week 24 is presented in Table 7. After 24 weeks of treatment, there were clinically relevant reductions in HbA_{1c} in all treatment groups in the treatment naïve patient population (Table 7). The empagliflozin 25 mg/linagliptin 5 mg FDC was superior to linagliptin 5 mg treatment (p<0.0001), but showed no statistically significant difference vs. empagliflozin 25 mg monotherapy. Since the high dose FDC did not show superiority to empagliflozin 25 mg, according to the pre-defined hierarchical testing procedure all subsequent analyses were considered exploratory.

Table 7: Summary of primary efficacy outcomes of empagliflozin/linagliptin FDCs and monocomponent therapies at Week 24 (in treatment-naïve patients) – FAS (LOCF)

	Empa 25 mg /Lina 5 mg	Empa 10 mg /Lina 5 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
Number of analysed patients, N	134	135	133	132	133
Mean baseline HbA_{1c} (SE)	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Mean HbA_{1c} at Week 24 (SE)	6.92 (0.07)	6.80 (0.07)	7.05 (0.08)	7.21 (0.09)	7.36 (0.09)
Adjusted[1] mean HbA_{1c} at Week 24 (SE)	6.94 (007)	6.79 (0.07)	7.07 (0.07)	7.19 (0.07)	7.35 (0.07)
Change from baseline at Week 24 **Mean HbA_{1c} (SE)** **Adjusted mean HbA_{1c} (SE)**	 -1.06 (0.09) -1.08 (0.07)	 -1.25 (0.08) -1.24 (0.07)	 -0.94 (0.09) -0.95 (0.07)	 -0.84 (0.08) -0.83 (0.07)	 -0.69 (0.08) -0.67 (0.07)
Comparison vs. empagliflozin 25 mg **Adjusted mean HbA_{1c} (SE)** **p-value**	 -0.14 (0.10) 0.1785	 - -	 - -	 - -	 - -
Comparison vs. empagliflozin 10 mg **Adjusted mean HbA_{1c} (SE)** **p-value**	 - -	 -0.41 (0.10) <0.0001	 - -	 - -	 - -
Comparison vs. linagliptin 10 mg **Adjusted mean HbA_{1c} (SE)** **p-value**	 -0.41 (0.10) <0.0001	 -0.57 (0.10) <0.0001	 - -	 - -	 - -

Abbreviations: Empa, empagliflozin; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SE, standard error

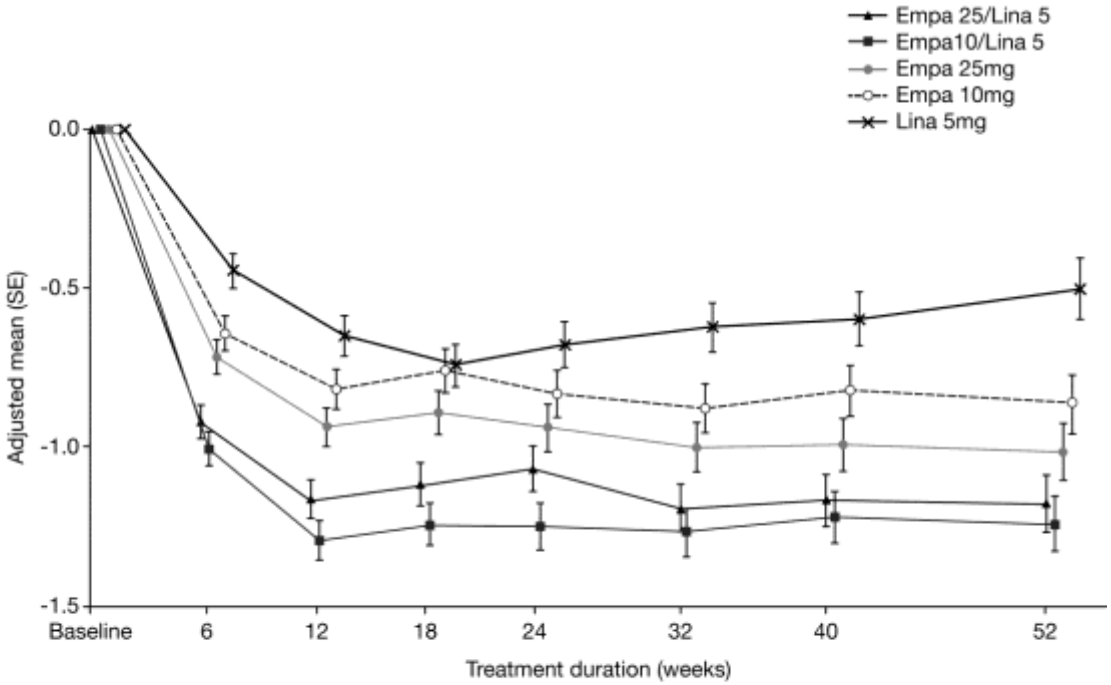
A summary of primary efficacy outcomes at Week 52 is presented in Table 8 and the change from baseline in HbA_{1c} over 52 weeks is shown in Figure 4. The changes were consistent with those seen at Week 24.

Table 8: Summary of primary efficacy outcomes of empagliflozin/linagliptin FDCs and monocomponent therapies at Week 52 (in treatment-naïve patients), MMRM-FAS (OC)

	Empa 25 mg /Lina 5 mg	Empa 10 mg /Lina 5 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
Number of analysed patients, N	134	134	133	131	133
Mean baseline HbA_{1c} (SE)	7.99 (0.08)	8.02 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Mean HbA_{1c} at Week 52 (SE)	6.64 (0.07)	6.66 (0.09)	6.78 (0.08)	6.92 (0.10)	7.08 (0.09)
Adjusted[1] mean HbA_{1c} at Week 52 (SE)	6.79 (0.09)	6.72 (0.09)	6.95 (0.09)	7.10 (0.09)	7.46 (0.09)
Change from baseline at Week 52 **Mean HbA_{1c} (SE)** **Adjusted mean HbA_{1c} (SE)**	 -1.28 (0.09) -1.18 (0.09)	 -1.33 (0.11) -1.25 (0.09)	 -1.05 (0.09) -1.02 (0.09)	 -1.03 (0.09) -0.87 (0.09)	 -0.80 (0.11) -0.51 (0.09)

Abbreviations: Empa, empagliflozin; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SE, standard error

Figure 4: Changes from baseline MMRM results over time (adjusted mean ± 95% CI) in HbA_{1c} following treatment with empagliflozin 25 mg/linagliptin 5 mg FDC, empagliflozin 10 mg/linagliptin 5 mg FDC, empagliflozin (10 mg and 25 mg) or linagliptin 5 mg for 52 weeks (treatment-naïve patients)



n with data at visit

	Baseline	6	12	18	24	32	40	52
Empa 25/Lina 5	134	134	130	126	123	121	115	109
Empa10/Lina 5	134	134	130	127	124	119	114	108
Empa 25mg	133	132	129	128	121	116	114	106
Empa 10mg	131	131	127	126	120	112	109	95
Lina 5mg	133	132	123	122	114	107	98	90

Abbreviations: CI, confidence interval; FDC, fixed dose combination; HbA_{1c}, glycosylated haemoglobin; Empa, empagliflozin; Lina, linagliptin; MMRM, mixed model repeated measures.
Source: Study 1275.1 CSR (7)

Secondary efficacy outcomes

A summary of secondary efficacy outcomes at Week 24 is presented in Table 9 (please note that these are exploratory according to the pre-defined hierarchical testing procedure). Among patients with HbA_{1c} of 7.0% or greater at baseline, 41.5% of patients in the empagliflozin 25 mg group and 38.8% of patients in the empagliflozin 10 mg group attained HbA_{1c} values of less than 7.0% after 24 weeks of treatment, compared with 55.4% of the patients in the empagliflozin 25 mg/linagliptin 5 mg FDC group, 62.3% of the patients in the empagliflozin 10 mg/linagliptin 5 mg FDC group, and 32.3% of patients in the linagliptin 5 mg group.

After 24 weeks of treatment, both doses of empagliflozin monotherapy and of the FDC of empagliflozin/linagliptin resulted in clinically relevant reductions in FPG; in the linagliptin 5 mg group, changes from baseline were small (Table 9). The adjusted mean (SE) change from baseline in FPG was -24.59 (2.40) mg/dL in the empagliflozin 25 mg group, and -24.62 (2.41) mg/dL in the empagliflozin 10 mg group, compared with -29.89 (2.68) mg/dL for the FDC empagliflozin 25 mg/linagliptin 5 mg group, -27.64 (2.38) mg/dL for the FDC empagliflozin 10 mg/linagliptin 5 mg group, and -7.86 (2.46) mg/dL in the linagliptin 5 mg group.

After 24 weeks of treatment, there were clinically relevant reductions in body weight with both doses of empagliflozin and empagliflozin/linagliptin FDC. There was no relevant change in body weight in the linagliptin 5 mg group (Table 9). The adjusted mean (SE) change from baseline in body weight was -2.13 (0.36) kg and -2.27 (0.37) kg in the empagliflozin 25 mg and 10 mg groups, respectively, compared with -2.00 (0.36) kg for empagliflozin 25 mg/linagliptin 5 mg FDC, -2.74 (0.36) kg for empagliflozin 10 mg/linagliptin 5 mg FDC, and -0.78 (0.36) kg in the linagliptin 5 mg group.

Table 9: Summary of secondary efficacy outcomes of empagliflozin/linagliptin FDCs and monocomponent therapies at Week 24 (in treatment-naïve patients)

	Empa 25 mg /Lina 5 mg	Empa 10 mg /Lina 5 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
HbA_{1c} response (<7%) - FAS (NCF)					
Number of analysed patients, N	121	122	118	121	127
Patients with HbA_{1c} <7.0% at Week 24 (%)	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
FPG (mg/dL) – FAS (OC)					
Number of analysed patients, N	133	133	132	130	132
Mean baseline FPG (SE)	155.71 (3.09)	157.34 (3.06)	152.90 (3.41)	158.80 (3.47)	155.79 (3.23)
Mean FPG at Week 24 (SE)	124.48 (2.28)	127.49 (2.49)	127.25 (2.28)	130.13 (2.70)	143.27 (3.15)
Adjusted[1] mean FPG at Week 24 (SE)	125.22 (2.38)	127.47 (2.38)	130.52 (2.40)	130.48 (2.41)	147.25 (2.46)
Change from baseline at Week 24					
Mean FPG (SE)	-29.41 (3.24)	-28.89 (2.81)	-22.54 (2.93)	-27.94 (2.90)	-9.45 (3.68)
Adjusted mean FPG (SE)	-29.89 (2.68)	-27.64 (2.38)	-24.59 (2.40)	-24.62 (2.41)	-7.86 (2.46)
Body weight (kg) – FAS (OC)					
Number of analysed patients, N	134	135	133	132	133
Mean baseline body weight (SE)	87.92 (1.57)	87.30 (1.59)	86.73 (1.71)	87.82 (2.08)	89.51 (1.74)
Mean body weight at Week 24 (SE)	85.90 (1.56)	84.58 (1.54)	84.61 (1.72)	85.60 (2.02)	88.66 (1.75)
Adjusted[1] mean body weight at Week 24 (SE)	85.85 (0.36)	85.11 (0.36)	85.72 (0.36)	85.58 (0.37)	87.07 (0.36)
Change from baseline at Week 24					
Mean body weight (SE)	-2.02 (0.28)	-2.72 (0.43)	-2.12 (0.48)	-2.22 (0.35)	-0.85 (0.29)
Adjusted mean body weight (SE)	-2.00 (0.36)	-2.74 (0.36)	-2.13 (0.36)	-2.27 (0.37)	-0.78 (0.36)

Abbreviations: Empa, empagliflozin; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SE, standard error; NCF, non-completers considered failures

A summary of secondary efficacy outcomes at Week 52 is presented in Table 10. Among patients with HbA_{1c} of 7.0% or greater at baseline, 45.8% of patients in the empagliflozin 25 mg group and 33.1% of patients in the empagliflozin 10 mg group attained HbA_{1c} values of less than 7.0% after 52 weeks of treatment, compared with 50.4% of the patients in the empagliflozin 25 mg/linagliptin 5 mg FDC group, 50.8% of the patients in the empagliflozin 10 mg/linagliptin 5 mg FDC group, and 27.6% of patients in the linagliptin 5 mg group.

After 52 weeks of treatment, both doses of empagliflozin monotherapy and of the FDC of empagliflozin/linagliptin resulted in clinically relevant reductions in FPG; in the linagliptin 5 mg group, changes from baseline were small (Table 10). The adjusted mean (SE) change from baseline in FPG was -20.60 (2.92) mg/dL in the empagliflozin 25 mg group, and -16.15 (3.03) mg/dL in the empagliflozin 10 mg group, compared with -25.13 (2.89) mg/dL for the FDC empagliflozin 25 mg/linagliptin 5 mg group and -22.59 (2.91) mg/dL for the FDC empagliflozin 10 mg/linagliptin 5 mg group, and 1.73 (3.13) mg/dL in the linagliptin 5 mg group.

The clinically relevant reductions in body weight observed at Week 24 with both doses of empagliflozin and both doses of the FDC of empagliflozin/linagliptin were maintained at Week 52 (Table 10). There was no relevant change in body weight in the linagliptin 5 mg group.

Table 10: Summary of secondary efficacy outcomes of empagliflozin/linagliptin FDCs and monocomponent therapy at Week 52 (in treatment-naïve patients)

	Empa 25 mg /Lina 5 mg	Empa 10 mg /Lina 5 mg	Empa 25 mg	Empa 10 mg	Lina 5 mg
HbA_{1c} response (<7%) - FAS (NCF)					
Number of analysed patients, N	121	122	118	121	127
Patients with HbA_{1c} <7.0% at Week 52 (%)	61 (50.4)	62 (50.8)	54 (45.8)	40 (33.1)	35 (27.6)
FPG (mg/dL) – FAS (OC)					
Number of analysed patients, N	133	133	132	130	132
Mean baseline FPG (SE)	155.71 (3.9)	157.34 (3.06)	152.90 (3.41)	158.80 (3.47)	155.79 (3.23)
Mean FPG at Week 52 (SE)	125.81 (2.41)	129.80 (3.66)	127.61 (2.48)	133.42 (3.25)	145.27 (3.94)
Adjusted[1] mean FPG at Week 52 (SE)	128.79 (2.89)	131.34 (2.91)	133.33 (2.92)	137.78 (3.03)	155.66 (3.13)
Change from baseline at Week 52					
Mean FPG (SE)	-27.01 (3.21)	-24.20 (4.26)	-18.77 (2.74)	-19.57 (3.49)	-2.33 (4.04)
Adjusted mean FPG (SE)	-25.13 (2.89)	-22.59 (2.91)	-20.60 (2.92)	-16.15 (3.03)	1.73 (3.13)
Body weight (kg) – FAS (OC)					
Number of analysed patients, N	123	124	121	121	120
Mean baseline body weight (SE)	88.13 (1.70)	86.91 (1.63)	87.58 (1.82)	87.40 (2.19)	89.83 (1.87)
Mean body weight at Week 52 (SE)	85.21 (1.74)	84.35 (1.69)	85.60 (1.86)	84.50 (2.39)	91.28 (2.20)
Adjusted[1] mean body weight at Week 52 (SE)	85.70 (0.42)	86.33 (0.42)	85.31 (0.42)	85.48 (0.44)	87.86 (0.46)
Change from baseline at Week 52					
Mean body weight (SE)	-2.51 (0.41)	-1.78 (0.34)	-2.98 (0.53)	-2.43 (0.45)	-0.51 (0.45)
Adjusted mean body weight (SE)	-2.33 (0.42)	-1.70 (0.42)	-2.72 (0.42)	-2.55 (0.44)	-0.16 (0.46)

Abbreviations: Empa, empagliflozin; HbA_{1c}, glycosylated haemoglobin; Lina, linagliptin; SE, standard error; NCF, non-completers considered failures

3.3.1.5 Efficacy conclusion: Study 1275.1

In conclusion, study 1275.1 demonstrated that treatment with empagliflozin 25 mg or 10 mg, or the FDCs of empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg, led to clinically meaningful reductions in HbA_{1c} in patients with metformin background medication after 24 weeks of treatment. However, it should be noted that although the FDC of empagliflozin

25 mg/linagliptin 5 mg showed statistical significance vs. linagliptin 5 mg this was not achieved vs. empagliflozin 25 mg. Therefore confirmatory testing did not proceed beyond the first hypothesis and all other analyses were considered to be exploratory.

Among patients with HbA_{1c} of 7.0% or greater at baseline, a greater proportion of patients in the empagliflozin monotherapy (38.8-41.5%) and FDC treatment groups (55.4-62.3%) attained HbA_{1c} values of less than 7.0% after 24 weeks of treatment than in the linagliptin 5 mg group; these changes were maintained at 52 weeks. Both empagliflozin monotherapy doses and FDCs of empagliflozin and linagliptin resulted in clinically relevant reductions in body weight after 24 weeks of treatment that were maintained over 52 weeks. There was no relevant change in body weight after treatment with linagliptin 5 mg. Overall, in all treatment groups, including both the 10 mg and 25 mg empagliflozin monotherapy groups, a positive benefit-risk profile for the treatment of patients with T2DM and insufficient glycaemic control was observed. A greater benefit was observed in treatment naïve patients than in those previously treated with metformin. Moreover, the beneficial improvements of body weight and blood pressure reductions observed previously in the empagliflozin monotherapy clinical development programme were maintained (7).

3.4 Empagliflozin monotherapy (placebo and active control)

3.4.1 Study 1245.20 (Roden et al., 2013): Empagliflozin monotherapy compared to sitagliptin and placebo

3.4.1.1 Methodology: Study 1245.20

A summary of the methodology for Study 1245.20 is provided in Table 11.

Table 11: Study methodology

Study	Study 1245.20 (Roden et al., 2013)(1)
Summary	In this multicentre, randomised, placebo controlled, phase III trial, adults (aged ≥ 18 years) who had not received oral or injected antidiabetic treatment in the previous 12 weeks were enrolled. Eligible patients had HbA_{1c} concentrations of 7 to 10. Patients were randomly allocated (1:1:1:1) with a computer generated random sequence, stratified by region, HbA_{1c}, and eGFR at screening, to placebo, empagliflozin 10 mg, empagliflozin 25 mg, or sitagliptin 100 mg OD for 24 weeks. Patients and investigators were masked to treatment assignment. The primary endpoint was change from baseline in HbA_{1c} at Week 24 by ANCOVA in all randomly allocated patients who were treated with at least one dose of study drug and had a baseline HbA_{1c} value. This study is completed and registered with ClinicalTrials.gov, number NCT01177813.
Objectives	To assess the safety, efficacy and tolerability of empagliflozin (10 mg or 25 mg OD) compared with placebo and sitagliptin given for 24 weeks as monotherapy in drug-naïve patients with T2DM mellitus and insufficient glycaemic control. The efficacy and safety of empagliflozin 25 mg OD in patients with T2DM and very poor glycaemic control (HbA_{1c} > 10%) was assessed in an open-label arm.
Design details	Study 1245.20 was a 24 week, randomised, placebo controlled, double blind, parallel group phase III trial, conducted in 124 trial sites (academic medical centres, hospitals, and private practices) in nine countries (Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland and the USA). The eligibility of participants was assessed before and at the end of a 2 week open label placebo run in phase. Participants were randomly allocated to receive either placebo, empagliflozin (25 mg or 10 mg) or sitagliptin 100 mg OD for 24 weeks. An open label treatment group was also used to provide data for patients with very poor glycaemic control (HbA_{1c} >10% at screening), apart from in Germany or Ireland, where this arm was not included.
Interventions	Eligible patients with an HbA_{1c} of 7.0 to 10.0% at screening who met the inclusion criteria after the placebo run in were randomly allocated in a triple dummy manner (1:1:1:1 ratio) to receive oral empagliflozin 10 mg OD, empagliflozin 25 mg OD, sitagliptin 100 mg OD, or placebo for 24 weeks. Eligible patients with HbA_{1c} of more than 10.0% at screening were assigned to open label empagliflozin 25 mg for 24 weeks without a placebo run in.
Key inclusion criteria	• Patients with previously untreated T2DM (no oral or injected anti-diabetes treatment for 12 weeks before randomisation or start of open-label treatment

Study	Study 1245.20 (Roden et al., 2013)(1)
	• Aged at least 18 years (≥ 20 years in Japan or 18 to 65 years in India) • BMI of 45 kg/m² or less • Insufficient glycaemic control despite a diet and exercise regimen (HbA_{1c} 7.0–10.0% [or HbA_{1c} 7.0–9.0% in Germany] at screening for patients eligible for randomised treatment, or >10.0% at screening for patients eligible for the open-label treatment group).
Key exclusion criteria	• Uncontrolled hyperglycaemia (glucose concentration >13.3 mmol/L after an overnight fast during the placebo run in phase and confirmed by a second measurement • eGFR (estimated with the MDRD equation) of less than 50 mL/min per 1.73 m² (or <60 mL/min per 1.73 m² in China • Contraindications to sitagliptin according to the local label • Treatment with antiobesity drugs within 3 months before informed consent • Treatment with systemic steroids at time of informed consent • Change in dose of thyroid hormones within 6 weeks before informed consent • Any uncontrolled endocrine disorder apart from T2DM.
Efficacy outcomes	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment (%). Key secondary endpoints were tested in the following hierarchical order: • Change from baseline in body weight to Week 24 • Change from baseline in SBP and in DBP to Week 24
Populations analysed	**Screened patients set (SCR)** – including all patients screened for the trial, with consent given and who completed at least 1 screening procedure at Visit 1. **Randomised set (RS)** – including all patients from the screened set who were randomised to a trial medication, regardless of whether any trial medication was taken. **Treated set (TS)** – including all patients treated with at least 1 dose of randomised trial medication. **Full analysis set (FAS)** – including all randomised and treated patients who had a baseline HbA_{1c} value. **Per-protocol set (PPS)** – including all patients in the FAS without important protocol violations leading to exclusion. **Open-label set (OLS)** – including all patients entered in the empagliflozin 25 mg open-label treatment arm.
Statistical analysis	To maintain an overall power of at least 85% when considering the first key secondary endpoint (change from baseline in body weight at Week 24), the sample size was increased to 210 patients per group, resulting in 840 randomly allocated patients overall. The treatment differences were tested in the primary and key secondary endpoints for each dose of empagliflozin vs. placebo by use of two parallel hierarchical procedures to preserve the family-wise error rate at 2.5% for each dose. Confirmatory tests for primary and key secondary endpoints were therefore based on two sided tests at a 2.5% level. All other exploratory tests were two sided at a 5% level (without adjustment for multiplicity). The differences between each dose of empagliflozin and sitagliptin were assessed in exploratory comparisons. ANCOVA model for the primary analysis was used, with treatment, region, and baseline eGFR as fixed effects and baseline HbA_{1c} as a linear covariate. Analysis was conducted in the FAS including all randomly allocated patients who were treated with at least one dose of study drug and had a baseline HbA_{1c} value. Efficacy data obtained after initiation of rescue therapy was regarded as missing before analyses were done and the LOCF approach to impute missing data was used. Key secondary endpoints and continuous exploratory endpoints with the statistical model described for the primary endpoint were analysed, with the baseline value of the respective endpoint used as an additional linear covariate. For analyses of blood pressure, data obtained after changes in antihypertensive therapy were regarded as missing before LOCF imputation. Analysis was conducted to identify the change from baseline in HbA_{1c} in patients with baseline HbA_{1c} of at least 8.5% and lower than 8.5% with the same statistical model as the primary analysis with treatment by baseline interaction (<8.5% vs. ≥ 8.5%) also included. The change from baseline in SBP in patients with controlled and uncontrolled blood pressure at baseline was analysed with the same statistical model as the key secondary blood pressure analysis with baseline blood pressure control and treatment by baseline blood pressure control interaction (<130/80 mm Hg vs. ≥ 130/80 mm Hg) also included. The effect of the methods used for handling of missing data and key protocol violations with sensitivity analyses were assessed. These sensitivity analyses included REML-based MMRM analyses. MMRM analyses were done on the FAS using OC, and included fixed effects of

Study	Study 1245.20 (Roden et al., 2013)(1)
	treatment, region, renal function, visit, and visit-by-treatment interaction, and the linear covariate baseline HbA_{1c} (and, for other endpoints, the baseline of the respective endpoint as an additional covariate). Logistic regression models were applied to assess binary endpoints, including baseline HbA_{1c}, region, and baseline eGFR (and baseline body weight for the analysis of response in weight). Analyses of efficacy endpoints in the open-label arm were based on OC; these were descriptive in nature. For these analyses, missing data was not imputed and values reported after start of rescue medication were excluded. Lipid parameters were analysed with ANCOVA on the treated set by use of an LOCF-IR imputation (i.e., LOCF without regarding values after rescue therapy as missing). Safety analyses were performed on the treated set (all patients treated with at least one dose of study drug) and were descriptive in nature. AEs (AEs) that occurred between first drug intake and 7 days after last treatment administration or that started before drug intake and deteriorated during treatment were reported.

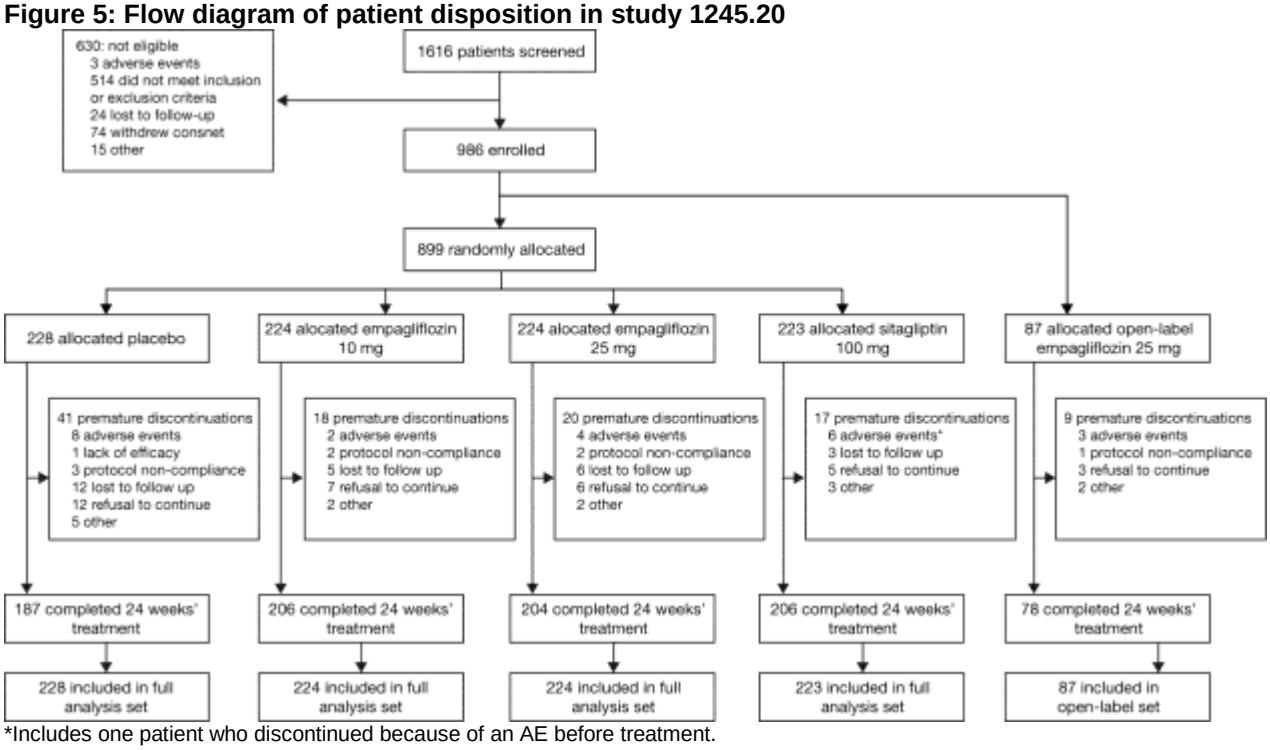
Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; LOCF, last observation carried forward; MDRD, modification of diet in renal disease; mg; milligrams; mm Hg, millimetre of mercury; mmol/L, millimoles per litre; MMRM; mixed effect model repeat measurement; OD, once daily; OLS, open-label set; PPS, per-protocol set; REML, restricted maximum likelihood; RS, randomised set; SBP; systolic blood pressure; SCR, screened patient set; TD2M, type 2 diabetes mellitus; TS, treated set.

3.4.1.2 Patient population: Study 1245.20

Patient disposition

A total of 899 patients were enrolled in the study and randomised in a 1:1:1:1 ratio: empagliflozin 10 mg (n=224); empagliflozin 25 mg (n=224); sitagliptin 100 mg (n=223); placebo (n=228) (Figure 5). 803 patients completed the study and 96 discontinued prematurely: 18 taking empagliflozin 10mg, 20 taking empagliflozin 25 mg, 17 taking sitagliptin 100 mg, and 41 taking placebo. An additional 87 patients were allocated to the open label empagliflozin 25 mg group, with nine patients discontinuing prematurely.

Figure 5: Flow diagram of patient disposition in study 1245.20



*Includes one patient who discontinued because of an AE before treatment.
Sources: Study 1245.20 CSR(5); Roden et al., 2013(1).

Patient demographics and baseline characteristics

A summary of patient baseline characteristics is provided in Table 12.

Table 12: Baseline characteristics

Characteristic	Placebo (n=228)	Empa 10 mg (n=224)	Empa 25 mg n=224)	Sita 100 mg (n=223)	Overall randomised (n=899)	Open label Empa 25 mg (n=87)‡
Male (n[%])	123 (54.0)	142 (63.0)	145 (65.0)	141 (63.0)	551 (61.0)	64 (74.0)
Age (years [SD])	54.9 (10.9)	56.2 (11.6)	53.8 (11.6)	55.1 (9.9)	55.0 (11.0)	50.2 (11.3)
Body weight (kg)	78.2 (19.9)	78.4 (18.7)	77.8 (18.0)	79.3 (20.4)	78.4 (19.2)	80.7 (19.5)
BMI (kg/m^2)	28.7 (6.2)	28.3 (5.5)	28.2 (5.5)	28.2 (5.2)	28.4 (5.6)	28.2 (5.5)
HbA_{1c} (% [SD])	7.91 (0.78)	7.87 (0.88)	7.86 (0.85)	7.85 (0.79)	7.88 (0.82)	11.50 (1.39)†
SBP (mmHg)	130.4 (16.3)	133.0 (16.6)	129.9 (17.5)	132.5 (15.8)	131.4 (16.6)	129.5 (14.1)
DBP (mmHg)	78.9 (9.6)	79.2 (9.6)	78.3 (9.4)	80.1 (10.0)	79.1 (9.6)	81.0 (9.6)
eGFR (mL/min per 1.73 m^2)*	86.8 (17.9)	87.7 (19.2)	87.6 (18.3)	87.6 (17.3)	87.4 (18.2)	94.7 (20.3)

Data are n (%) or mean (SD).
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; HbA_{1c}, glycosylated haemoglobin; SBP, systolic blood pressure; SD, standard deviation; Sita, sitagliptin.
* Information not available for one patient in the open-label empagliflozin group † Patients in the open-label group had HbA_{1c} >10.0% at baseline; ‡ Information not available for one patient in the open-label empagliflozin group.

3.4.1.3 Results: Study 1245.20

Primary efficacy outcome

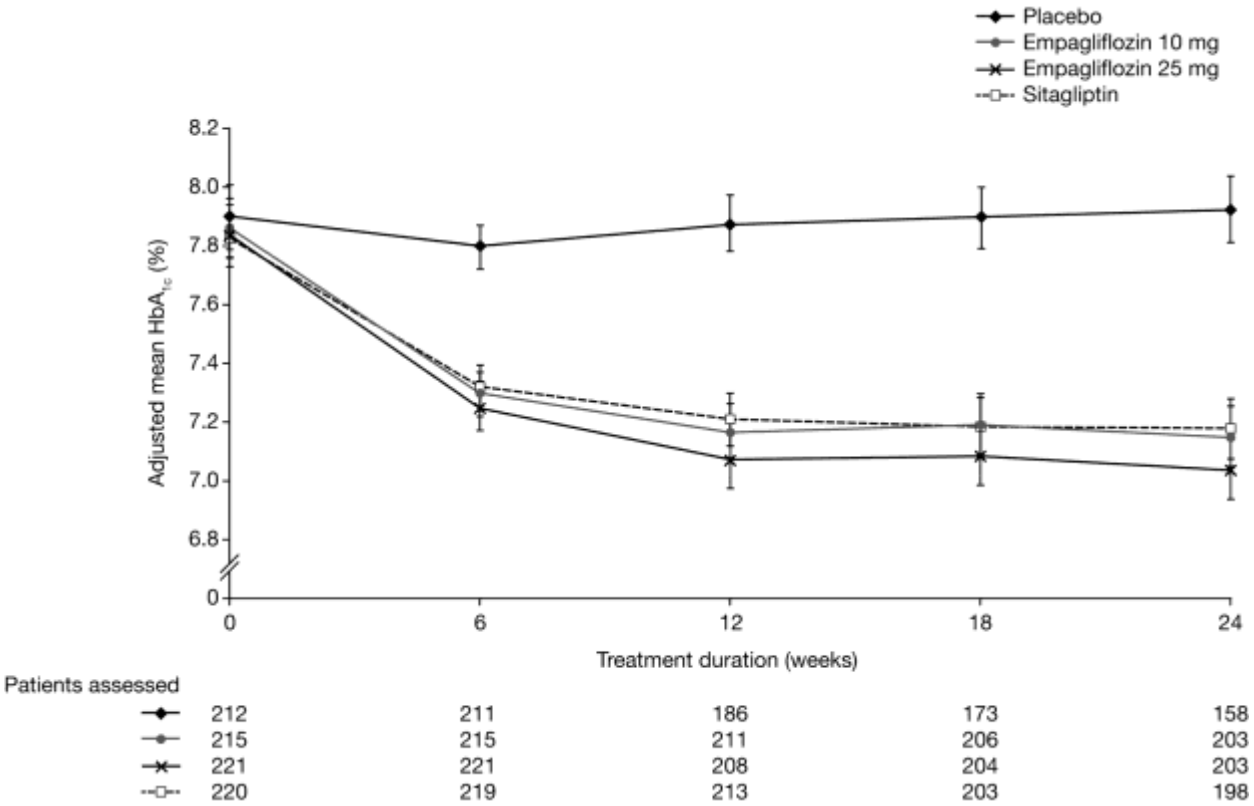
A summary of the primary efficacy outcome is presented in Table 13. Treatment with both doses of empagliflozin demonstrated superiority over placebo, with a significantly greater reduction in HbA_{1c} from baseline. Treatment with empagliflozin 25 mg showed a numerically greater reduction in HbA_{1c} than treatment with sitagliptin (Figure 6).

Table 13: Summary of the primary efficacy outcome

	Baseline	Adjusted mean difference to placebo	Difference in adjusted mean treatment effect ((CI); p value)†
HbA_{1c} (% [SE])			
Placebo	7.91 (0.05)		
Empagliflozin 10 mg (n=224)	7.87 (0.06)	-0.74 (0.07)	(-0.90 to -0.57; p<0.0001)
Empagliflozin 25 mg (n=224)	7.86 (0.06)	-0.85 (0.07)	(-1.01 to -0.69; p<0.0001)
Sitagliptin 100 mg (n=223)	7.85 (0.05)	-0.73 (0.07)	(-0.88 to -0.59)

Abbreviations: CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; SE, standard error.
†97.5% CI for empagliflozin 10 mg and for empagliflozin 25 mg, 95% CI for sitagliptin; ‡ % (SE) for baseline values and adjusted mean difference to placebo.
Sources: Study 1245.20 CSR(5); Roden et al., 2013(1).

Figure 6: Changes over time (adjusted mean ± 95% CI) in HbA_{1c} following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo for 24 weeks



Patients assessed					
Placebo	212	211	186	173	158
Empagliflozin 10 mg	215	215	211	206	203
Empagliflozin 25 mg	221	221	208	204	203
Sitagliptin	220	219	213	203	198

Abbreviations: CI, confidence interval; HbA_{1c}, glycosylated haemoglobin.
Source: Roden et al., 2013(1).

Secondary efficacy outcomes

A summary of secondary efficacy outcomes is presented in Table 14. Treatment with both doses of empagliflozin demonstrated a significantly greater reduction in body weight and SBP after 24 weeks of treatment compared to placebo. Treatment with empagliflozin 10 mg and 25 mg also reduced body weight and BP compared with sitagliptin treatment.

Table 14: Summary of secondary efficacy outcomes

	Baseline	Adjusted mean difference to placebo	Difference in adjusted mean treatment effect ((CI); p value)†
Body weight (kg)			
Placebo	78.23 (1.32)		
Empagliflozin 10 mg (n=224)	78.35 (1.25)	-1.93 (0.24)	(-2.48 to -1.38; p<0.0001)
Empagliflozin 25 mg (n=224)	77.80 (1.20)	-2.15 (0.24)	(-2.70 to -1.60; p<0.0001)
Sitagliptin 100 mg (n=223)	78.31 (1.37)	0.52 (0.25)	(-0.04 to 1.00)
SBP (mm Hg [SE])			
Placebo	130.4 (1.1)		
Empagliflozin 10 mg (n=224)	133.0 (1.1)	-2.6 (1.1)	(-5.2 to 0.0; p=0.0231)
Empagliflozin 25 mg (n=224)	129.9 (1.2)	-3.4 (1.1)	(-6.0 to -0.9; p=0.0028)
Sitagliptin 100 mg (n=223)	132.7 (1.2)	0.8 (1.2)	
DBP (mm Hg [SE])			
Placebo	78.9 (0.6)		
Empagliflozin 10 mg (n=224)	79.2 (0.6)	-0.6 (0.7)	(-2.1 to 0.9; p=0.3987)
Empagliflozin 25 mg (n=224)	78.3 (0.6)	-1.5 (0.7)	(-3.0 to 0.00; p=0.0296)
Sitagliptin 100 mg (n=223)	80.1 (0.7)	1.1 (0.7)	(-0.2 to 2.5)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; mm Hg, millimetre of mercury; SBP, systolic blood pressure; SE, standard error.
†97.5% CI for empagliflozin 10 mg and for empagliflozin 25 mg, 95% CI for sitagliptin.

3.4.1.4 Efficacy conclusion: Study 1245.20

The percentage of patients with HbA_{1c} ≥ 7.0% at baseline who reached HbA_{1c} <7.0% at Week 24 with empagliflozin 10 mg and 25 mg was significantly greater than for those treated with placebo (35% [OR = 4.12; p<0.0001] and 44% [OR = 6.15; p<0.0001], respectively). The reductions in HbA_{1c} levels, body weight and BP for empagliflozin treatment were numerically greater than those seen for sitagliptin treatment. In the open label arm, the mean changes from baseline at Week 24 were -3.10% for HbA_{1c}, -1.93 kg for body weight, -3.8 mmHg for SBP, and -1.5 mmHg for diastolic blood pressure (DBP).

In conclusion, this study demonstrates that treatment with empagliflozin 10 mg and empagliflozin 25 mg OD over 24 weeks as monotherapy was superior to placebo in reducing HbA_{1c} levels, body weight, and SBP in patients with T2DM and insufficient glycaemic control. The reductions in DBP following empagliflozin treatment did not reach statistical significance. The reductions in HbA_{1c} levels, body weight, and BP after treatment with empagliflozin were numerically greater than those seen for sitagliptin treatment (1, 5).

3.4.2 Study 1245.31 (Roden et al., 2014): Empagliflozin monotherapy compared to sitagliptin and placebo, 76 week extension study

3.4.2.1 Methodology: Study 1245.31

A summary of the methodology for Study 1245.31 is provided in Table 15.

Table 15: Study methodology

Study	Study 1245.31 (Roden et al., 2014)(9)
Summary	Of 899 patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, placebo or sitagliptin 100 mg in a 24 week study (reported as EMPA-REG MONOTM, NCT01177813), 615 patients (68.4%) continued in a double blind extension for ≥ 52 weeks. Patients were treated until the last patient to enter completed the trial. Safety was assessed for ≥ 76 weeks (in all patients who received ≥ 1 dose of study drug), while efficacy was assessed at Week 76. Exploratory efficacy endpoints were changes from baseline (of EMPA-REG MONOTM) in HbA_{1c}, body weight, SBP and DBP. The difference between the adjusted means in the placebo and treatment groups was assessed with ANCOVA in patients who received ≥ 1 study drug dose and had a baseline HbA_{1c} value, using LOCF.
Objectives	To investigate the long term safety, tolerability and efficacy of empagliflozin (10 mg or 25 mg OD) compared with sitagliptin (100 mg OD) or placebo as monotherapy (preceding trial 1245.20) in patients with T2DM mellitus. The extension study also compared empagliflozin monotherapy with placebo on a background of pioglitazone (preceding trial 1245.19), placebo in a background of metformin alone (preceding trial 1245.23 Met) and placebo on a background of metformin with SU (preceding trial 1245.23). However, study 1245.20 is used as a comparator in this submission.
Design details	This study was a 24 week, randomised, placebo controlled, double blind, parallel group phase III trial. Participants were randomly allocated to receive either placebo, empagliflozin (25 mg or 10 mg) or sitagliptin 100 mg OD for 24 weeks.(1;16) Patients continued on the treatment to which they had been randomised in study 1245.20 in double blind fashion; no re-randomisation was performed in the extension trial. Analyses of study 1245.20 were carried out separately for other studies within the extension study 1245.31. All data of the preceding trial were combined with the data of the extension trial, and the final analysis was performed after the last patient had completed 52 weeks of treatment. Patients from the preceding trial were included in the analyses irrespective of participation in the extension; no separate analyses were done for the extension period alone.
Interventions	Patients were randomly allocated in a triple-dummy manner (1:1:1:1 ratio) during study 1245.20 to receive oral empagliflozin 10 mg OD, empagliflozin 25 mg OD, sitagliptin 100 mg OD, or placebo for 24 weeks. Patients were then treated for a further 52 weeks on the same treatment. Patients were to remain in the trial until the last patient had been treated for a total of 76 weeks.
Key inclusion criteria	• Patients with previously untreated T2DM (no oral or injected antidiabetic treatment for 12 weeks before randomisation or start of open label treatment • Aged at least 18 years (≥ 20 years in Japan or 18 to 65 years in India) • BMI of 45 kg/m² or less • Insufficient glycaemic control despite a diet and exercise regimen (HbA_{1c} 7.0–10.0% [or HbA_{1c} 7.0–9.0% in Germany] at screening for patients eligible for randomised treatment, or >10.0% at screening for patients eligible for the open-label treatment group).
Key exclusion criteria	• Uncontrolled hyperglycaemia (glucose concentration >13.3 mmol/L after an overnight fast during the placebo run-in phase and confirmed by a second measurement • eGFR (estimated with the MDRD equation) of less than 50 mL/min per 1.73 m² (or <60 mL/min per 1.73 m² in China) • Contraindications to sitagliptin according to the local label • Treatment with antiobesity drugs within 3 months before informed consent • Treatment with systemic steroids at time of informed consent • Change in dose of thyroid hormones within 6 weeks before informed consent • Any uncontrolled endocrine disorder apart from T2DM.
Efficacy outcomes	No primary efficacy endpoint was defined in the trial protocol (the primary efficacy endpoint was analysed at Week 24 of the preceding trial, study 1245.20). For the purpose of disclosure of the trial results on clinicaltrials.gov, a primary endpoint has to be formally selected. This was the change from baseline in HbA_{1c} at Week 52 and 76, since this was the primary endpoint analysed at Week 24 of the preceding trial.

Study	Study 1245.31 (Roden et al., 2014)(9)
	The following key secondary endpoints were tested after a total treatment duration of 52 and 76 weeks (preceding trial and extension): • Change from baseline in HbA_{1c} • Change from baseline in body weight • Change from baseline in SBP and in DBP • Change from baseline in waist circumference • Change from baseline in FPG
Populations analysed	**Screened patients set (SCR)** – including all patients screened for the trial, with consent given and who completed at least 1 screening procedure at Visit 1. **Randomised set (RS)** – including all patients from the screened set who were randomised to a trial medication, regardless of whether any trial medication was taken. **Treated set (TS)** – including all patients treated with at least 1 dose of randomised trial medication. **Full analysis set (FAS)** – including all randomised and treated patients who had a baseline HbA_{1c} value. **Per-protocol set (PPS)** – including all patients in the FAS without important protocol violations leading to exclusion. **Open-label set (OLS)** – including all patients entered in the empagliflozin 25 mg open-label treatment arm.
Statistical analysis	No confirmatory statistical analysis was performed, as this study was considered an extension of the preceding trial 1245.20; therefore no primary efficacy endpoint in a statistical sense was defined for this trial. For the final analysis, the data of the preceding trial 1245.20 were combined with those obtained in the extension trial, and the final analysis was performed after the last patient had completed 52 weeks of treatment in the extension trial (database lock on 28 June 2013). All patients participating in the preceding trial were included in this analysis and no separate analysis of the extension trial was performed. For secondary efficacy endpoints, the change from baseline at Week 76 was assessed using an ANCOVA; patients were assigned to treatment groups as randomised. The main efficacy analyses were based on the FAS, which contained all randomised patients who received at least 1 dose of study drug and had a baseline HbA_{1c} assessment, irrespective of participation in the extension trial. Missing values due to a treatment duration of less than 76 weeks and values after intake of rescue medication were replaced by the last observed measurement on treatment (LOCF). A sensitivity analysis was performed for patients who completed 76 weeks of treatment (FAS-completers-76). The secondary endpoints were further analysed using a restricted maximum likelihood based MMRM applied to the FAS based on OC (data that were observed while patients were on treatment, i.e. excluding the missing data). For categorical endpoints and use of rescue therapy, treatments were compared using a logistic regression model. Time to first rescue therapy was analysed by Kaplan-Meier estimates and treatment groups were compared using a log rank test. Endpoints based on biomarkers were evaluated using descriptive statistics and ANCOVA modelling. Safety analyses were performed on the treated set with treatment assignment based on the first treatment received in the preceding trial. Analyses were performed using descriptive statistics. Time-to-event analyses were performed for adjudicated events, hypoglycaemic events, and for certain AESIs.

Abbreviations: AESIs, adverse event of special interest; ANCOVA, analysis of covariance; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; LOCF, last observation carried forward; MDRD, modification of diet in renal disease; mg; milligrams; ,mL/min, millilitres per minute; mmol/L, millimoles per litre; MMRM; mixed effect model repeat measurement; OC, observed cases; OLS, open-label set; PPS, per-protocol set; RS, randomised set; SBP, systolic blood pressure; SCR, screened patient set; SU, sulfonylurea; TD2M, type 2 diabetes mellitus; TS, treated set.

3.4.2.2 Patient population: Study 1245.31

Patient disposition

The efficacy and safety analyses were based on all treated patients from the preceding trial *(*Study 1245.20*)*, and based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed. From study 1245.20, a total of 899 patients were enrolled and randomised in a 1:1:1:1 ratio; empagliflozin

10 mg (n=224); empagliflozin 25 mg (n=224); sitagliptin 100 mg (n=223); placebo (n=228) (Figure 5, page 61).

Over the entire period of the trial, discontinuation from treatment was more common for placebo (50.9%) than for empagliflozin 10 mg (36.2%), empagliflozin 25 mg (39.3%), and sitagliptin (42.2%). Discontinuation occurred most frequently due to patients not entering the extension trial (20.9%). Treatment compliance was high and balanced across treatments, with 95.2% of the patients within the 80 to 120% range.

Patient demographics and baseline characteristics

The majority of patients were male (61.3%). Most were Asian (64.1%) or White (33.6%), with a mean age of 55.0 years (SD 11.0 years). Mean (SD) baseline HbA_{1c} was 7.88 (0.82) % and the mean (SD) weight was 78.42 (19.22) kg. A total of 38.0% of the patients were blood pressure controlled at baseline (<130/80 mmHg), and hypertension (50.7%) was most common with regard to medical history. There were no clinically meaningful differences in baseline characteristics between patients who continued in the extension and patients who did not continue in the extension.

3.4.2.3 Results: Study 1245.31

A total of 39.4% of the patients discontinued the trial, which resulted in a large number of missing data. Therefore the analyses of the FAS based on the LOCF approach must be interpreted in the context of the totality of data including sensitivity analyses. The results on the FAS-completers (LOCF or OC approach) were similar to those on the FAS (LOCF); some deviations from the FAS results were observed, but no general trend emerged with regard to the treatment effect of the empagliflozin doses.

Primary efficacy outcome

A summary of primary efficacy outcomes at Week 52 and Week 76 are presented in Table 16 and Table 17, respectively. Treatment with both doses of empagliflozin (10 mg and 25 mg) showed a significant decrease in HbA_{1c} from baseline, relative to placebo (Figure 7) at Week 76, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). Changes in HbA_{1c} over time are shown in Figure 8.

Table 16: Summary of the primary efficacy outcome for the adjusted mean change at Week 52 with empagliflozin 10 mg and 25 mg compared to sitagliptin and placebo – FAS (LOCF)

Outcome	Empagliflozin dose	Difference to placebo		Difference to sitagliptin	
		Adjusted mean change (SE)	95% CI	Adjusted mean change (SE)	95% CI
HbA_{1c} (%)	10 mg	-0.79 (0.08)	(-0.94, -0.64)	-0.12 (0.08)	(-0.27, 0.03)
	25 mg	-0.91 (0.08)	(-1.06, -0.76)	-0.24 (0.08)	(-0.39, -0.09)

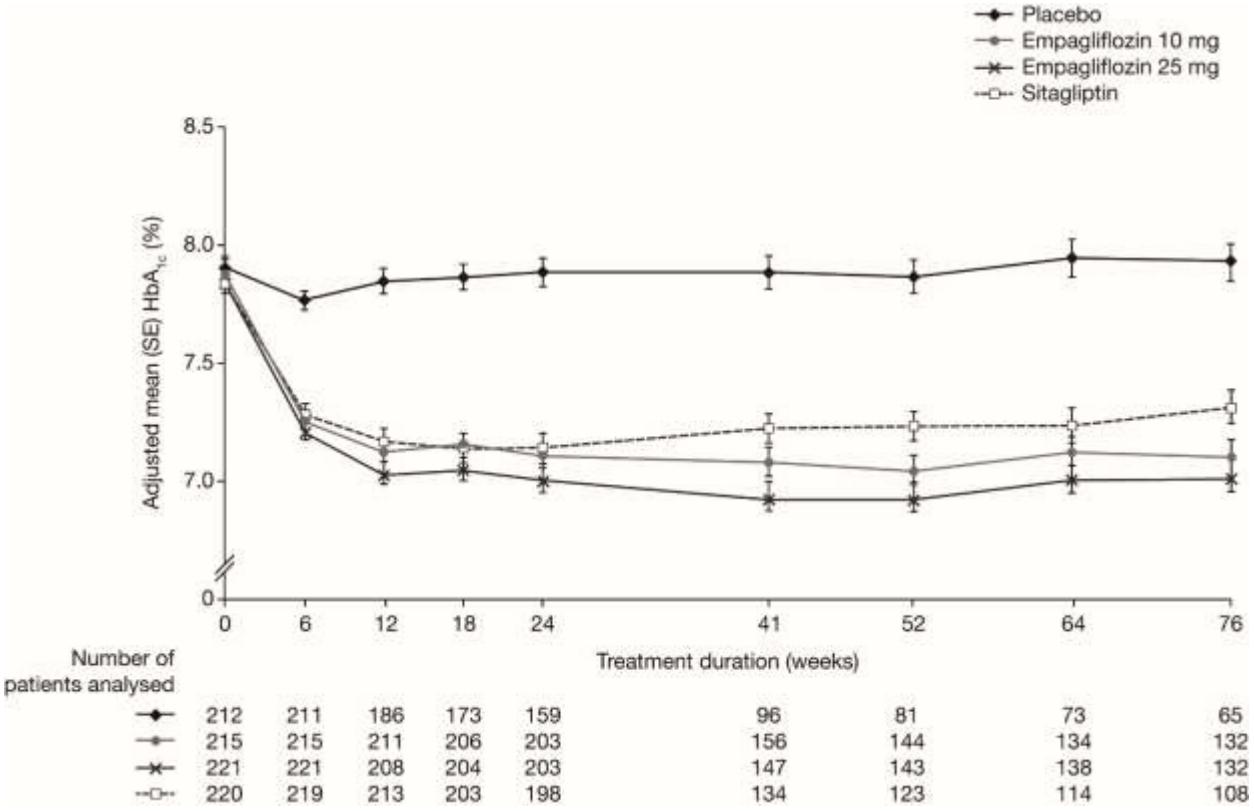
Adjusted values are based on ANCOVA with LOCF; data after the initiation of rescue medication were excluded.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; LOCF, last observation carried forward; SE, standard error.

Table 17: Summary of the primary efficacy outcome for the adjusted mean change at Week 76 with empagliflozin 10 mg and 25 mg compared to sitagliptin and placebo – FAS (LOCF)

Outcome	Empagliflozin dose	Difference to placebo		Difference to sitagliptin	
		Adjusted mean change (SE)	95% CI	Adjusted mean change (SE)	95% CI
HbA_{1c} (%)	10 mg	-0.78 (0.08)	(-0.94, -0.63)	-0.12 (0.08)	(-0.28, 0.04)
	25 mg	-0.89 (0.08)	(-1.04, -0.73)	-0.22 (0.08)	(-0.38, -0.07)

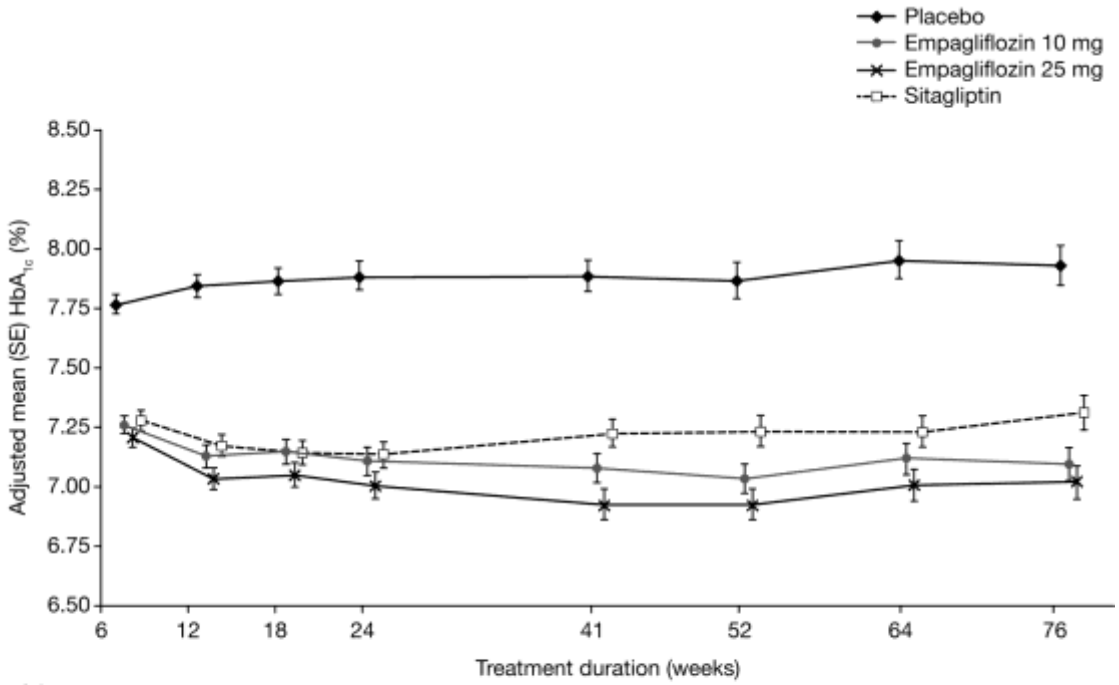
Adjusted values are based on ANCOVA with LOCF; data after the initiation of rescue medication were excluded.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; LOCF, last observation carried forward; SE, standard error.

Figure 7: Changes from baseline (adjusted mean ± SE) in HbA_{1c} (%) following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo over 76 weeks – FAS (OC)



Abbreviations: FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; OC, observed cases; SE, standard error.
Source: Roden et al., 2014 (9)

Figure 8: Changes over time (adjusted mean ± SE) in HbA_{1c} (%) following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo over 76 weeks - FAS (OC)



N with data at visit

Placebo	211	186	173	159	96	81	73	65
Empagliflozin 10 mg	215	211	206	203	156	144	134	132
Empagliflozin 25 mg	221	208	204	203	147	143	138	132
Sitagliptin	219	213	203	198	134	123	114	108

Abbreviations: FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; OC, observed cases; SE, standard error.
Source: Study 1245.31 CSR (8)

Secondary efficacy outcomes

A summary of secondary efficacy outcomes is presented in Table 18 and Table 19. The analysis of secondary endpoint parameters over time showed a reduction in the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 76, as based on an MMRM model applied to the FAS (OC). Mean SBP values fluctuated after Week 24 for empagliflozin 10 mg but were consistently reduced compared with placebo. Clinically meaningful and sustained reductions in FPG, body weight (Figure 9; Figure 10), waist circumference and SBP (Figure 11; Figure 12) were observed at Week 76, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). Compared with sitagliptin, empagliflozin 25 mg reduced HbA_{1c} and both empagliflozin doses reduced weight and SBP (Table 18). Changes in DBP are shown in Figure 13 and Figure 14.

ANCOVA data of mean changes over time based on the FAS (LOCF) or FAS completers (LOCF or OC approach) were consistent with the MMRM data for all secondary endpoint parameters. The percentage of treatment responders for both empagliflozin groups was numerically higher than placebo and sitagliptin with regard to patients achieving HbA_{1c} less than 7.0%. Use of rescue medication was less frequent in the empagliflozin groups than in the placebo and sitagliptin groups.

Table 18: Summary of the key secondary efficacy outcomes for the adjusted mean change at Week 76 of empagliflozin 10 mg and 25 mg compared to sitagliptin and placebo – FAS (LOCF)

Outcome	Empagliflozin dose	Difference to placebo		Difference to sitagliptin	
		Adjusted mean change (SE)	95% CI	Adjusted mean change (SE)	95% CI
Body weight (kg)	10 mg	-1.81 (0.28)	(-2.35, -1.26)	-2.34 (0.28)	(-2.89, -1.90)
	25 mg	-2.02 (0.28)	(-2.56, -1.48)	-2.56 (0.28)	(-3.10, -2.01)
Waist circumference (cm)	10 mg	-1.6 (0.5)	(-2.7, -0.6)	-2.0 (0.6)	(-3.1, -0.9)
	25 mg	-1.7 (0.5)	(-2.8, -0.6)	-2.1 (0.6)	(-3.2, -1.0)
FPG (mg/dL)	10 mg	-31.7 (2.9)	(-37.4, -25.9)	-15.4 (3.0)	(-21.2, -9.6)
	25 mg	-34.9 (2.9)	(-40.7, -29.1)	-18.7 (3.0)	(-24.5, -12.8)
SBP (mm Hg)	10 mg	-3.4 (1.1)	(-5.5, -1.2)	-3.7 (1.1)	(-5.9, -1.6)
	25 mg	-3.4 (1.1)	(-5.6, -1.2)	-3.8 (1.1)	(-6.0, -1.6)
DBP (mm Hg)	10 mg	-1.0 (0.7)	(-2.3, 0.4)	-1.5 (0.7)	(-2.8, -0.2)
	25 mg	-1.0 (0.7)	(-2.4, 0.3)	-1.6 (0.7)	(-2.9, -0.2)

Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FAS, full analysis set; FPG, fasting plasma glucose; LOCF, last observation carried forward; SBP, systolic blood pressure; SE, standard error.

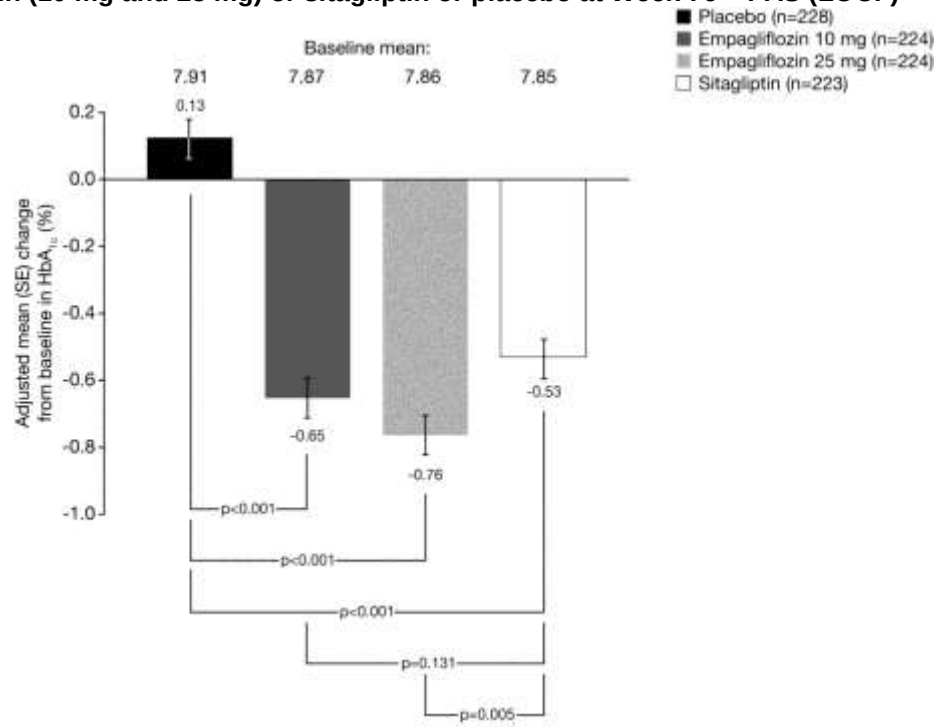
The key secondary outcomes reported at Week 52 are shown in Table 19.

Table 19: Summary of the key secondary efficacy outcomes for the adjusted mean change at Week 52 of empagliflozin 10 mg and 25 mg compared to sitagliptin and placebo – FAS (LOCF)

Outcome	Empagliflozin dose	Difference to placebo		Difference to sitagliptin	
		Adjusted mean change (SE)	95% CI	Adjusted mean change (SE)	95% CI
Body weight (kg)	10 mg	-2.22 (0.27)	(-2.75, -1.69)	-2.84 (0.27)	(-3.37, -2.31)
	25 mg	-2.14 (0.27)	(-2.66, -1.61)	-2.75 (0.27)	(-3.28, -2.22)
Waist circumference (cm)	10 mg	-2.1 (0.5)	(-3.1, -1.0)	-2.4 (0.5)	(-3.5, -1.4)
	25 mg	-1.7 (0.5)	(-2.8, -0.7)	-2.1 (0.5)	(-3.1, -1.0)
FPG (mg/dL)	10 mg	-32.3 (2.8)	(-37.8, -26.7)	-15.0 (2.9)	(-20.6, -9.4)
	25 mg	-37.2 (2.8)	(-42.8, -31.7)	-19.9 (2.8)	(-25.5, -14.4)
SBP (mm Hg)	10 mg	-4.6 (1.1)	(-6.8, -2.5)	-3.3 (1.1)	(-5.4, -1.1)
	25 mg	-4.2 (1.1)	(-6.4, -2.1)	-2.8 (1.1)	(-5.0, -0.7)
DBP (mm Hg)	10 mg	-1.1 (0.7)	(-2.4, 0.2)	-0.9 (0.7)	(-2.3, 0.4)
	25 mg	-1.7 (0.7)	(-3.1, -0.4)	-1.6 (0.7)	(-2.9, -0.2)

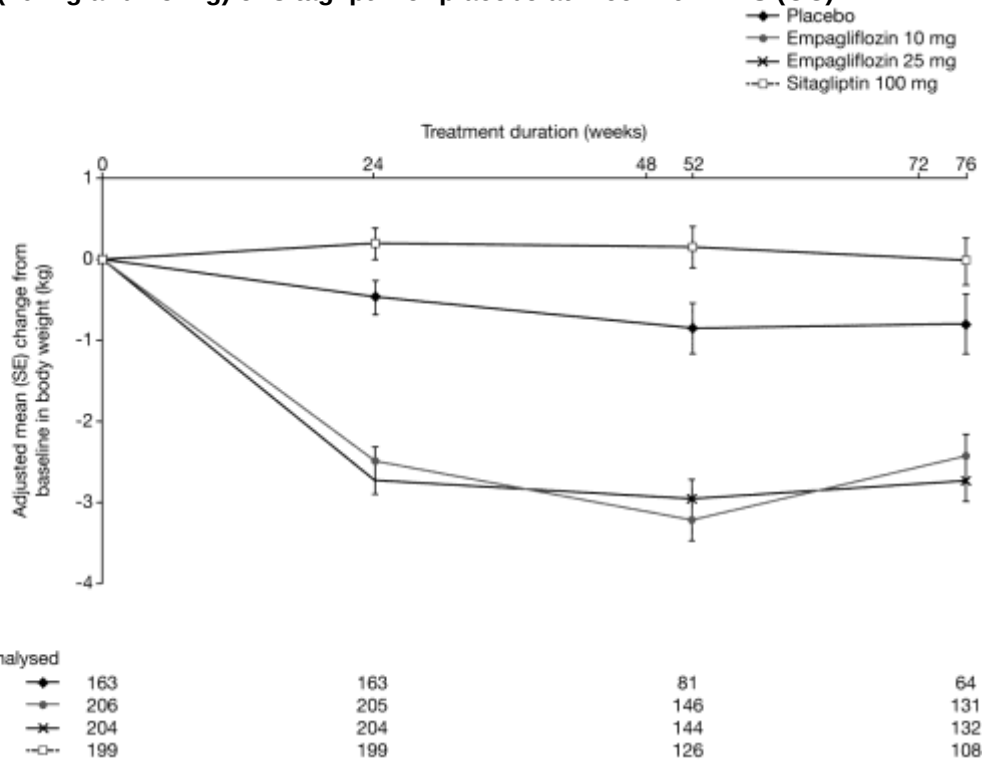
Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FAS, full analysis set; FPG, fasting plasma glucose; LOCF, last observation carried forward; SBP, systolic blood pressure; SE, standard error.

Figure 9: Changes from baseline (adjusted mean ± SE) in body weight following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (LOCF)



Abbreviations: FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; LOCF, last observation carried forward; SE, standard error.
Source: Study 1245.31 CSR (8)

Figure 10: Changes in body weight over time (adjusted mean ± SE) following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (OC)

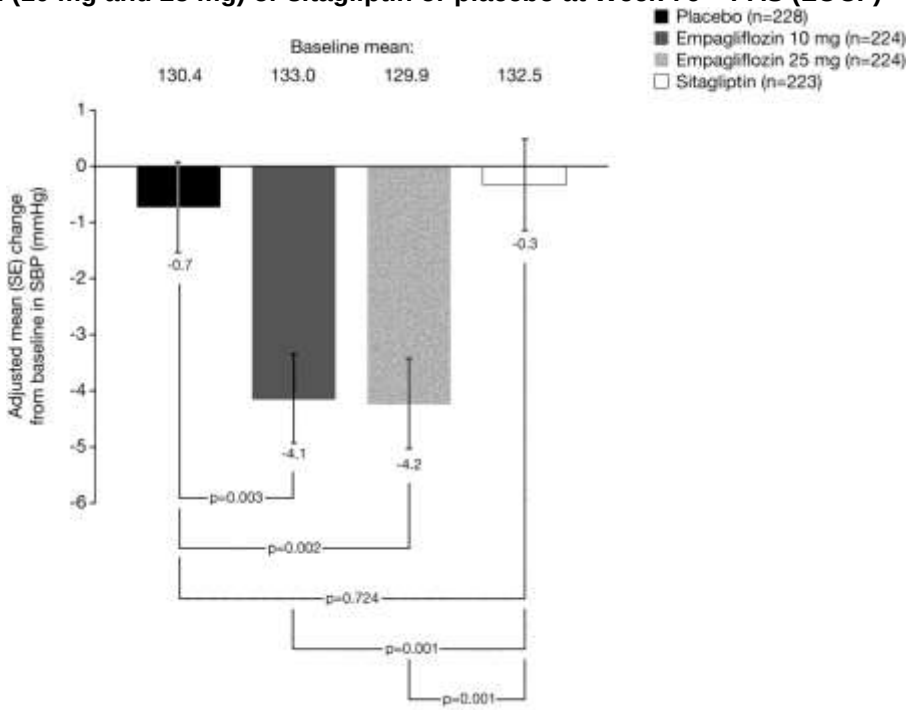


Number of patients analysed

Placebo	163	163	81	64
Empagliflozin 10 mg	206	205	146	131
Empagliflozin 25 mg	204	204	144	132
Sitagliptin 100 mg	199	199	126	108

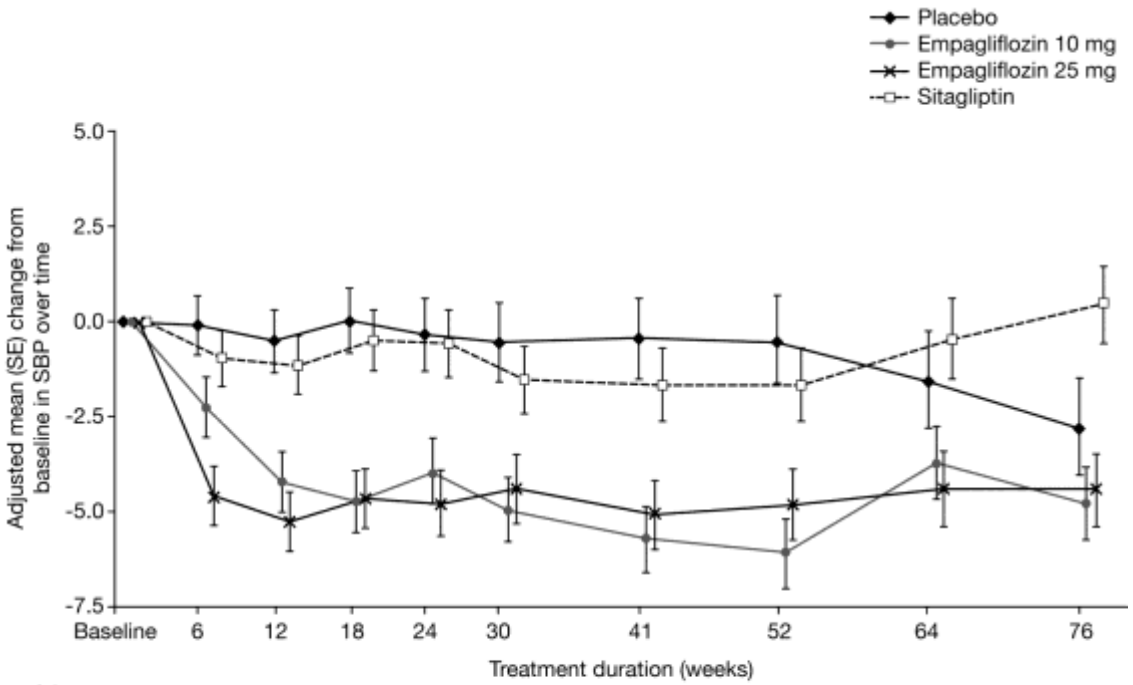
Abbreviations: FAS, full analysis set; OC, observed cases; SE, standard error.
Source: Study 1245.31 CSR (8)

Figure 11: Changes from baseline (adjusted mean ± SE) in SBP following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (LOCF)



Abbreviations: FAS, full analysis set; LOCF, last observation carried forward; SBP, systolic blood pressure; SE, standard error.
Source: Study 1245.31 CSR (8)

Figure 12: Changes over time (adjusted mean ± SE) in SBP following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (OC)

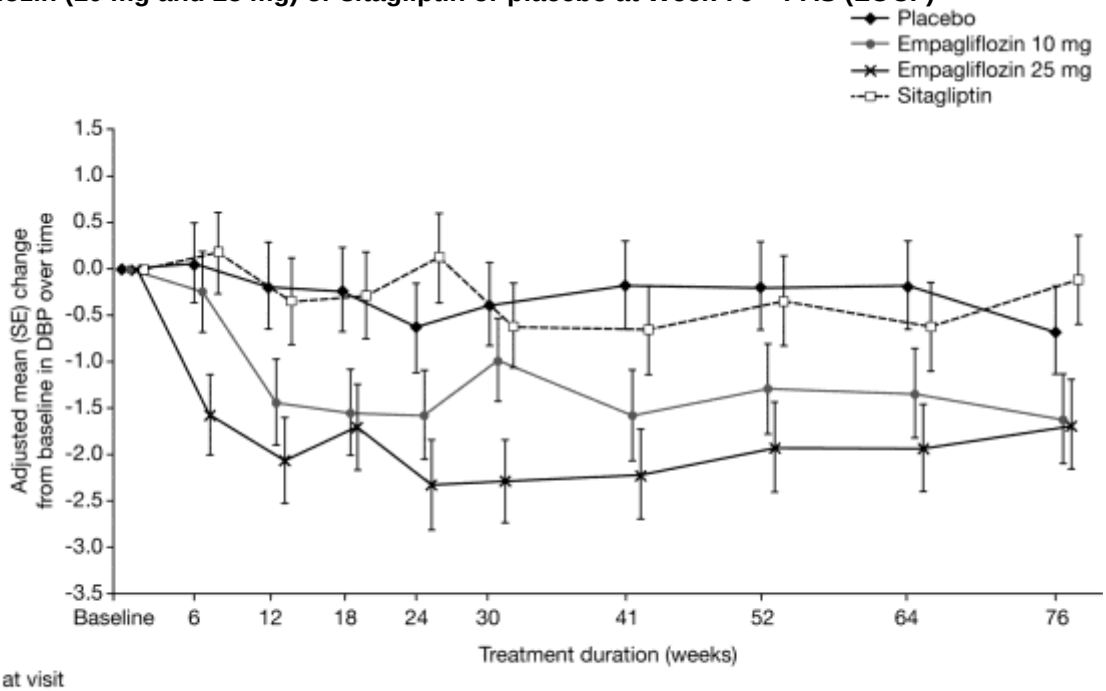


N with data at visit

	Baseline	6	12	18	24	30	41	52	64	76
Placebo	210	210	186	174	157	102	94	81	72	64
Empagliflozin 10 mg	215	215	212	206	203	159	156	144	134	131
Empagliflozin 25 mg	220	220	209	205	202	149	147	143	137	131
Sitagliptin	219	218	212	203	198	143	134	123	113	108

Abbreviations: FAS, full analysis set; OC, observed cases; SBP, systolic blood pressure; SE, standard error.
Source: Study 1245.31 CSR (8)

Figure 13: Changes from baseline (adjusted mean ± SE) in DBP following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (LOCF)

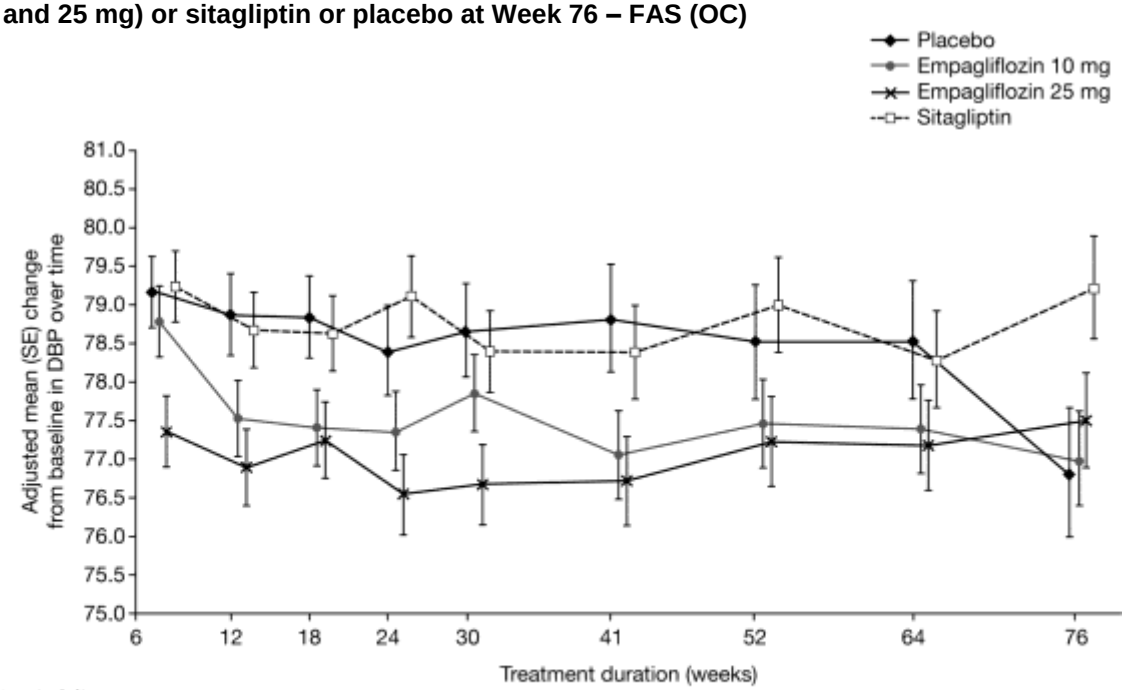


N with data at visit

Placebo	228	228	228	228	228	228	228	228	228	228
Empagliflozin 10 mg	224	224	224	224	224	224	224	224	224	224
Empagliflozin 25 mg	224	224	224	224	224	224	224	224	224	224
Sitagliptin	223	223	223	223	223	223	223	223	223	223

Abbreviations: DBP, diastolic blood pressure; FAS, full analysis set; LOCF, last observation carried forward; SE, standard error.
Source: Study 1245.31 CSR (8)

Figure 14: Changes over time (adjusted mean ± SE) in DBP following treatment with empagliflozin (10 mg and 25 mg) or sitagliptin or placebo at Week 76 – FAS (OC)



N with data at visit

Placebo	210	186	174	157	102	94	81	72	64
Empagliflozin 10 mg	215	212	206	203	159	156	144	134	131
Empagliflozin 25 mg	220	209	205	202	149	147	143	137	131
Sitagliptin	218	212	203	198	143	134	123	113	108

Abbreviations: DBP; diastolic blood pressure; FAS, full analysis set; OC, observed cases; SE, standard error.
Source: Study 1245.31 CSR (8)

3.4.2.4 Efficacy conclusion: Study 1245.31

In conclusion, this study demonstrates that treatment with empagliflozin 10 mg and empagliflozin 25 mg OD over 76 weeks as monotherapy is superior to placebo or active comparator sitagliptin. Treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful and sustained improvement of glucose control, weight and blood pressure for 76 weeks of treatment (8, 9).

3.5 Safety profile of FDC empagliflozin and linagliptin

In study 1275.1, the two patient populations (treatment naïve patients and patients with metformin background) were presented separately. AEs were documented for treatment naïve patients only. In the treatment naïve patient set, the frequency of patients with AEs on treatment was similar across all treatment groups (75.7% of patients in the FDC empagliflozin 25 mg/linagliptin 5 mg group, 72.8% of patients in the FDC empagliflozin 10 mg/linagliptin 5 mg group, 68.9% of patients in the empagliflozin 25 mg group, 81.5% of patients in the empagliflozin 10 mg group, and 71.9% of patients in the linagliptin 5 mg group) (Table 20).

3.5.1 AEs

Table 20: Overall incidence of AEs in study 1275.1 for treatment naïve patients only

	Empa 25 mg/Lina 5 mg (n=136)	Empa 10 mg/Lina 5 mg (n=136)	Empa 25 mg (n=135)	Empa 10 mg (n=135)	Lina 5 mg (n=135)
Any AEs	103 (75.7)	99 (72.8)	93 (68.9)	110 (81.5)	97 (71.9)
Any severe AEs	8 (5.9)	8 (5.9)	10 (7.4)	10 (7.4)	1 (0.7)
Any serious AEs	6 (4.4)	7 (5.1)	9 (6.7)	10 (7.4)	2 (1.5)
Any treatment-related AEs†	23 (16.9)	14 (10.3)	22 (16.3)	16 (11.9)	17 (12.6)
AEs that led to discontinuation	9 (6.6)	8 (5.9)	5 (3.7)	7 (5.2)	2 (1.5)
Deaths	0	1 (0.7)	2 (1.5)	1 (0.7)	0

Data are n(%).
Abbreviations: AE, adverse event; Empa, empagliflozin; Lina, linagliptin
† As assessed by the investigator
Source: Study 1275.1 CSR (7)

Overall, the proportions of patients reporting serious[I] AEs were low and similar across randomised treatment groups: six patients (4.4%) in the FDC empagliflozin 25 mg/linagliptin 5 mg group, seven patients (5.1%) in the FDC empagliflozin 10 mg/linagliptin 5 mg group, nine patients (6.7%) in the empagliflozin 25 mg group, ten patients (7.4%) in the empagliflozin 10 mg group, and two patients (1.5%) in the linagliptin 5 mg group.

Most AEs were mild or moderate in intensity, with severe events[II] reported in 5.9% of patients in each of the FDC groups, 7.4% in each of the empagliflozin monotherapy groups and 0.7% in the linagliptin group. The most common adverse reactions reported during

[II] A serious AE was defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires of prolongs patient hospitalisation, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

[II] The intensity of AEs was judged by the investigator as mild (awareness of signs or symptoms which were easily tolerated), moderate (enough discomfort to cause interference with usual activity), or severe (incapacitating or causing inability to work or to perform usual activities).

clinical trials were UTIs, headache, and hyperglycaemia. Table 21 lists the adverse drug reactions that occurred in at least 5% of patients treated with FDC empagliflozin/linagliptin, empagliflozin or linagliptin in clinical trials.

Table 21: Most commonly reported AEs

System organ class AE	Empa 25 mg/Lina 5 mg (n=136)	Empa 10 mg/Lina 5 mg (n=136)	Empa 25 mg (n=135)	Empa 10 mg (n=135)	Lina 5 mg (n=135)
Infections and Infestations					
UTI	15 (11.0)	17 (12.5	8 (5.9)	17 (12.6)	12 (8.9)
Nasopharyngitis	10 (7.4)	5 (3.7)	5 (3.7)	9 (6.7)	8 (5.9)
Upper respiratory tract infection	8 (5.9)	5 (3.7)	9 (6.7)	2 (1.5)	12 (8.9)
Influenza	7 (5.1)	7 (5.1)	3 (2.2)	6 (4.4)	2 (1.5)
Metabolism and nutrition disorders					
Hyperglycaemia	8 (5.9)	5 (3.7)	4 (3.0)	10 (7.4)	14 (10.4)
Dyslipidaemia	9 (6.6)	9 (6.6)	4 (3.0)	8 (5.9)	3 (2.2)
Nervous system disorders					
Headache	9 (6.6)	8 (5.9)	7 (5.2)	9 (6.7)	16 (11.9)
Dizziness	7 (5.1)	3 (2.2)	4 (3.0)	5 (3.7)	6 (4.4)
GI disorders					
Constipation	2 (1.5)	2 (1.5)	8 (5.9)	4 (3.0)	2 (1.5)
Musculoskeletal and connective tissue disorders					
Back pain	5 (3.7)	4 (2.9)	9 (6.7)	4 (3.0)	3 (2.2)
Arthralgia	4 (2.9)	8 (5.9)	6 (4.4)	7 (5.2)	6 (4.4)
Weight decreased	1 (0.7)	1 (0.7)	7 (5.2)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; Empa, empagliflozin; Lina, linagliptin; UTI, urinary tract infection.

Amongst drug naïve patients, there were no significant differences in changes from baseline in total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides between empagliflozin/linagliptin and the individual components, apart from a greater increase in total cholesterol with empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg (Table 22). There were no significant differences in changes from baseline in high density lipoprotein (HDL) cholesterol between empagliflozin/linagliptin and the empagliflozin components, but there was a greater increase in HDL cholesterol with empagliflozin/linagliptin than with linagliptin.

Table 22: Cholesterol levels in study 1275.1 at Week 52

	Empa 25 mg/Lina 5 mg		Empa 10 mg/Lina 5 mg		Empa 25 mg		Empa 10 mg		Lina 5 mg	
	Baseline	**Change from baseline***	**Baseline**	**Change from baseline***	**Baseline**	**Change from baseline***	**Baseline**	**Change from baseline***	**Baseline**	**Change from baseline***
HDL cholesterol	1.2 (0.0)	0.1 (0.0)	1.1 (0.0)	0.1 (0.0)	1.2 (0.0)	0.1 (0.0)	1.2 (0.0)	0.1 (0.0)	1.2 (0.0)	0.0 (0.0)
Difference vs. empagliflozin 25 mg		0.0 (0.0) p=0.126								
Difference vs. empagliflozin 10 mg				0.0 (0.0) p=0.507						
Difference vs. linagliptin 5 mg		0.1 (0.0) p=0.004		0.1 (0.0) p<0.001						
LDL cholesterol	2.9(0.1)	0.0 (0.1)	3.0 (0.1)	-0.1 (0.1)	2.9 (0.1)	0.1 (0.1)	3.0 (1.0)	0.0 (0.1)	2.9 (0.1)	-0.1 (0.1)
Difference vs. empagliflozin 25 mg		-0.0 (0.1) p=0.759								
Difference vs. empagliflozin 10 mg				-0.1 (0.1) p=0.355						
Difference vs. linagliptin 5 mg		0.1 (0.1) p=0.155		0.0 (0.1) p=0.639						
Triglycerides	2.0 (0.1)	-0.1 (0.1)	2.1 (0.1)	-0.0 (0.1)	2.0 (0.1)	-0.1 (0.1)	2.3 (0.1)	0.2 (0.1)	2.1 (0.3)	-0.2 (0.1)
Difference vs. empagliflozin 25 mg		0.0 (0.1) p=0.905								
Difference vs. empagliflozin 10 mg				-0.2 (0.1) p=0.227						
Difference vs. linagliptin 5 mg		0.1 (0.1) p=0.534		0.1 (0.1) p=0.292						

Data are mean (SE) based on ANCOVA with treatment.
Abbreviations: ANCOVA, analysis of covariance; Empa, empagliflozin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lina, linagliptin; SE, standard error.
† Changes from baseline at week 52 or at follow-up.

3.5.2 Mortality

A total of four deaths were reported in this study (one patient [0.7%] in the FDC empagliflozin 10 mg/linagliptin 5 mg treatment group, two patients [1.5%] in the empagliflozin 25 mg and one patient [0.7%] in the empagliflozin 10 mg treatment group). Few AEs led to premature discontinuation of trial medication, the highest reported in the higher dose FDC group. AEs leading to discontinuation in the empagliflozin monotherapy groups included GTI, myocardial infarction, migraine, UTI and toxic hepatitis.

AEs were mostly of mild or moderate intensity and severe AEs were reported for a minority of patients, with frequencies equally distributed between the randomised treatment groups (7).

3.6 Safety profile of empagliflozin monotherapy over 24 weeks

In study 1245.20, the overall frequency of AEs was comparable across the randomised treatment groups, with small numerical differences (empagliflozin 10 mg: 54.9%; empagliflozin 25 mg; 60.0%; sitagliptin: 53.4%; placebo: 61.1%) and comparable to the open label group (64.4%) (Table 23).

3.6.1 AEs

Table 23: Overall incidence of AEs in study 1245.20

	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)	Sitagliptin 100 mg (n=223)	Open label empagliflozin 25 mg (n=87)
Any AEs	140 (61.1)	123 (54.9)	135 (60.5)	119 (53.4)	56 (64.4)
Any severe AEs	4 (1.7)	8 (3.6)	7 (3.1)	5 (2.2)	1 (1.1)
Any serious AEs	6 (2.6)	8 (3.6)	5 (2.2)	6 (2.7)	3 (3.4)
Any treatment-related AEs†	17 (7.4)	27 (12.1)	39 (17.5)	19 (8.5)	11 (12.6)
AEs that led to discontinuation	8 (3.5)	2 (0.9)	4 (1.8)	5 (2.2)	3 (3.4)
Deaths	1 (0.4)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Data are n(%).
Abbreviations: AE, adverse event.
† As assessed by the investigator.

Most patients reported AEs of mild or moderate intensity. Severe AEs[III] were reported by eight patients (3.6%) in the empagliflozin 10 mg group, seven patients (3.1%) in the empagliflozin 25 mg group, four patients (1.8%) in the sitagliptin group, and four patients in the placebo group (1.7%). One severe AE (1.1%) was reported in the open label arm. The frequency of drug related AEs, as assessed by the investigator, was 12.1% in the empagliflozin 10 mg group, 17.5% in the empagliflozin 25 mg group, 8.5% in the sitagliptin

[III] The intensity of AEs was judged by the investigator as mild (awareness of signs or symptoms which were easily tolerated), moderate (enough discomfort to cause interference with usual activity), or severe (incapacitating or causing inability to work or to perform usual activities).

group, and 7.4% in the placebo group. In the open-label arm, the frequency of drug related AEs was 12.6%. There were two patients with significant AEs (pre-specified events), one in each empagliflozin randomised group.

Premature discontinuation of trial medication due to AEs was recorded for two patients (0.9%) in the empagliflozin 10 mg group, four patients (1.8%) in the empagliflozin 25 mg group, four patients (1.8%) in the sitagliptin group, eight patients (3.5%) in the placebo group, and three patients (3.4%) in the open label arm. Serious AEs were reported by eight patients (3.6%) in the empagliflozin 10 mg group, five patients (2.2%) in the empagliflozin 25 mg group, six patients (2.7%) in the sitagliptin group, six patients (2.6%) in the placebo group, and three patients (3.4%) in the open label arm.

The most common adverse reactions reported during clinical trials were UTIs, headache, and hyperglycaemia. Table 24 lists the adverse drug reactions that occurred in at least 5% of patients treated with empagliflozin, sitagliptin and placebo in clinical trials.

Table 24: Most commonly reported AEs

System organ class AE	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)	Sitagliptin 100 mg (n=223)	Open label empagliflozin 25 mg (n=87)
Infections and Infestations					
Nasopharyngitis	17 (7.4)	16 (7.1)	11 (4.9)	15 (6.7)	1 (1.1)
UTI	9 (3.9)	14 (6.3)	8 (3.6)	11 (4.9)	3 (3.4)
Metabolism and nutrition disorders					
Hyperglycaemia	35 (15.3)	5 (2.2)	4 (1.8)	13 (5.8)	14 (16.1)
Dyslipidaemia	10 (4.4)	13 (5.8)	10 (4.5)	6 (2.7)	7 (8.0)

Abbreviations: AE, adverse event; UTI, urinary tract infection.

3.6.2 Mortality

One event was fatal, in the placebo group (0.4%); however, no deaths were reported in either of the empagliflozin treatment groups (10 mg and 25 mg), nor the sitagliptin treatment group or the open-label arm with empagliflozin 25 mg.

3.7 Safety profile of empagliflozin monotherapy over 76 weeks

In the extension study 1245.31, the overall frequency of AEs was comparable across the randomised treatment groups, with small numerical differences (empagliflozin 10 mg: 76.8%; empagliflozin 25 mg; 78.0%; sitagliptin: 72.2%; placebo: 76.4%) (Table 25).

3.7.1 AEs

Table 25: Overall incidence of AEs in study 1245.31

	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)	Sitagliptin 100 mg (n=223)
Any AEs	175 (76.4)	172 (76.8)	174 (78.0)	161 (72.2)
Any severe AEs	14 (6.1)	17 (7.6)	15 (6.7)	17 (7.6)
Any serious AEs	23 (10.0)	25 (11.2)	16 (7.2)	18 (8.1)
Any treatment-related AEs†	36 (15.7)	49 (21.9)	52 (23.3)	31 (13.9)
AEs that led to discontinuation	15 (6.6)	11 (4.9)	9 (4.0)	11 (4.9)
Deaths	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)

Data are n(%).
Abbreviations: AE, adverse event.
† As assessed by the investigator.

Most patients reported AEs of mild or moderate intensity. Severe AEs were reported by 17 patients (7.6%) in the empagliflozin 10 mg group, 15 patients (6.7%) in the empagliflozin 25 mg group, 17 patients (7.6%) in the sitagliptin group, and 14 patients in the placebo group (6.1%).

The frequency of drug related AEs, as assessed by the investigator, was: 21.9% in the empagliflozin 10 mg group, 23.3% in the empagliflozin 25 mg group, 13.9% in the sitagliptin group, and 15.7% in the placebo group. Premature discontinuation of trial medication due to AEs was recorded for 11 patients (4.9%) in the empagliflozin 10 mg group, nine patients (4.0%) in the empagliflozin 25 mg group, 11 patients (4.9%) in the sitagliptin group and 15 patients (6.6%) in the placebo group. Serious AEs were reported by 25 patients (11.2%) in the empagliflozin 10 mg, 16 patients (7.2%) in the empagliflozin 25 mg, 18 patients (8.1%) in the sitagliptin group and 23 patients (10.0%) in the placebo group.

Confirmed hypoglycaemic events were reported for two patients (0.9%) in the placebo group, two patients (0.9%) in the empagliflozin 10 mg group, two patients (0.9%) in the empagliflozin 25 mg group, and two patients (0.9%) in the sitagliptin group (Table 28). All episodes were of mild intensity; none of the patients required assistance (apart from one patient on empagliflozin 10 mg) or discontinued trial medication because of the hypoglycaemic event. No event led to hospitalisation of the patient. Please see Appendix F (provided separately) for the definition and classification of hypoglycaemic events.

Decreased renal function was not reported in patients on placebo but was reported for four patients on empagliflozin 10 mg, three patients on empagliflozin 25 mg, and three patients on sitagliptin. Mean changes in serum creatinine and eGFR from baseline after 76 weeks were small (ranging from -1.93 to -0.01 µmol/L for serum creatinine and 0.00 to 0.63 mL/min/1.73 m^2 for eGFR) and similar across treatment groups (8). Two patients in the empagliflozin 10 mg group showed a ≥ 2-fold increase from baseline in creatinine values and creatinine greater than upper limit of normal (no patient in the placebo group, empagliflozin 25 mg group, or sitagliptin group).

Overall, 27 patients had hepatic AEs: six patients in the placebo group, seven patients in the empagliflozin 10 mg group, seven patients in the empagliflozin 25 mg group, and seven patients in the sitagliptin group.

Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. Mean haematocrit values slightly

decreased from baseline to last value on treatment with placebo, did not change with sitagliptin, and increased with empagliflozin 10 mg and empagliflozin 25 mg. A decrease in uric acid was noted in the empagliflozin groups compared with placebo or sitagliptin. The analysis mean change from baseline in lipid parameters showed an increase relative to placebo at Week 76 in total cholesterol with empagliflozin 25 mg, in high density lipoprotein (HDL) cholesterol with both empagliflozin groups, and in low density lipoprotein (LDL) cholesterol with empagliflozin 25 mg. Neither dose showed a relevant difference to placebo in mean change from baseline for the LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides (Figure 15).

Generally, parameters that showed decrease or increase from baseline to last value on treatment showed a return towards baseline at the 4 week follow up visit.

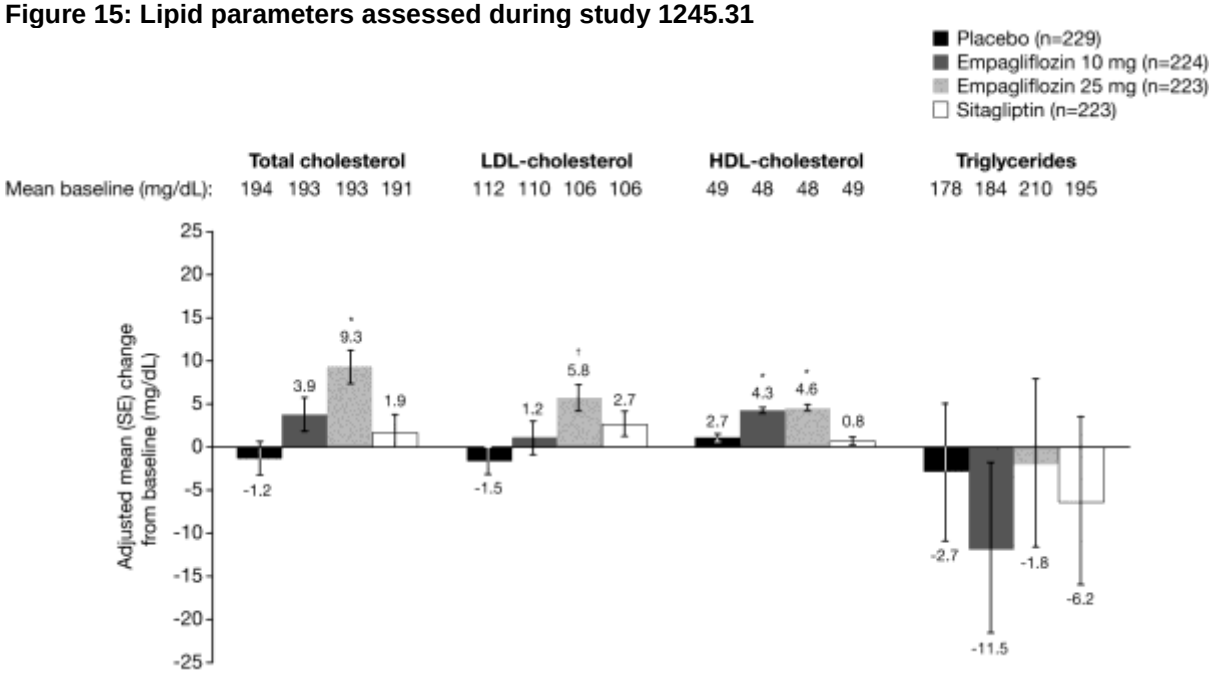
The most common adverse reactions reported during clinical trials were nasopharyngitis, hyperglycaemia and UTI. Table 26 lists the adverse drug reactions that occurred in at least 5% of patients treated with empagliflozin, sitagliptin and placebo in clinical trials. Overall, the most common AEs reported were within the medical dictionary for regulatory activities (MedDRA) system organ class 'infections and infestations': 37.1% for placebo, 42.0% for empagliflozin 10 mg, 40.8% for empagliflozin 25 mg and 37.2% for sitagliptin.

Table 26: Most commonly reported AEs

System organ class AE	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)	Sitagliptin 100 mg (n=223)
Infections and Infestations				
Nasopharyngitis	85 (37.1)	94 (42.0)	91 (40.8)	83 (37.2)
UTI	21 (9.2)	20 (8.9)	14 (6.3)	18 (8.1)
Upper respiratory tract infection	12 (5.2)	17 (7.6)	16 (7.2)	19 (8.5)
Bronchitis	10 (4.4)	11 (4.9)	6 (2.7)	12 (5.4)
Genital infection	4 (1.7)	13 (5.8)	14 (6.3)	2 (0.9)
Metabolism and nutrition disorders				
Hyperglycaemia	63 (27.5)	20 (8.9)	11 (4.9)	28 (12.6)
Dyslipidaemia	15 (6.6)	16 (7.1)	14 (6.3)	14 (6.3)
Vascular disorders				
Hypertension	13 (5.7)	11 (4.9)	5 (2.2)	14 (6.3)
GI disorders				
Diarrhoea	9 (3.9)	12 (5.4)	6 (2.7)	8 (3.6)
Musculoskeletal and connective tissue disorders				
Back pain	12 (5.2)	7 (3.1)	7 (3.1)	19 (8.5)

Abbreviations: AE, adverse event; UTI, urinary tract infection.

Figure 15: Lipid parameters assessed during study 1245.31



Based on ANCOVA in treated set (patients who received ≥ 1 dose of study drug in the initial study).
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard deviation.
*Difference vs. placebo: p<0.001; †Difference vs. placebo: p<0.01.

3.7.2 Mortality

Two events were fatal in study 1245.31, one in the placebo group (myocardial infarction) (0.4%) and one in the sitagliptin group (sudden death) (0.4%).

3.8 Other relevant AEs of importance

Hypoglycaemia

Empagliflozin was well tolerated and, as expected in view of its mechanism of action, and similar to other SGLT-2 inhibitors, empagliflozin treatment was not associated with an increased risk of hypoglycaemia (1) In the study evaluating the efficacy and safety of empagliflozin (25 mg/10 mg) monotherapy, hypoglycaemia occurred at the same rate in the placebo and active treatment arms (<1%). This was sustained during the 76 week extension study (9). There were no reports of hypoglycaemia in the open label empagliflozin 25 mg group. Across all treatment and placebo arms, no hypoglycaemic events required assistance (1) and only one patient on empagliflozin 10 mg required assistance during the extension study (9).

In the study evaluating efficacy and safety of FDC empagliflozin/linagliptin compared to empagliflozin (25 mg/10 mg) and linagliptin (5 mg) monotherapy, hypoglycaemia was reported at Week 52 in both treatment naïve and metformin background patients. In the treatment naïve group, the proportion of patients with confirmed hypoglycaemic events at Week 52 was 3.6% in the FDC empagliflozin 25 mg/linagliptin 5 mg group, 2.2% in the FDC empagliflozin 10 mg/linagliptin 5 mg group, 3.5% in the empagliflozin 25 mg group, 1.4% in the empagliflozin 10 mg group and 2.3% in the linagliptin 5 mg group. In the metformin background patients, 0.7% of patients in the empagliflozin 25 mg group, 3.0% in the empagliflozin 10 mg group and 0.7% in the linagliptin 5 mg group had a confirmed hypoglycaemic event. No confirmed hypoglycaemic events were reported in the FDC groups. No severe hypoglycaemic events were reported in any population of patients (7).

Cardiovascular safety

Cardiovascular (CV) safety is important in the development of new antidiabetic agents. In study 1275.1, in the patient population with metformin background, at Week 52, one patient in the FDC empagliflozin 25 mg/linagliptin 5 mg, two patients in the FDC empagliflozin 10 mg/linagliptin 5 mg group, one patient in the empagliflozin 25 mg, one patient in the empagliflozin 10 mg and one patient in the linagliptin 5 mg group were reported with 4-major adverse cardiovascular event (MACE). Similarly, in the treatment naïve population, four patients in the FDC empagliflozin 25 mg/linagliptin 5 mg group, one patient in the empagliflozin 25 mg group and one patient in the linagliptin 5 mg group reported with 4-MACE (7).

Blood pressure

Compared with placebo and sitagliptin, empagliflozin treatment resulted in a meaningful reduction in SBP, which were not associated with increases in pulse rate. Greater reductions in SBP occurred with empagliflozin in patients with uncontrolled blood pressure (≥ 130/80 mm Hg) at baseline.

Patients with AEs related to volume depletion were rare. The summary of product characteristics (SPC) for empagliflozin suggests that the overall frequency of volume depletion (including the predefine terms blood pressure (ambulatory) decreased, decreased

SBP, dehydration, hypotension, hypovolaemia, orthostatic hypotension and syncope) was similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.5%, empagliflozin 25 mg: 0.3%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin (4.4%) compared to placebo (2.1%) (15).

GI AEs

GI AEs are commonly experienced in patients taking OADs (120). Placebo and active control trials have reported GI AEs, either in monotherapy or FDC therapy studies when compared to placebo or active comparator. Including constipation, GI AEs were highest in the empagliflozin 25 mg and 10 mg monotherapy groups. The linagliptin 5 mg group was also similar (10.6%) (7). In study 1245.20, GI AEs were higher than placebo (7.9%), but similar between empagliflozin 25 mg and 10 mg doses (10.8% and 11.2%, respectively) and sitagliptin (9.4%). The open label extension with empagliflozin 25 mg reported 10.3% of patients with GI AEs (5).

3.9 Additional safety issues for the medicine in the indication under review

In late March 2014, the European Medicines Agency (EMA) published a public assessment report of empagliflozin following an application for marketing authorisation. The EMA report was undertaken by the Committee for Medicinal Products for Human Use (CHMP) (EMA/CHMP/137741/2014) (121).

The CHMP presented the following conclusion on the safety of empagliflozin: “although genital and urinary infections were not monitored specifically, the results presented showed that there was an increased risk of genital infections with empagliflozin. In patients with moderate renal impairment, empagliflozin treatment was associated with a higher frequency of decreased renal function, genital infection and UTI. Therefore, empagliflozin cannot be recommended in patients with moderate renal impairment. There was a higher frequency of UTIs, volume depletion and decreased renal function in patients ≥ 75 years. Subgroup analyses demonstrated that this higher frequency of volume depletion was independent of renal function category. Empagliflozin cannot be recommended in patients >75 years. There was an increase in the number of hypoglycaemic episodes with empagliflozin in combination with metformin and a SU (121).

Although it was not expected that empagliflozin would be associated with hepatic injuries, the number of patients with serious hepatic AEs was remarkably higher in the empagliflozin groups compared to placebo and comparators. In all but one of these cases the independent committee of hepatic experts judged that the causal relationship with the treatment was not probable. The occurrence of serious liver enzyme elevations was low and there were no imbalances unfavourable for empagliflozin in less severe signs of liver impairment (*sic*) (121). No effects on bone mineral density and bone fractures were found. However, treatment duration was too short and the numbers of patients very small. Harmful effects of empagliflozin cannot be excluded.” (121)

In their report, the EMA announced that the CHMP had completed its review of empagliflozin. The Committee concluded that based on the review of data on quality, safety and efficacy, the risk benefit balance of empagliflozin in the treatment of T2DM to improve

glycaemic control in adults as monotherapy or add on combination therapy was favourable. As a result, the EMA granted the market authorisation (121).

4. Comparative efficacy and safety

NMA methods

- A network meta-analysis (NMA) was conducted in order to estimate the relative efficacy and safety of empagliflozin monotherapy compared with the other SGLT-2 inhibitors canagliflozin and dapagliflozin; as well as repaglinide, SUs, DPP-4 inhibitors and pioglitazone all used as monotherapies, as outlined in the NICE scope.
- The systematic review identified sufficient studies to form networks for the following outcomes:
  - ***Efficacy:***
    - Change in HbA_{1c} (%)
    - Change in weight (kg).
  - ***Safety:***
    - Incidence of overall hypoglycaemia
    - Incidence of UTI.
- The majority of the analyses were performed using fixed effects models as there were insufficient studies to estimate the between-study variance with precision.

NMA results

- Empagliflozin and other SGLT-2 inhibitors demonstrated significantly greater reductions in HbA_{1c} compared with placebo at 24 weeks; empagliflozin also demonstrated significantly greater reductions in HbA_{1c} compared with placebo at 52 weeks and ≥ 52 weeks
- Significantly greater improvements in weight gain were observed with empagliflozin and other SGLT-2 inhibitors compared with placebo at 24 weeks and this significantly greater reduction was also maintained for empagliflozin at 52 weeks
- There were no significant differences in the incidence of hypoglycaemia or UTI between all the treatments that were compared in the network and placebo

4.1 Network meta-analysis

4.1.1 Methods overview

A network meta-analysis (NMA) was conducted in order to estimate the relative efficacy and safety of empagliflozin monotherapy compared with the other SGLT-2 inhibitors canagliflozin and dapagliflozin; as well as repaglinide, SUs, DPP-4 inhibitors and pioglitazone used as monotherapies, as outlined in the NICE scope (52). Other SGLT-2 inhibitors (e.g. ipragliflozin, tofogliglozin and luseglifozin) were not included in the NICE scope, and thus not included in the NMA.

The licensed DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) were considered for inclusion in the NMA to increase the power of the analysis and to ensure a completed network. However, in the pharmacoeconomic evaluation (Section 5.2.5.2), sitagliptin is the only DPP-4 inhibitor considered as proxy for DPP-4 inhibitors as it

is the most widely prescribed drug in this class. All other treatments in the NMA networks included all doses reported in the included studies, and were subsequently considered in the pharmacoeconomic evaluation at the most commonly prescribed dose.

Whereas standard meta-analytical techniques evaluate the relative efficacy of one treatment compared with a single comparator, NMA methods can estimate the relative efficacy of any number of different treatments by taking account of the entire network of RCT evidence simultaneously (122). An NMA was conducted in order to synthesise all available evidence on an entire network of treatments and estimate the relative efficacy of each treatment compared with all comparators within a single analysis.

4.1.1.1 Inclusion/exclusion criteria and data extraction

All studies meeting the systematic review inclusion criteria (Table 1) were considered for inclusion in the NMA. The final data set included 69 publications reporting on 60 unique RCTs (1, 9, 53-119). Details of the methodology of the included studies are presented in Section 2; Table 2. The patient baseline characteristics for all included studies are presented in Appendix C (provided separately).

4.1.1.2 Outcomes and timepoints considered in the NMA

Table 27 summarises the efficacy and safety outcomes and timepoints that were included in the NMA. Data for LDL and HDL were extracted from included studies in the systematic review, but due to low and inconsistent reporting and high heterogeneity, a meta-analysis network was not possible.

Table 27: Overview of outcomes and timepoints included in the NMA

Outcome	Time points		
	24 weeks	52 weeks	≥ 52 weeks*
Efficacy outcomes			
Change in HbA_{1c}, %	Yes‡	Yes¶	Yes
Change in weight, kg	Yes††	Yes‡‡	N/A
Change in SBP, mmHg	Yes	NF	N/A
Change in DBP, mmHg	Yes	NF	N/A
Safety outcomes			
Incidence of overall hypoglycaemia	Yes†	Yes†	N/A
Incidence of UTI	Yes†	NF	N/A
Incidence of GTI	NF	NF	N/A

Abbreviations: DBP, diastolic blood pressure; GTI, genital tract infection HbA_{1c}, glycosylated haemoglobin; kg, kilogram; N/A, not applicable; NF, not feasible; SBP, systolic blood pressure; UTI, urinary tract infection.
*This network was explored in the absence of sufficient data for a 76 week evidence network;
† Results of these analyses associated with wide CrIs due to rare/zero events and sparse evidence networks;
‡ Results for analysis which adjusted for baseline HbA_{1c} presented;
Results for analysis which adjusted for baseline HbA_{1c} not presented as covariate coefficient not statistically significant;
†† Results for analysis which adjusted for baseline weight not presented as covariate coefficient not statistically significant;
‡‡Covariate/meta-regression analysis was not feasible i.e. analysis does not adjust for baseline weight.

The 24 week time point was allowed to vary by 6 weeks to allow for a pooled analysis of short-term endpoints. The 52 week time point was allowed to vary by 4 weeks as this captured all available data reporting at approximately 1 year – the closest follow up beyond 56 weeks was 76 weeks. A network at 76 was not feasible as just two studies in the SR

identified reported outcome data at 76 weeks and these did not share a common comparator.

As per the final NICE scope malignancies were explored as an outcome of interest, however they were not included as part of the systematic review protocol. Malignancies were rarely reported across the identified studies and it could not be concluded if, where malignancies were reported, these could be considered an adverse effect of treatment.

Table 28 summarises the studies that were included in each network for which results have been reported in Sections 4.1.3 and 4.1.4.

Table 28: Studies included in networks for the NMA

Endpoint	Change in HbA_{1c}			Change in weight		Change in DBP	Change in SBP	Incidence of hypo		Incidence of UTI
Timepoint (weeks)	**24**	**52**	**≥ 52**	**24**	**52**	**24**	**24**	**24**	**52**	**24**
Arjona Ferreira, 2013a (53)		✓	✓		✓				✓	
Arjona Ferreira, 2013b (54)		✓	✓		✓				✓	
Aronoff, 2000 (55)	✓			✓				✓		
Aschner, 2006 (56)	✓			✓				✓		✓
Bailey, 2012 (57)	✓			✓		✓	✓	✓		✓
Barnett, 2012 (58)	✓			✓						
Barzilai, 2011 (59)	✓									✓
Boardman, 2011 (60) (abstract)										
Charbonnel, 2005 (61)		✓	✓		✓				✓	
Chen, 2013 (62) (abstract)	✓							✓		
Chou, 2012 (63)	✓							✓		✓
Coniff, 1995 (64)	✓			✓				✓		
Cuddihy, 2011 (65) (abstract)										
DeFronzo, 2008 (66)	✓			✓						
Dejager, 2007 (67)	✓			✓				✓		
Del Prato, 2011 (68)	✓							✓		
Derosa, 2003 (69)		✓	✓		✓					
Dills, 1996 (70)										
Drouin, 2000 (71)										
Erem, 2014 (72)										
Ferrannini, 2010 (73)	✓			✓		✓	✓	✓		✓
Foley, 2009 (75)			✓							
Foley, 2011 (74)										
Frederich, 2012 (76)	✓			✓						
Gantz, 2014 (77) (abstract)	✓									

Endpoint	Change in HbA_{1c}			Change in weight		Change in DBP	Change in SBP	Incidence of hypo		Incidence of UTI
Timepoint (weeks)	**24**	**52**	**≥ 52**	**24**	**52**	**24**	**24**	**24**	**52**	**24**
Goldstein, 2007 (78)	✓			✓				✓		
Gonzalez-Galvez, 2014 (79) (abstract)										
Gupta, 2013[††] (80) (abstract)										
Henry, 2014 (81)	✓	✓	✓		✓				✓	
Inagaki, 2014a (83)	✓			✓		✓	✓	✓		✓
Inagaki, 2014b (82) (abstract)										
Jain, 2006 (84)	✓	✓	✓		✓				✓	
Ji, 2014 (85)	✓			✓				✓		✓
Jibran, 2006 (86)	✓	✓	✓	✓						
Jovanovich, 2004 (87)	✓			✓				✓		
Kaku, 2013 (89) (abstract)	✓			✓				✓		✓
Kaku, 2014(88) (abstract)	✓									
Kikuchi, 2012 (90)	✓			✓						✓
Lawrence, 2004 (91)										
Lewin, 2014a (92) (abstract)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lewin, 2014b (93) (abstract)										
Majima, 2006 (94)										
Marbury, 1999 (95)										
Miyazaki, 2002 (96)										
Mohan, 2009 (97)				✓						
Pan, 2012 (98)	✓			✓				✓		✓
Papanas, 2006 (99)										
Pi-Sunyer, 2007 (100)	✓			✓						
Pratley, 2014 (101)	✓			✓		✓	✓	✓		
Raz, 2006 (102)	✓			✓				✓		✓
Roden, 2013 (1)	✓			✓		✓	✓	✓		✓

Endpoint	Change in HbA_{1c}			Change in weight		Change in DBP	Change in SBP	Incidence of hypo		Incidence of UTI
Timepoint (weeks)	**24**	**52**	**≥ 52**	**24**	**52**	**24**	**24**	**24**	**52**	**24**
Roden, 2014 (9) (abstract)	✓	✓	✓	✓	✓			✓	✓	✓
Rosenstock, 2007 (104)	✓			✓						
Rosenstock, 2010 (103)	✓			✓						
Rosenstock, 2013 (105)		✓	✓		✓				✓	
Russell-Jones, 2012 (106)	✓			✓			✓	✓		
Saleem, 2011 (107)	✓	✓	✓							
Schade, 1998 (108)										
Scherbaum, 2002 (109)	✓			✓				✓		✓
Scherbaum, 2008a (110)		✓								
Scherbaum, 2008b (111)			✓		✓				✓	
Segal, 1997 (112)										
Shihara, 2011 (113)										
Stenlof, 2013 (114)	✓			✓		✓	✓	✓		✓
Stenlof, 2014 (115)										
Tan, 2004 (117)		✓	✓		✓				✓	
Tan, 2005 (116)										
Teramoto, 2007 (118)										
Yamanouchi, 2005 (119)		✓	✓							

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; UTI, urinary tract infection.

4.1.2 Statistical methods

This section outlines the approach to analyses, specifically the statistical model used and underlying assumptions; all analyses were conducted in WinBUGS. All statistical models were fitted by adapting code written by the NICE Decision Support Unit (DSU) for their evidence synthesis series.

4.1.2.1 Fixed vs. random effects

Both fixed and random effects meta-analyses were conducted for the base case models. Random effects analyses were performed using a vague prior. The model fit of the fixed and random effects models conducted for each outcome was compared using the deviance information criterion (DIC). In comparing models, the fixed effects model was considered to be the model of choice unless the DIC of the random effects model was at least 3–5 points lower than that of the fixed effects model, thereby providing sufficient improvement in model fit to justify the additional complexity of a random effects model (123). Model fit was also assessed by comparing the residual deviance of the model with the number of data points in the model. Models were judged to be of reasonable fit where the average residual deviance (i.e. residual deviance divided by number of data points) was close to 1. The between-study precision was examined for each random effects model. It may be the case that analyses are underpowered to estimate the between study heterogeneity. The majority of the analyses were performed using fixed effects models as there were insufficient studies to estimate the between-study variance with precision.

4.1.2.2 Modelling approach, assumptions and missing data

For modelling the changes in HbA_{1c} and weight from baseline, it was assumed that the mean changes in these outcomes observed in trials followed a normal distribution and treatment differences were modelled using a hierarchical Bayesian regression model for each outcome. Since changes of a continuous measure are unconstrained on the real line, i.e. they can be positive or negative and theoretically there is no limit on magnitude, the identity link function was used.

Since outcomes are reported inconsistently, certain assumptions had to be made in order that the data could be transformed into an appropriate format for analysis. For example, change in HbA_{1c} may be reported as change from baseline per treatment (arm level data), change from baseline vs. a reference treatment (study level data), or as baseline and endpoint values. The following steps were taken in order that the network was as inclusive as possible:

- Where only mean and endpoint values were reported for each treatment arm, a subtraction was carried out to derive the change value.
- Where uncertainty was not reported as a standard error of change from baseline for each treatment arm, this quantity was computed using techniques described in the Cochrane methods manual and NICE TSDs (123).
- Where a p-value was reported as a range, for example ‘p<0.01’ the upper bound of the range was used. This represents a conservative approach to quantifying uncertainty as outlined in the Cochrane handbook (124).
- Where a measure of uncertainty could not be computed, standard errors were imputed as per the methods outlined in the Cochrane handbook (124). The robustness of

conclusions to changes in the assumptions of imputation was explored. The limitations in using this approach are noted.

Following the above steps, the data were reported as mean changes from baseline.

The final outcomes reported from the continuous outcome model (change in HbA_{1c}, weight, DBP, SBP) were the treatment specific changes in HbA_{1c}/weight from baseline. For modelling dichotomous count data (i.e. incidence of hypoglycaemia, UTI and GTI) a binomial model with logit link function was used.

Zero events

A major strength of the Bayesian Markov Chain Monte Carlo (MCMC) NMA approach is that zero cells are allowed and special precautions are not usually need into account for the occasional trial with a zero cell count (123). However in extreme cases such as those where several trials have zero events or many of the trials are small the models may be numerically unstable either failing to converge, or converging to a posterior with very high standard deviation (123). A specific problem arises in sparse networks where for example there is one trial per treatment comparison (123). If this trial contains a zero event then it may not be possible to estimate a treatment effect. A solution to this issue is to revert to the practice of assigning a continuity correction (as per the frequentist approach) (124).

4.1.2.3 Meta-regression

In the base case analysis, only treatments were fitted as covariates and therefore the implicit assumption was that any change in the outcome being measured was due to the effect of treatment only. Meta-regression analysis allows for the fact that changes in the outcome may be due to effect modifiers, such as baseline weight or baseline HbA_{1c}. Continuous covariates (change in $HbA_{1c,}$ weight, DPB, SBP etc.) can be adjusted at the trial level so that the calculated treatment effects apply to patients with the average level of covariate. For example, if the average baseline HbA_{1c} measured in the included trials was 9%, the covariate can be centred on this value, so that any treatment effects calculated apply to patients with HbA_{1c} of 8% upon initiation of treatment. The base case analyses were repeated for change in HbA_{1c} and weight, adjusting for the baseline HbA_{1c}/weight as a trial level covariate.

All covariate-adjusted models were compared with the base case in terms of DIC and residual deviance. Covariate-adjusted models were considered the model of choice on the basis of subjective assessment of the following criteria being satisfied:

1. Enough improvement in model fit to justify additional parameters.
2. Covariate coefficient CrI does not cross the null value

As noted in the DSU documents, the most relevant approach to decision making is to model the covariate effect as being common to all treatments (125). The assumption being made with this approach is that, if a covariate effect exists, it affects all treatments linearly and equally so.

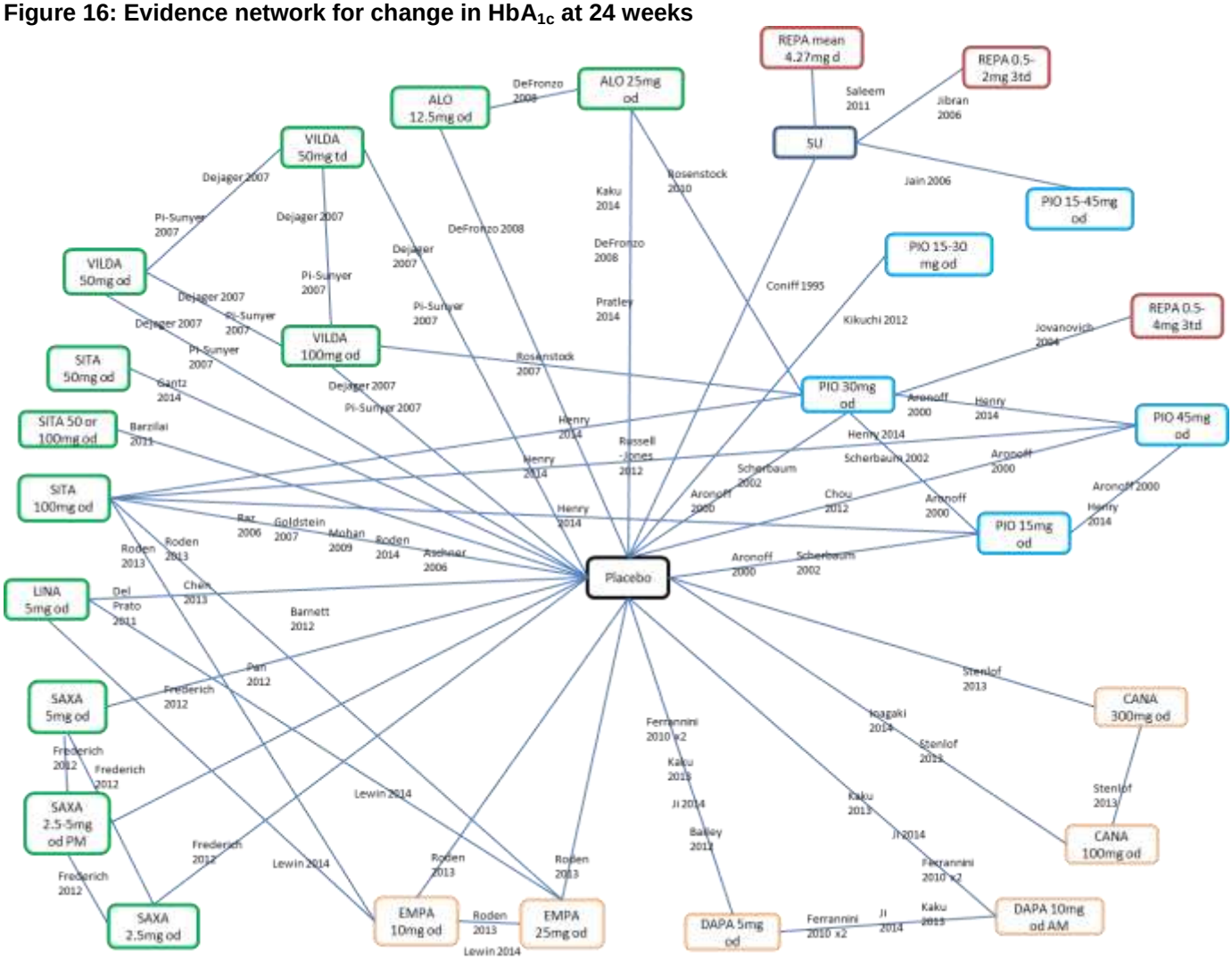
4.1.3 Network meta-analysis results: efficacy outcomes

4.1.3.1 Outcome 1: Change in HbA_{1c}

Change in HbA_{1c} at 24 weeks

The evidence network for change in HbA_{1c} at 24 weeks included 37 studies and is presented in Figure 16. A fixed effects model is presented for this outcome; the random effects model proved to be underpowered to estimate the between study heterogeneity, although the results of the conclusions of the random effects analysis remained consistent with the fixed effects model results.

Figure 16: Evidence network for change in HbA_{1c} at 24 weeks



Abbreviations: ALO, alogliptin; CANA, canagliflozin; DAPA, dapagliflozin;DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SAXA, saxagliptin; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

Base case analysis: The results of the base case analysis for all treatments vs. placebo are presented for the fixed effects model in Table 29.

Significantly greater reductions in HbA_{1c} at 24 weeks compared with placebo were observed for all SGLT-2 inhibitors, including empagliflozin; DPP-4 inhibitors; and most doses of pioglitazone and repaglinide. The reductions in HbA_{1c} at 24 weeks were not significant for

pioglitazone 15–45 mg OD, repaglinide 0.5–2 mg TID, repaglinide 4.27 mg OD and SUs compared with placebo.

Table 29: Fixed effects model for % change in HbA_{1c} at 24 weeks relative to placebo – base case analysis†

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD			
Empagliflozin 25 mg OD			
Alogliptin 12.5 mg OD			
Alogliptin 25 mg OD			
Canagliflozin 100 mg OD			
Canagliflozin 300 mg OD			
Dapagliflozin 10 mg OD			
Dapagliflozin 5 mg OD			
Linagliptin 5 mg OD			
Pioglitazone15 mg OD			
Pioglitazone 30 mg OD			
Pioglitazone 45 mg OD			
Pioglitazone 15–30 mg OD			
Pioglitazone 15–45 mg OD			
Repaglinide 0.5–2 mg TID			
Repaglinide 0.5–4 mg TID			
Repaglinide 4.27 mg OD			
Saxagliptin 2.5–5 mg OD			
Saxagliptin 2.5 mg OD			
Saxagliptin 5 mg OD			
Sitagliptin 100 mg OD			
Sitagliptin 25 or 100 mg OD			
Sitagliptin 50 mg OD			
SUs			
Vildagliptin 100 mg OD			
Vildagliptin 50 mg OD			
Vildagliptin 50 mg BD			

Abbreviations: BD, twice daily; CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; OD, once daily; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Covariate analysis: A meta-regression analysis was performed, adjusting for baseline HbA_{1c}. A graph of the baseline HbA_{1c} levels of studies included within the network is shown in Appendix D (provided separately). The results for the covariate adjusted fixed effects

model are presented in Table 30 for all treatments vs. placebo. Adjusting for study level covariates led to similar conclusions about effectiveness compared with the base case, with the majority of treatments demonstrating significantly greater reductions in HbA_{1c} compared with placebo. In contrast to the base case analysis, repaglinide 0.5–2 mg TID demonstrated a significantly greater reduction in HbA_{1c} compared with placebo; however pioglitazone 15–45 mg OD and SUs remained non-significantly different.

Table 30: Fixed effects model for % change in HbA_{1c} at 24 weeks relative to placebo – covariate analysis†

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 12.5 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 25 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 100 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 300 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 5 mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone15 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 30 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15–30 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15–45 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 0.5–2 mg TID	[redacted]	[redacted]	[redacted]
Repaglinide 0.5–4 mg TID	[redacted]	[redacted]	[redacted]
Repaglinide 4.27 mg OD	[redacted]	[redacted]	[redacted]
Saxagliptin 2.5–5 mg OD	[redacted]	[redacted]	[redacted]
Saxagliptin 2.5 mg OD	[redacted]	[redacted]	[redacted]
Saxagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 or 100 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 50 mg OD	[redacted]	[redacted]	[redacted]
SUs	[redacted]	[redacted]	[redacted]
Vildagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
Vildagliptin 50 mg OD	[redacted]	[redacted]	[redacted]
Vildagliptin 50 mg BD	[redacted]	[redacted]	[redacted]

Abbreviations: BD, twice daily; CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; OD, once daily; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Statistics pertaining to model fit and heterogeneity show that the fixed effects covariate adjusted model provided the best fit (Table 31).

Table 31: Model fit and heterogeneity for change in HbA_{1c} model

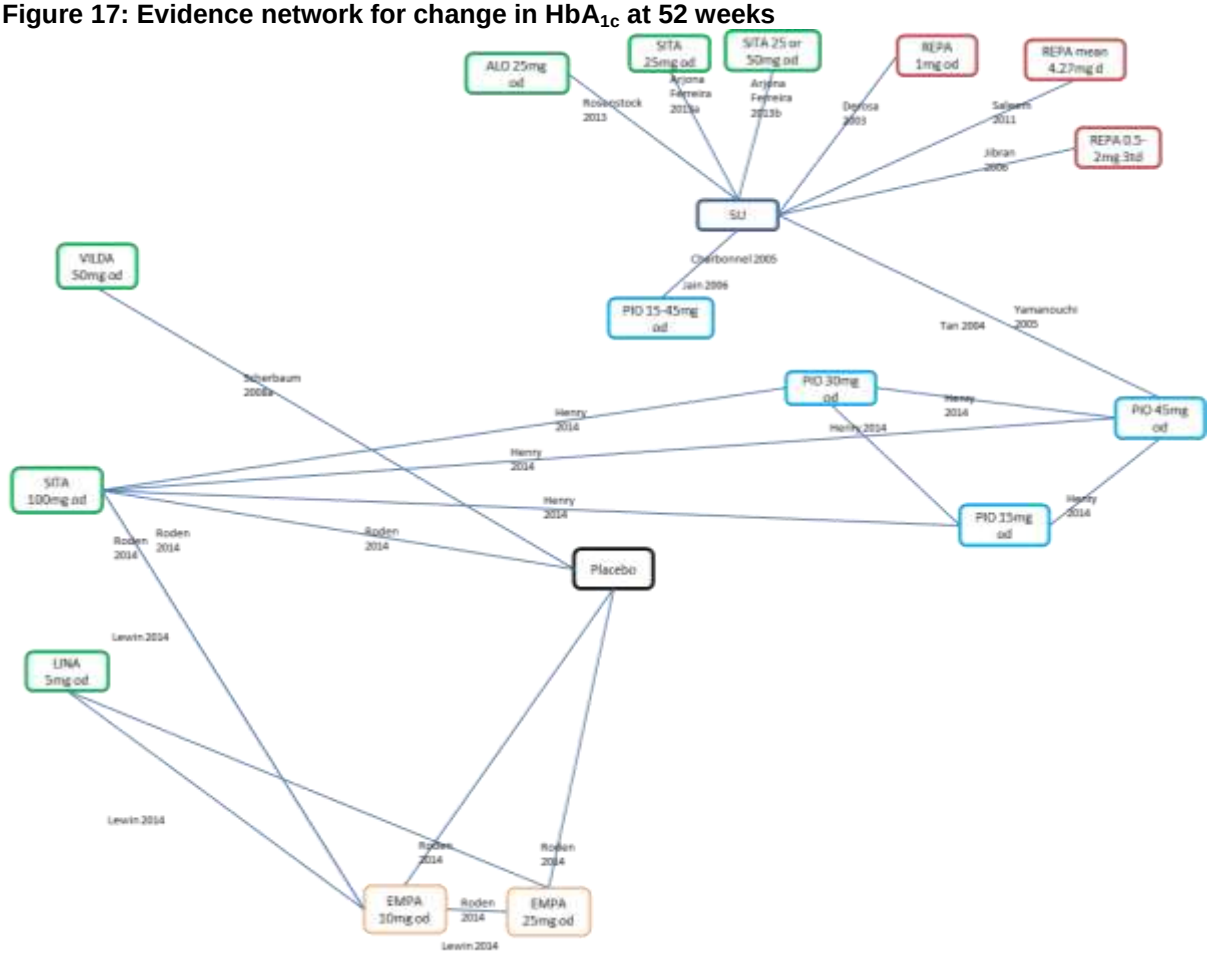
Model	DIC	Residual deviance
Fixed effects (base case)	[redacted]	[redacted]
Fixed effects covariate adjusted	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; HbA_{1c}, glycosylated haemoglobin.
†Compared with 96 data points

Change in HbA_{1c} at 52 weeks

The evidence network analysed for change in HbA_{1c} at 52 weeks included 14 studies and is shown in Figure 17. The results of the fixed effects model are presented for this outcome. The random effects model failed to converge, even after 1,000,000 iterations. This problem persisted despite sensitivity analyses to change the prior distributions. Therefore, the fixed effects model was considered to be the most robust.

Figure 17: Evidence network for change in HbA_{1c} at 52 weeks



Abbreviations: ALO, alogliptin;DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

Base case analysis: The results of the base case analysis for all treatments vs. placebo are presented for the fixed effects model in Table 32.

Significantly greater reductions in HbA_{1c} at 52 weeks compared with placebo were observed for empagliflozin (10 mg and 25 mg), all DPP-4 inhibitors, pioglitazone, SUs and repaglinide 0.5-2 mg TID. Reduction in HbA_{1c} at 52 weeks was not significant for repaglinide 1 mg TID and repaglinide 4.27 mg OD compared with placebo (Table 32).

Table 32: Fixed effects model for % change in HbA_{1c} at 52 weeks relative to placebo – base case analysis†

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 25 mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15-45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 30 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 0.5-2 mg TID	[redacted]	[redacted]	[redacted]
Repaglinide 1 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 4.27 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 or 50 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 mg OD	[redacted]	[redacted]	[redacted]
SUs	[redacted]	[redacted]	[redacted]
Vildagliptin 50 mg OD	[redacted]	[redacted]	[redacted]

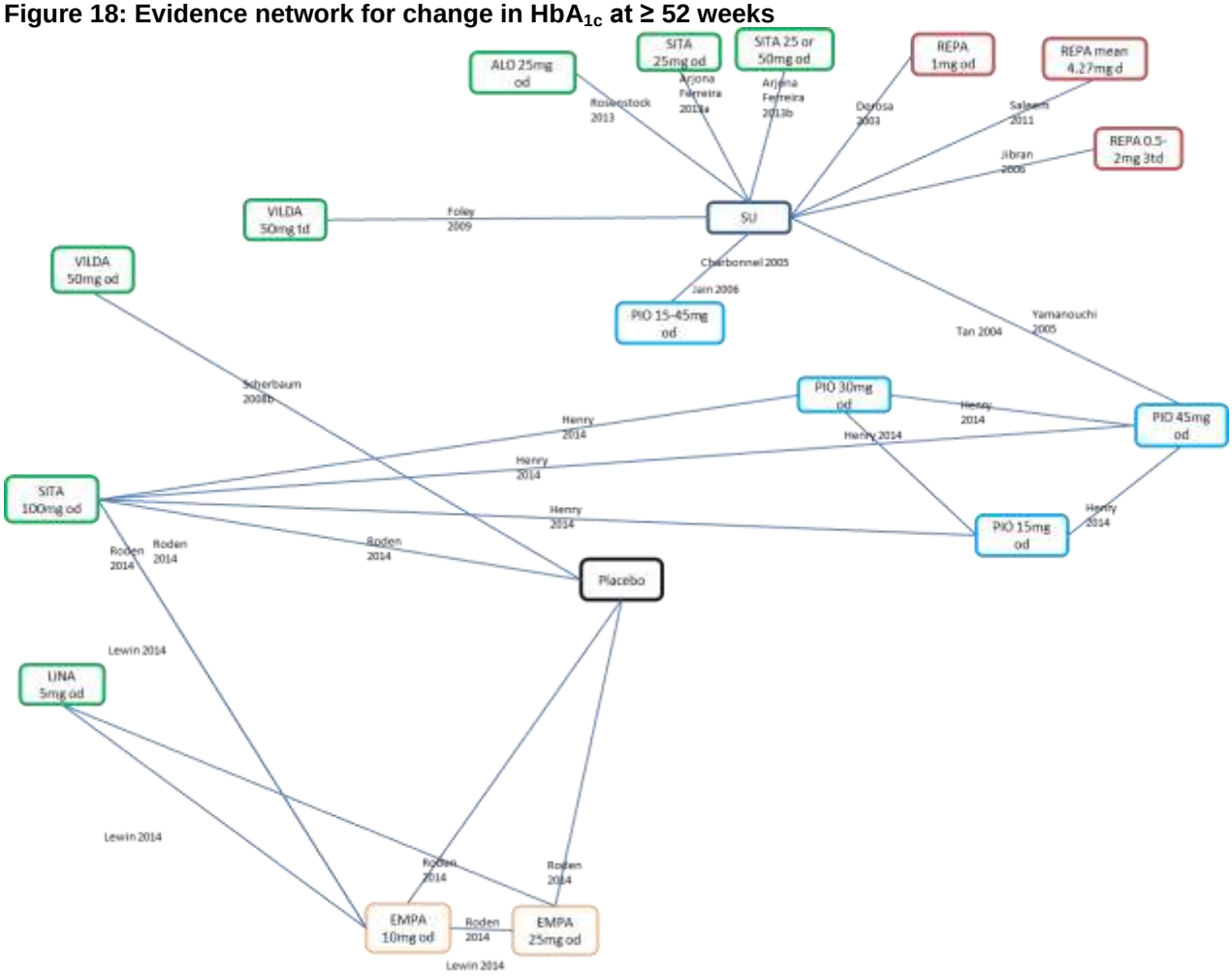
Abbreviations: CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; OD, once daily; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Covariate analysis: A meta-regression analysis was explored to adjust for baseline HbA_{1c}. A graph of the baseline HbA_{1c} levels of studies included within the network is show in Appendix D (provided separately). The fixed effects covariate adjusted model failed to converge even after 1,000,000 iterations. This problem persisted despite sensitivity analyses to change the prior distributions. In the absence of a covariate analysis for the change in HbA_{1c} at 52 weeks, the results of the base case analysis must be considered in terms of the heterogeneity introduced into the network in terms of the mean baseline HbA_{1c} levels of the included studies.

Change in HbA_{1c} at ≥ 52 weeks

The evidence network analysed for change in HbA_{1c} at ≥ 52 weeks is shown in Figure 18. This analysis was based on the 52 week analysis but also included 76 week data for Roden 2014 and an additional study with data at 104 weeks (Foley 2009). The fixed effects model is presented for this outcome; the random effects model failed to converge even after 1,000,000 iterations.

Figure 18: Evidence network for change in HbA_{1c} at ≥ 52 weeks



Abbreviations: ALO, alogliptin; DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

Base case analysis: The results of the base case analysis for all treatments vs. placebo are presented for the fixed effects model in Table 33.

Significantly greater reductions in HbA_{1c} at ≥ 52 weeks compared with placebo were observed for empagliflozin, all DPP-4 inhibitors (with the exception of vildagliptin 50 mg BD), pioglitazone and SUs. The reductions in HbA_{1c} at ≥ 52 weeks were not significant for all doses of repaglinide compared with placebo.

Table 33: Fixed effects model for % change in HbA_{1c} at ≥ 52 weeks relative to placebo – base case analysis[†]

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 25 mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15-45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15 mg OD	[redacted]	[redacted]	[redacted]

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Pioglitazone 30 mg OD			
Pioglitazone 45 mg OD			
Repaglinide 0.5-2 mg TID			
Repaglinide 1 mg TID			
Repaglinide 4.27 mg OD			
Sitagliptin 100 mg OD			
Sitagliptin 25 or 50 mg OD			
Sitagliptin 25 mg OD			
SU			
Vildagliptin 50 mg OD			
Vildagliptin 50 mg BD			

Abbreviations: BD, twice daily; CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; OD, once daily; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Covariate analysis: A meta-regression analysis was explored to adjust for baseline HbA_{1c}. A graph of the baseline HbA_{1c} levels of studies included within the network is show in Appendix D (provided separately). The fixed effects covariate adjusted model failed to converge even after 1,000,000 iterations. In the absence of a covariate analysis for the change in HbA_{1c} at ≥ 52 weeks the results of the base case analysis must be considered in terms of the heterogeneity introduced into the network in terms of the mean baseline HbA_{1c} levels of the included studies.

Sensitivity analysis: Change in HbA_{1c} at 24 weeks

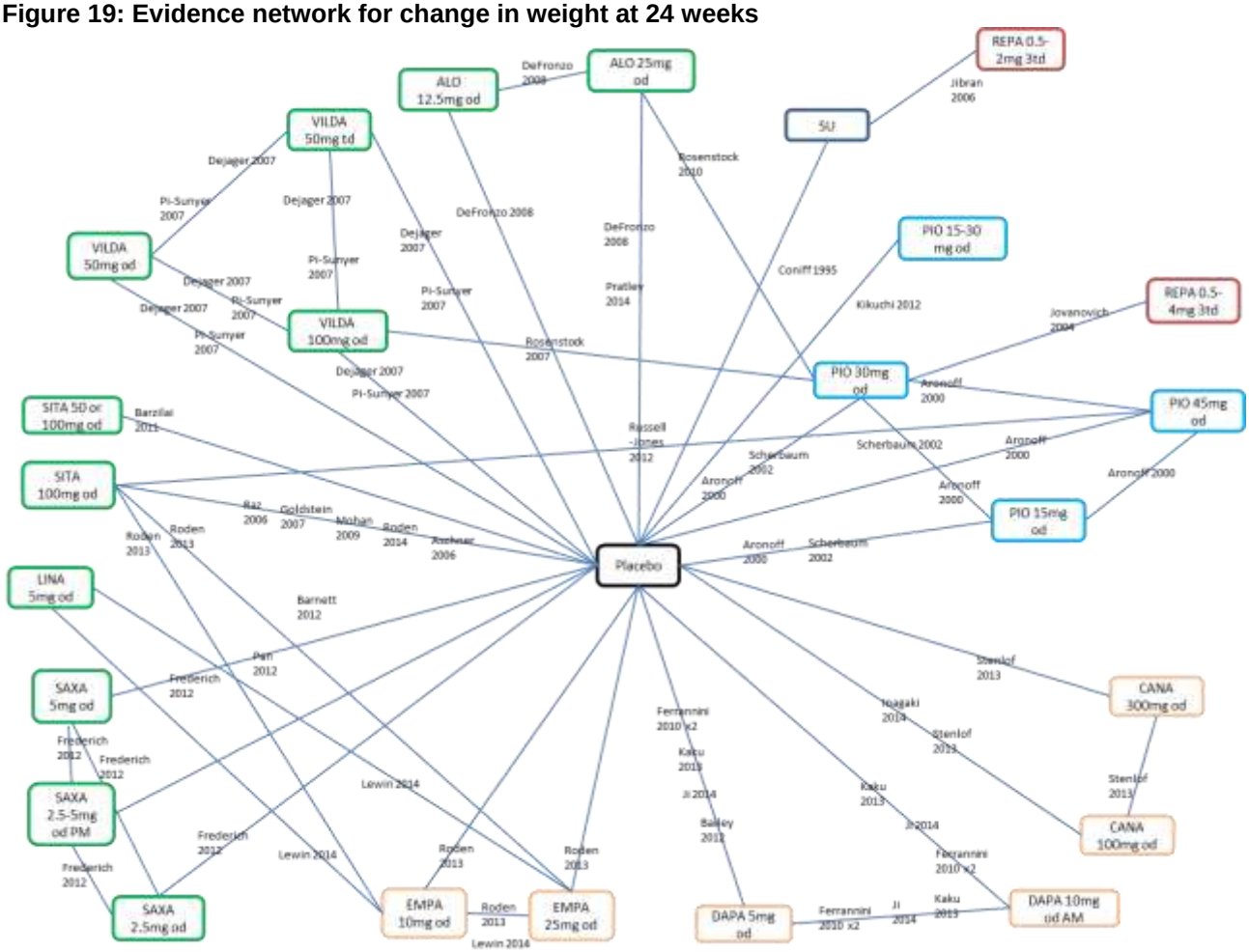
A sensitivity analysis was conducted to explore the impact of removing studies or treatment arms for which studies were not designed to compare. This analysis is presented in Appendix D (provided separately).

4.1.3.2 Outcome 2: Change in weight

Change in weight at 24 weeks

The evidence network analysed for change in weight at 24 weeks included 29 studies and is shown in Figure 19. A fixed effects model was utilised for this outcome; the random effects model proved to be underpowered to estimate the between study heterogeneity.

Figure 19: Evidence network for change in weight at 24 weeks



Abbreviations: ALO, alogliptin; CANA, canagliflozin; DAPA, dapagliflozin;DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SAXA, saxagliptin; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

Base case analysis: The results of the base case analysis are presented for the fixed effects model in Table 34 (treatment comparisons vs. placebo).

Significantly greater reductions in weight at 24 weeks compared with placebo were observed for all SGLT-2 inhibitors, including empagliflozin.

Significantly greater increases in weight at 24 weeks compared with placebo were observed for all doses of pioglitazone, SUs, saxagliptin 2.5 mg OD, sitagliptin 100 mg OD, and vildagliptin 100 mg OD and 50 mg BD. The increase in weight at 24 weeks was not significant compared with placebo for alogliptin (12.5 mg OD and 25 mg OD), linagliptin 5 mg OD, repaglinide (0.52 mg TID and 0.54 mg TID) saxagliptin (2.5–5 mg OD and 5 mg OD), sitagliptin (25 or 100 mg OD) and vildagliptin (50 mg OD).

Table 34: Fixed effects model for change in weight (kg) at 24 weeks relative to placebo – base case analysis[†]

Treatment vs. placebo	Lower 95% CrI	Treatment difference in weight, kg	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 12.5 mg OD	[redacted]	[redacted]	[redacted]

Treatment vs. placebo	Lower 95% CrI	Treatment difference in weight, kg	Upper 95% CrI
Alogliptin 25 mg OD			
Canagliflozin 100 mg OD			
Canagliflozin 300 mg OD			
Dapagliflozin 10 mg OD			
Dapagliflozin 5 mg OD			
Linagliptin 5 mg OD			
Pioglitazone 15-30 mg OD			
Pioglitazone15 mg OD			
Pioglitazone 30 mg OD			
Pioglitazone 45 mg OD			
Repaglinide 0.5-2 mg TID			
Repaglinide 0.5-4 mg TID			
Saxagliptin 2.5-5 mg OD			
Saxagliptin 2.5 mg OD			
Saxagliptin 5 mg OD			
Sitagliptin 100 mg OD			
Sitagliptin 25 or 100 mg OD			
SU			
Vildagliptin 100 mg OD			
Vildagliptin 50 mg OD			
Vildagliptin 50 mg BD			

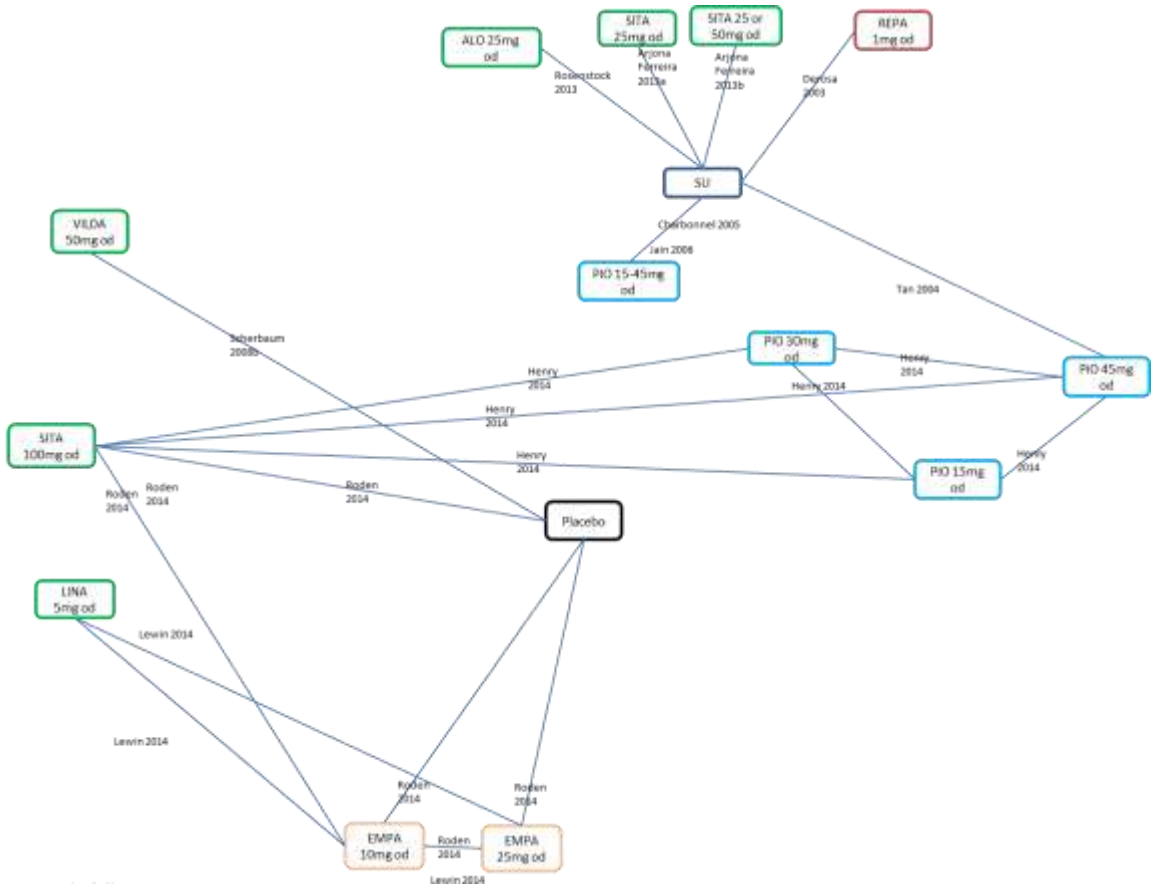
Abbreviations: BD, twice daily; CrI, credible interval; OD, once daily; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Covariate analysis: A meta-regression analysis was explored to adjust for baseline weight. A graph of the mean baseline weight of study populations included within the network is show in Appendix D (provided separately). Note that base-line weight data was not available for six of the studies included in the base case network and the studies were removed from the covariate analysis (a complete case analysis of 23 studies). The fixed effects covariate model did not offer any improvement in model fit compared with the base case model of the 23 studies in terms of DIC. In addition the coefficient estimating the impact of baseline weight on the change in weight effect was not statistically significant (95% CrI crossed the null value). The results of the covariate analysis were consistent with the base case.

Change in weight at 52 weeks

The evidence network analysed for change in weight at 52 weeks included 11 studies and is shown in Figure 20. A fixed effects model was used for this outcome; the random effects model did not offer an improvement in model fit and proved to be underpowered to estimate the between study heterogeneity.

Figure 20: Evidence network for change in weight at 52 weeks



Abbreviations: ALO, alogliptin; DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

Base case analysis: The results of the base case analysis are presented for all treatments vs. placebo for the fixed effects model in Table 35. Empagliflozin was the only SGLT-2 inhibitor included in the network.

Significantly greater reductions in weight at 52 weeks compared with placebo were observed for empagliflozin (10 mg OD and 25 mg OD). Significant increases in weight at 52 weeks compared with placebo were observed for all doses of pioglitazone, repaglinide (1 mg OD), sitagliptin (100 mg OD) and SUs. The increase in weight at 52 weeks was not significant compared to placebo for alogliptin (25 mg OD) and sitagliptin (25 or 50 mg OD and 25 mg OD), linagliptin (5 mg OD) and vildagliptin (50 mg OD).

Table 35: Fixed effects model for change in weight (kg) at 52 weeks relative to placebo – base case analysis†

Treatment vs. placebo	Lower 95% CrI	Treatment difference in weight, kg	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 25 mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15-45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 30 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 1 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 or 50 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 mg OD	[redacted]	[redacted]	[redacted]
SU	[redacted]	[redacted]	[redacted]
Vildagliptin 50 mg OD	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; OD, once daily; SU, sulfonylurea.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 0 for continuous outcomes).

Covariate analysis: A graph of the mean baseline weight of study populations included within the network is show in Appendix D (provided separately). It was not feasible to perform a meta-regression analysis to adjust for baseline weight as seven of the ten studies in the network included baseline weight data. Meta regression should only be considered where the evidence network includes at least ten studies with covariate information (124) .

4.1.3.3 Additional efficacy outcomes

Additional efficacy outcomes include change in DBP and change in SBP. The evidence networks and base case analyses for these outcomes are presented in Appendix D (provided separately).

4.1.4 Network meta-analysis results: safety outcomes

4.1.4.1 Outcome 4: Incidence of overall hypoglycaemia

General summary of incidence of hypoglycaemia

Whilst evidence networks were feasible for the incidence of hypoglycaemia, studies included within the network reported low numbers of events, and many treatment arms reported zero events. As outlined in Section 4.1.2.2, where several trials have zero events or many of the trials are small the models may be numerically unstable. In the analyses of hypoglycaemia the models failed to converge until a continuity correction was assigned to studies with zero events. The results of the analyses were associated with very wide credible intervals which all crossed the null value (OR=1) for all treatment comparisons from which no firm conclusions can be made. Factors contributing to the wide credible intervals include:

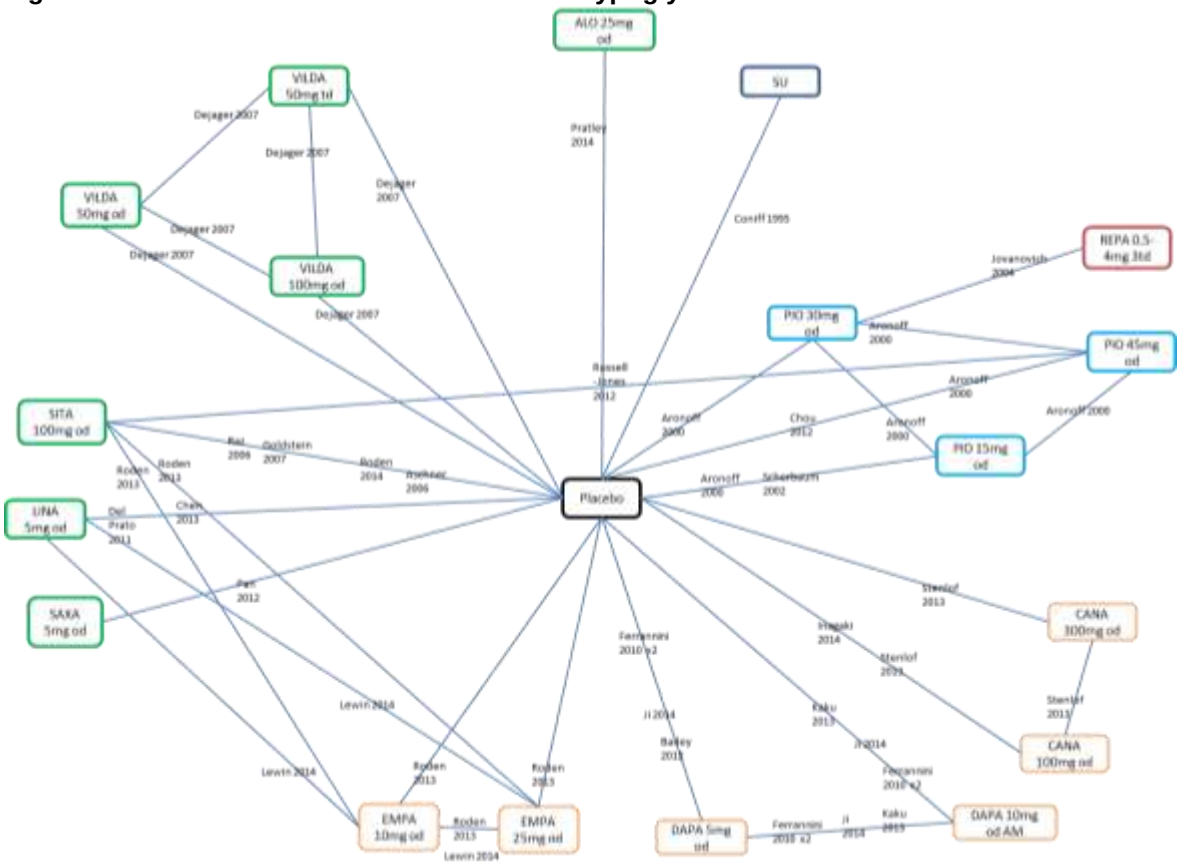
- Indirectness of the evidence (i.e., many trials, or bridges, that exist between comparators)
- Sparseness of data (few trials per comparison/few patients in one or more treatment arms)
- Rarity of events (zero or one event in a treatment arm for a given outcome)

Although the 24 week evidence network is bigger than the 52 week network, the 24 week network included study data with many zero and rare events. In comparison a single study of the 52 week network reported zero events and the majority or studies included event numbers which would not be considered rare. Whilst the 52 week network is considered sparse in comparison to the 24 week network in this instance the rarity of events in the 24 week network is contributing to the wider CrIs observed in the 24 week network. For both networks, the 24 week and 52 week, the findings are reported below.

Incidence of hypoglycaemia at 24 weeks

The evidence network analysed for the incidence of hypoglycaemia at 24 weeks includes 18 studies and is shown in Figure 21. A random effects model was chosen for this outcome as the fixed effects model failed to converge despite the use of continuity corrections for trials with zero events.

Figure 21: Evidence network for incidence of hypoglycaemia at 24 weeks



Abbreviations: ALO, alogliptin; CANA, canagliflozin; DAPA, dapagliflozin; DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; LINA, linagliptin; PIO, pioglitazone; REPA, repaglinide; SAXA, saxagliptin; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs; red=REPA.

The results of the analysis are presented for all treatments vs. placebo for the random effects model in Table 36. None of the treatments that were included in the network demonstrated a statistically significant difference in the incidence of hypoglycaemia at 24 weeks compared with placebo (CrIs for all treatments crossed 1).

There were insufficient studies to estimate the between study variance with precision – the wide CrIs in the random effects models reflect uncertainty as a result of lack of data as opposed to the true variance in treatment effects.

Table 36: Random effects model for incidence of hypoglycaemia at 24 weeks relative to placebo – base case analysis†

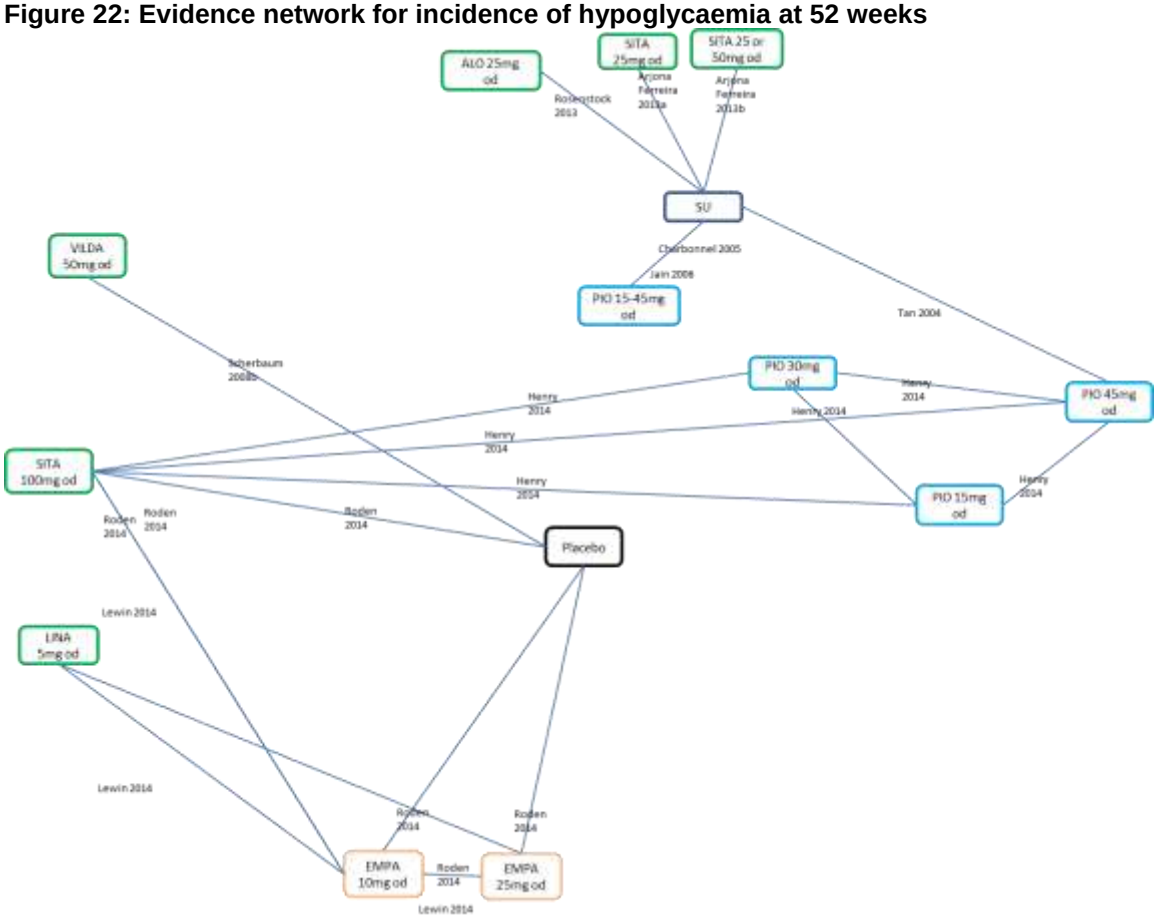
Treatment vs. placebo	Lower 95% CrI	OR	Upper 95% CrI
Empagliflozin 10 mg OD			
Empagliflozin 25 mg OD			
Alogliptin 25 mg OD			
Canagliflozin 100 mg OD			
Canagliflozin 300 mg OD			
Dapagliflozin 10 mg OD			
Dapagliflozin 5 mg OD			
Linagliptin 5 mg OD			
Pioglitazone 15 mg OD			
Pioglitazone 30 mg OD			
Pioglitazone 45 mg OD			
Repaglinide 0.5-4 mg TID			
Saxagliptin 5 mg OD			
Sitagliptin 100 mg OD			
SU			
Vildagliptin 100 mg OD			
Vildagliptin 50 mg OD			
Vildagliptin 50 mg BD			

Abbreviations: BD, twice daily; CrI, credible interval; OD, once daily; OR, odds ratio; SU, sulfonylurea; TID, three times daily.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 1 for dichotomous outcomes).

Incidence of hypoglycaemia at 52 weeks

The evidence network analysed for the incidence of hypoglycaemia at 52 weeks includes ten studies and is shown in Figure 22. Note that 76 week data only was available for Roden 2014—each treatment arm of the study had the same event number (n=2) therefore the relative treatment effect is the same as that for the data available for 24 weeks, where each arm of the study also had the same event number (n=1).

Figure 22: Evidence network for incidence of hypoglycaemia at 52 weeks



Abbreviations: ALO, alogliptin; DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; LINA, linagliptin; PIO, pioglitazone; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; SU, sulfonylurea; VILDA, vildagliptin.
Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO; dark blue=SUs.

The results of the analysis are presented for all treatments vs. placebo for the fixed effects model in Table 37. None of the treatments that were included in the network demonstrated a statistically significant difference in the incidence of hypoglycaemia at 52 weeks compared with placebo (CrIs for all treatments crossed 1).

Table 37: Fixed effects model for incidence of hypoglycaemia at 52 weeks relative to placebo – base case analysis[†]

Treatment vs. placebo	Lower 95% CrI	OR	Upper 95% CrI
Empagliflozin 10mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Alogliptin 25mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15-45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 30mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 25 or 50mg OD	[redacted]	[redacted]	[redacted]

Treatment vs. placebo	Lower 95% CrI	OR	Upper 95% CrI
Sitagliptin 25mg OD	[redacted]	[redacted]	[redacted]
SU	[redacted]	[redacted]	[redacted]
Vildagliptin 50mg OD	[redacted]	[redacted]	[redacted]

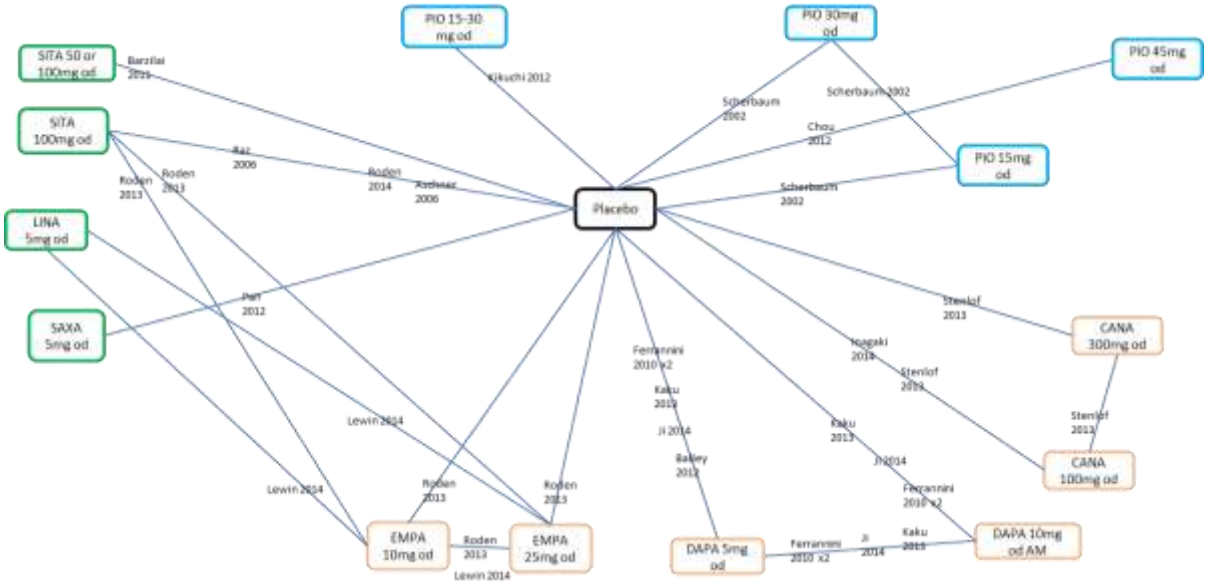
Abbreviations: CrI, credible interval; OD, once daily; OR, odds ratio; SU, sulfonylurea
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 1 for dichotomous outcomes).

4.1.4.2 Outcome 5: Incidence of UTI

Incidence of UTI at 24 weeks

The evidence network analysed for the incidence of UTI at 24 weeks includes 14 studies and is shown Figure 23. The evidence network included trials with zero events and as a result the models were numerically unstable failing to converge (see Section 4.1.2.2). As a result a continuity correction approach was taken. The fixed effects model provided a better model fit compared with the random effects model.

Figure 23: Evidence network for incidence of UTI at 24 weeks



Abbreviations: CANA, canagliflozin; DAPA, dapagliflozin; DPP-4, dipetidyl-peptidase 4; EMPA, empagliflozin; LINA, linagliptin; PIO, pioglitazone; SAXA, saxagliptin; SGLT-2, sodium-glucose co-transporter-2; SITA, sitagliptin; UTI, urinary tract infection. Orange= SGLT-2 inhibitors; green= DPP-4 inhibitors; blue=PIO.

The results of the base case analysis are presented for all treatments vs. placebo for the fixed effects model in Table 38. None of the treatments that were included in the network demonstrated a significant difference in the incidence of UTI compared with placebo at 24 weeks (CrIs for all treatments crossed 1). The results of the analysis were however associated with wide credible intervals for all treatment comparisons from which no firm conclusions can be made. Factors contributing to the wide credible intervals include:

- Indirectness of the evidence (i.e., many trials, or bridges, that exist between comparators)
- Sparseness of data (few trials per comparison/few patients in one or more treatment arms)
- Rarity of events (zero or one event in a treatment arm for a given outcome).

Table 38: Fixed effects model for the incidence of UTI at 24 weeks relative to placebo – base case analysis†

Treatment vs. placebo	Lower 95% CrI	OR	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 100 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 300 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 5 mg OD	[redacted]	[redacted]	[redacted]
Linagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone15 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 30 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 15-30 mg OD	[redacted]	[redacted]	[redacted]
Saxagliptin 5 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 50 or 100 mg OD	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; OD, once daily; OR, odds ratio; UTI, urinary tract infection.
† Note: Bold and italicised results highlight those for which the 95% CrI does not cross the null value (null value = 1 for dichotomous outcomes).

Incidence of UTI at 52 weeks

An evidence network for the incidence of UTI at 52 weeks was not feasible due to the high number of non-reported outcomes across studies and thus not making a network linkage possible.

4.1.4.3 Additional safety outcomes

There was one additional safety outcome; incidence of GTI. The evidence network included trials with zero events and as a result the models were numerically unstable failing to converge. This is discussed further in Appendix D (provided separately).

4.1.4.4 Additional sensitivity analyses

Additional sensitivity analyses were performed to remove results from two studies from the analysis (Lewin 2015 and the sitagliptin 100 mg treatment arm of Roden 2014). These showed that the removal of these trials had minimal impact on the results of the NMA. Further details are provided in Appendix D (provided separately).

4.1.5 Discussion

A network meta-analysis (NMA) was conducted in order to estimate the relative efficacy and safety of empagliflozin monotherapy compared with the other SGLT-2 inhibitors canagliflozin and dapagliflozin; as well as repaglinide, SUs, DPP-4 inhibitors and pioglitazone used as monotherapies, as outlined in the NICE scope. A number of efficacy and safety outcomes reported at various timepoints were included in the NMA and the majority of the analyses

were performed using fixed effects models as there were insufficient studies to estimate the between-study variance with precision.

All SGLT-2 inhibitors, including empagliflozin demonstrated a significantly greater reduction in HbA_{1c} at 24 weeks compared with placebo. Empagliflozin (which was the only SGLT-2 inhibitor for which data were available) also demonstrated significantly greater reductions in HbA_{1c} compared with placebo at 52 weeks and ≥ 52 weeks. Empagliflozin 25 mg OD demonstrated greater reductions in HbA_{1c} vs. placebo in comparison with the DPP-4 inhibitors and dapagliflozin at 24 weeks.

Similarly, empagliflozin and the other SGLT-2 inhibitors demonstrated a greater reduction in weight vs. placebo in comparison with all the comparators at 24 weeks. Empagliflozin (which was the only SGLT-2 inhibitor for which data were available) also demonstrated greater reductions in weight vs. placebo in comparison with all comparators at 52 weeks.

For the safety outcomes of incidence of hypoglycaemia and UTI, there were no significant differences between any of the treatments included in the network and placebo.

4.1.5.1 Limitations of the analysis

One of the limitations of this analysis is the between-study heterogeneity. A potential source of heterogeneity was the difference in follow up times across studies. The 24 week time point was allowed to vary by 6 weeks to allow for a pooled analysis of short-term endpoints. The 52 week time point was allowed to vary by 4 weeks as this captured all available data reporting at approximately 1 year – the closest follow up beyond 56 weeks was 76 weeks. Additional sources of heterogeneity included patient populations in terms of baseline clinical values and outcome definitions.

The inclusion of elderly patients and renally impaired patients in studies included within the evidence network may be a potential source of heterogeneity. The majority of studies included within the systematic review clearly reported that the patient populations were not elderly or did not include patients with renal impairment. Three studies reported patient populations which may be considered elderly; Barzilai, 2011 (≥ 65 years); Papanas, 2006; (mean ages 66–67; study not included in NMA) and Rosenstock, 2013 (65–90 years). Two studies clearly identified as including patients with renal impairment Arjona Ferreira 2013a (end-stage renal disease receiving dialysis) and Arjona Ferreira 2013b (Chronic renal insufficiency). Three studies reported including some patients with renal impairment Del Prato 2011 (3.6%), Ji 2014 (<3%) and Stenlof 2014 (“some had mild or moderate renal impairment”).

The assumption is made that these factors will not significantly modify the relative treatment effects. Also, prior research suggests that a higher baseline HbA_{1c} is associated with a larger mean decrease in HbA_{1c}. The results of the covariate adjusted analysis of HbA_{1c} at 24 weeks suggested a differential impact of baseline HbA_{1c} (coefficient was significant). The 24 week covariate adjusted analysis of change in weight provided no evidence to show a differential effect of baseline weight. The majority of the analysis were performed using fixed effects models as there were insufficient studies to estimate the between study variance with precision. The wide CrIs in the random effects models reflect uncertainty as a result of lack of data as opposed to the true variance in treatment effects.

5. Pharmacoeconomic evaluation

5.1 Summary of cost-effectiveness

Pharmacoeconomic evaluations

- Two models were built and evaluated (A and B) using a UKPDS model backbone.
- Clinical Practice Research Datalink (CPRD)-derived patient-level baseline data of 9,211 recently diagnosed patients was used in both models (A and B).
- Model A is a simple and transparent 1 year decision tree analysing a 40 year time horizon on the UKPDS model.
- Model B is built to account for treatment intensifications as well as additional treatment effects beyond the UKPDS model (hypoglycaemia, weight change, urinary tract infections) and is closer in approach to the recent Original Health Economic Model (OHEM) from the Guideline Development Group (GDG) and NICE.

Results

- Model A: demonstrates empagliflozin is cost effective when compared to current monotherapy options. The SGLT-2 class exhibit similar levels of cost effectiveness. Both doses of empagliflozin dominate both doses of dapagliflozin, but are both dominated by canagliflozin 100mg.
- Model B: demonstrates results that are largely consistent with those from the OHEM used by NICE and establishes more favourable ICERs for empagliflozin than most of the other comparators with 52 week data (even though the efficacy of SU is overestimated, see Figure 28). Model B also demonstrates that empagliflozin is at least as cost effective as the other SGLT-2 inhibitors it was compared with using best available (24 week) data. The difference in results from model A are due to the underestimation (by half) of the costs for all treatments in 1-yearly runs of the UKPDS OM1 for 40 years compared to its full 40 year runs, as well as the higher treatment costs seen over 40 years in model B. These results are in line with model A, thus providing a validation of both modelling approaches.

Conclusion

- Pharmacoeconomic evaluations of diabetes therapies are a closely contested arena – with a number of comparators, close treatment costs and even closer QALYs.
- Within this scenario, using a two-pronged approach, one simple (model A) and the other closer to the recent OHEM from the GDG and NICE (model B), empagliflozin has been demonstrated to be cost effective (in patients unable to take metformin) and that the direction of results are consistent across the two modelling approaches.

5.2 Pharmacoeconomic evaluations

The approach taken to determine the cost-effectiveness of empagliflozin monotherapy vs. other drugs used in clinical practice in England and Wales (SGLT-2 inhibitors, DPP-4 inhibitors, SUs, pioglitazone and repaglinide) is based on NICE's latest draft (Oct 2014) pharmacoeconomic evaluation of therapies used in type 2 diabetes (called the 'Original

Health Economic Model' in its latest publicly available draft of the 'Appendix F: Full Health Economic Report') (126).

Small differences in QALYs and costs over lifetime for treatments under consideration in this therapy area also mandate careful validation of any modelled results.

To provide a validated set of results, two distinct modelling approaches (model A and model B) have been used. These are described below.

In both models:

- The UKPDS model is used to predict most of the diabetes-related costs and outcomes.
- 'Clinical Practice Research Datalink' (CPRD) data has been sourced to provide baseline patient-level characteristics for 9,211 patients.
- The effects that differ between comparators have been considered but not accounted for in UKPDS model – such as weight and AEs. For example, hypoglycaemia and urinary tract infections (UTIs), in the front-end to the UKPDS model (analogous to NICE's modelling approach).

5.2.1 UKPDS model backbone

Both models harness the 'United Kingdom Prospective Diabetes Study Outcomes Model version 1' (UKPDS OM1) as per its design (to extrapolate diabetes risk and predict long-term costs and outcomes). The recent Original Health Economic Model (OHEM) developed by the Guideline Development Group (GDG) at NICE is also used.

5.2.1.1 Justification

The GDG at NICE evaluated ten diabetes-related outcomes models in developing the OHEM. After using a set of hierarchical selection criteria, two were forwarded for further review – the 'Centre for Outcomes Research Diabetes Model' (CDM) and the UKPDS OM1. The GDG finally selected the UKPDS OM1 due to a combination of a preference for a model based on a single large RCT, the additional flexibility the UKPDS OM1 provides over the CDM, and for consistency with the previous Type 2 guidelines issued by NICE. The three Van Haalen criteria (conceptual validity, model fit, and model quality) of model selection were also found to be met by the UKPDS OM1 (126).

The GDG and NICE justification for basing the OHEM on UKPDS OM1 is equally applicable to both of the modelling approaches within this submission in order to be consistent with the recent OHEM.

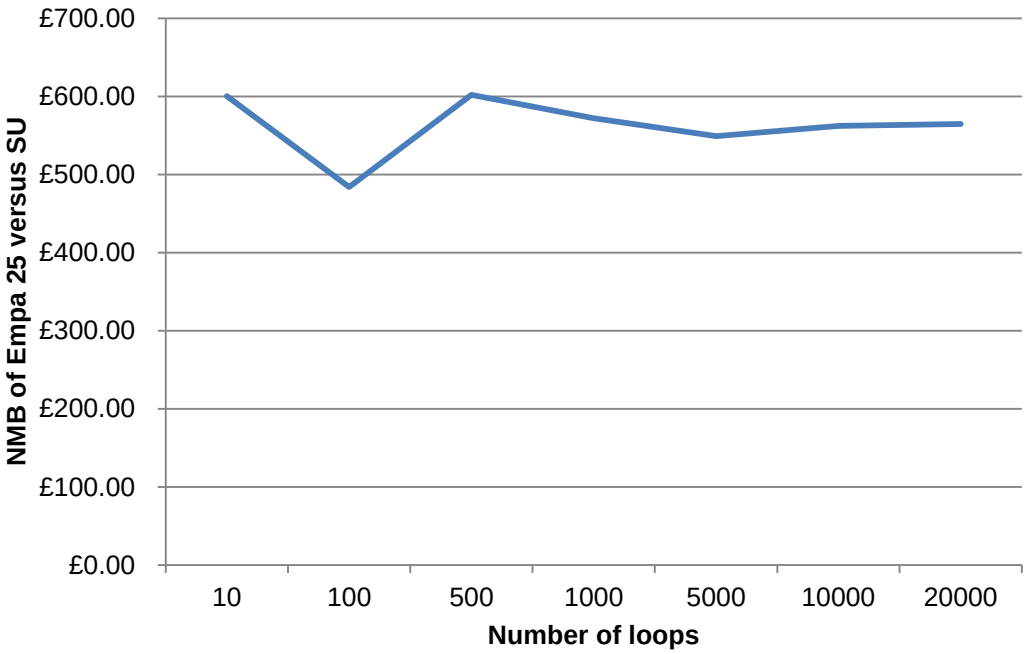
A further practical benefit of choosing the UKPDS model, that applies equally to the OHEM as to both models (A and B) in the submission, is that it cannot be tampered with, by virtue of being locked at the C# code as well as any VBA code its Excel version uses.

The UKPDS OM1 is both a MS Excel-based version, and a standalone version. Both use identical equations and C# programming code for the model besides giving consistent outputs. The GDG and NICE chose the standalone version for the OHEM although this also used an MS Excel front-end. MS-Excel based front ends have been used for both models (A and B), and the Excel-based version of the UKPDS OM1 has been selected, for a more convenient interaction between the front-end and the UKPDS OM1.

To inform the number of internal loops (designed to reduce Monte Carlo error in the UKPDS OM1) required for both models (A and B), an empirical analysis on the effect of the number of loops on the differences in Net Monetary Benefit (NMB) between empagliflozin and

sulfonylurea with our baseline 9,211 patients was conducted. As can be seen from Figure 24, though the level of Monte Carlo error generally reduces and stabilises with increased number of loops, the results stabilise after 1,000 loops per patient. We have therefore chosen to run 10,000 loops per patients for our UKPDS OM1 runs for both models A and B.

Figure 24: Graph displaying results of empirical analysis of Monte-Carlo error



Abbreviations: Empa, empagliflozin; NMB, net monetary benefit; SU, sulfonylurea.

5.2.1.2 Limitations

In working on the OHEM, the GDG and NICE identified the following limitations of the UKPDS OM1:

- Age of the underlying RCT: despite this, no alternative model had relied on a more recent RCT of the scale matching that of the UKPDS model.
- The UKPDS OM1 being based on people with newly diagnosed type 2 diabetes: this would be an issue when modelling outcomes for patients with therapy intensifications. The GDG recognised that this effect could be partially mitigated by increasing the duration since diagnosis variable in the model, while alternative models also suffered from this issue without a better alternative solution.
- Limited set of (seven) outcomes modelled only for their first occurrence by UKPDS OM1: however, the GDG preferred using the UKPDS OM1 over other models that provided more outcomes but risked biasing the results by including more than one potentially dissimilar RCT.
- The UKPDS OM2 was reported in the literature in 2013 (127). It accounts for weight changes and other practical improvements on the UKPDS OM1. The GDG and NICE had expected the UKPDS OM2 to be available in time for the OHEM, and it was also expected to be available for use in models A and B. However, as of the time of finalising this submission (early June 2015), no final availability date for the release of the UKPDS OM2 has been announced.

All of the above limitations also apply to both models A and B.

A further practical limitation, equally faced by the OHEM, is the requirement for separate front-end to the model for any analysis beyond the direct scope of the UKPDS OM1 (evaluating the outcomes and costs of individual patients or cohorts, and comparing up to two different groups). Comparing multiple therapies and intensifications, as for the OHEM and both models A and B, necessitates the development of robust, custom-built front ends.

Two distinct approaches to modelling the front end in models A and B were undertaken:

- Model A is the simpler, and therefore more transparent, approach where the baseline 9,211 real-world patients undergo different comparator therapies for a year (see Section 5.2.2 for how these patients were identified). The UKPDS model then undergoes a full 40-year (maximum allowable in UKPDS OM1/ lifetime) run, with those treatment effects applied, for each such set. Results are then collated and evaluated in the front end. This accounts for the short-term nature of the treatment-efficacy evidence and allows the UKPDS model to produce a credible extrapolation.
- Model B accounts for treatment intensifications, by making the UKPDS model run for a year at a time for the whole of the 40 years (lifetime), for our newly diagnosed 9,211 baseline patients. This approach accounts for treatment switching, costs and outcomes throughout and is closer to the approach taken by the OHEM.

These are both described in more detail below.

5.2.2 Baseline CPRD-derived patient-level data

The 'Clinical Practice Research Datalink' (CPRD) was used to inform both models (A and B; see below for details) in this submission.

A search was carried out on the CPRD dataset to identify all patients who had started on OAD therapy as their first anti-diabetic treatment in 2014. This gave a dataset of 9,211 patient for the inputs required in the UKPDS OM1. A summary of the characteristics gained via CPRD and used to populate both models in this submission (A and B) is given in Table 39.

Table 39: Summary of patient characteristics used in the model

Variable	Value	SD
Male	57.2%	NA
AF	6.63%	NA
PVD	3.18%	NA
Current smoker	16.7%	NA
Former Smoker	36.5%	NA
Non Smoker	46.8%	NA
Age at Diagnosis	60.25	12.34
Duration of Diabetes	2.89 years	3.89 years
Weight	89.81 Kg	20.03 Kg
Weight (Male)	94.85 Kg	18.51 Kg
Weight (Female)	83.06 Kg	20.01 Kg
Height	1.70m	0.11m
Height (Male)	1.75m	0.08m

Variable	Value	SD
Height (Female)	1.61m	0.08m
LDL	4.02 mmol/l	1.11 mmol/l
HDL	1.20 mmol/l	0.35 mmol/l
SBP	134.65 mmHg	15.49 mmHg
HbA_{1c}	8.49%	1.91%
Diabetes related pre-existing events		
IHD	6.13%	NA
CHF	1.92%	NA
Amputation	0.29%	NA
Blindness	0.23%	NA
Renal Failure	0.05%	NA
Stroke	1.62%	NA
MI	2.21%	NA

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; HbA_{1c}, glycosylated haemoglobin (haemoglobin A_{1c}); HDL, high density lipoprotein; IHD, ischaemic heart disease; LDL, low density lipoprotein; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation.

5.2.2.1 Justification

The OHEM used data from 'The Health Improvement Network' (THIN), and explicitly noted that "other GP based databases were available and THIN was only chosen as it was readily available via an existing contract". However, instead of core patient-level THIN data, matrices of patient factors were used in the OHEM. The CPRD dataset was used for this submission as it was readily accessible. Furthermore, direct patient level data from individuals matching the criteria for entry in models A and B (see below) and OHEM's cost-effectiveness models were available.

A search was conducted to identify the newly diagnosed patients on OAD treatment in order to gain a representative real-world sample of recently diagnosed patients being considered for monotherapy, as well as those whose treatment outcomes and switching could be realistically and credibly simulated in both models (A and B). The codes utilised for the search on the CPRD can be found in Appendix G (provided separately).

The above approach excluded patients who had been put on first course of metformin in the last year, but did not specifically exclude patients treated with alternatives to metformin due to patient choice. Although for these cost-effectiveness models we are interested in patients contraindicated or intolerant to metformin, there is no literature or clinical evidence that would suggest that these two groups of patients differed in any systematic way in the baseline characteristics required for the UKPDS model. This approach resulted in a large, representative dataset of patients which was more robust than that which would have been obtained if only contraindicated or intolerant patients had been included.

5.2.2.2 Limitations

Where a record of any of the seven diabetes-related events considered in the UKPDS OM1 was missing, the record was not considered.

Where any other data field was missing, mean values and standard errors were taken from patients with non-missing values, and applied using a normal distribution and a random

number sequence. Because of the likely correlation, the same random number sequence was used for weight and BMI and similarly for LDL and HDL.

In the case of missing values for height and weight, which were likely to be affected by gender, separate distributions were used for males and females.

Race data is sparsely populated in the CPRD database, and therefore this was assigned using a random number sequence to achieve the same proportions of each race as was used for the OHEM.

It should be noted that events in the UKPDS model are only considered if they are related to diabetes. It was considered that, within the CPRD dataset, only including any events after the diagnosis of diabetes might bias the dataset by not including patients recorded in the dataset as having diabetes once a diabetes-related event had taken place (e.g. diagnosis of diabetes soon after the occurrence of a diabetes-related stroke). This had to be balanced against the risk that events which were not related to diabetes would be taken into account by the model. Therefore, instead of setting the threshold for considering an event to be related to diabetes at the date of diagnosis with diabetes, we set this threshold at 2 years before the diagnosis of diabetes. The duration for even these events were counted form the date of diagnosis of diabetes, in order that the UKPDS OM1 would not give an error.

5.2.2.3 Other baseline data

Baseline risks for additional outcomes, hypoglycaemia (non-severe and severe) and UTI were taken from established literature (128) and are shown in Table 40 and Table 41 below.

Table 40: Baseline risks used for hypoglycaemia in SU

	Lower 95% CI/CrI	Annual Risk	Upper 95% CI/CrI	Source
All hypoglycaemic events	0.067	0.164	0.350	Posterior Mean of SU arms
Severe hypoglycaemic events	0.006	0.009	0.013	Leese et al, 2003 (128)
Non-severe hypoglycaemic events	0.061	0.155	0.337	All events minus severe events

Abbreviations: CI, confidence interval; CrI, credible interval; SU, sulfonylurea.

Table 41: Baseline risks used for UTIs in placebo

	Lower 95% CrI	Annual Risk	Upper 95% CrI	Source
UTIs	0.025	0.035	0.045	Posterior Mean of placebo arms

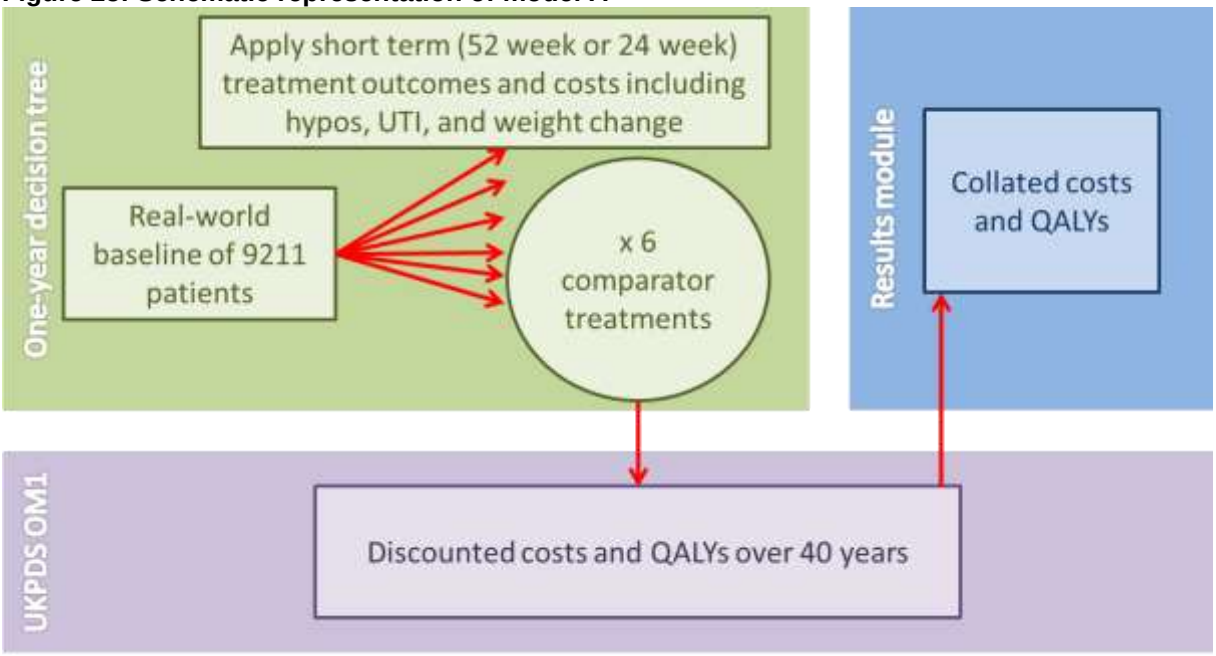
Abbreviations: CrI, credible interval; UTI, urinary tract infection.

5.2.3 Model A approach

In recent submissions there has been a trend towards attempting to replicate the future path of diabetes as closely as possible in order to fully capture all of the benefits of a treatment. This is highly valuable, however as more complexity is added in additional lines of treatment (for example in predicting the impact of discontinuations and treatment switching in subsequent years), the level of structural uncertainty increases. Given that clinical trial data are only available over a relatively short period, with 52 weeks being the longest reasonable period to form a network based on data from the systematic review, this analysis takes a different and simpler approach. It assumes that a patient only receives the treatment and the efficacy of treatment for this known one-year period; afterwards the path of the disease is

predicted by the well validated UKPDS model. It also assumes that there are no discontinuations, and any treatment switches in subsequent years are not taken into account, due to the uncertainty present. Figure 25 shows this model schematically.

Figure 25: Schematic representation of model A



Abbreviations: hypos, hypoglycaemias; QALYs, quality-adjusted life year; UTI, urinary tract infection.

5.2.3.1 Model A justification

The majority of the effects of a diabetes treatment are in the long term. However, treatment-related outcomes data are limited to the short term.

Hence, a simple 1-year decision tree is first used to capture short-term treatment-related effects (hypoglycaemia, UTIs and weight gain/loss). Then, individual treatment-related 40-year UKPDS model runs are conducted to derive credible predictions of outcomes and costs related to each of the compared treatments. These are then simply collated and presented in the front end for model A. By minimising the assumptions required, a simple, transparent, and robust model is produced.

5.2.3.2 Model A limitations

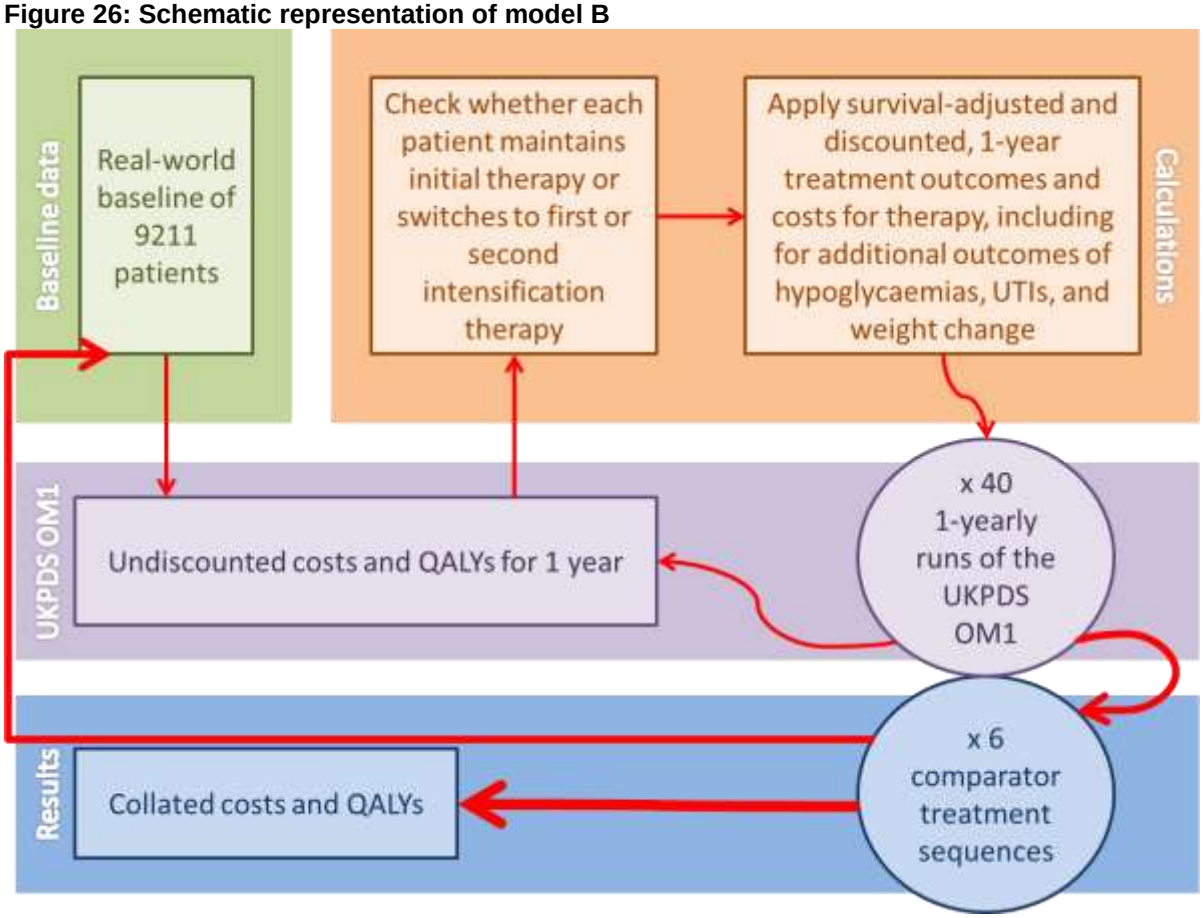
As required for the UKPDS OM1, our CPRD-derived baseline data is for type 2 diabetes patients who started treatment with their first OAD. Model A applies treatment effects for all compared treatments to these newly treated patients. It therefore does not account for treatment intensification and assumes that there is no long-term impact of short-term treatment-related effects such as UTIs and hypoglycaemia. Since data on treatment-related outcomes are not available for longer than 78 weeks, and in most cases, any longer than 52 weeks, this option was chosen to avoid any treatment-effect related assumptions beyond the duration of the original clinical trials, instead relying on credible UKPDS OM1 predictions of costs and outcomes for patients treated with different therapies. In addition, empagliflozin is weight reducing, with longer term data than other therapies (based on 76 week data; Section 4.1.3.2). Therefore, this approach underestimates the benefits of empagliflozin therapy (see Section 3.4.2.3).

5.2.4 Model B approach

The OHEM from the GDG and NICE explicitly models treatment intensification, as well as additional outcomes such as the effects of hypoglycaemia, UTI, and weight change in its front-end to the UKPDS OM1.

Model B also takes both of these major points into account and explicitly models them in the developed front end to the UKPDS OM1. Figure 26 shows this model schematically.

Figure 26: Schematic representation of model B



Abbreviations: QALY, quality-adjusted life year; UKPDS OM1, United Kingdom Prospective Diabetes Study Outcomes Model version 1; UTI, urinary tract infection.

5.2.4.1 Model B justification

Model B builds on the core strengths of the OHEM approach (including incorporation of treatment intensification, addition of further treatment outcomes and inclusion of costs related to hypoglycaemic events, UTIs, and weight changes). Further changes are described below.

- Baseline data used is not modelled and is a true reflection of recent real-world newly diagnosed (as required by the UKPDS OM1) patients in England and Wales, with the full set of data used from 9,211 real patients from CPRD data. This deals robustly with much of the uncertainty in the baseline characteristics of patients produced in the (Baseline) ‘Generation Module’ of the OHEM (126)
- While the OHEM relies on two runs of the UKPDS model, one for undiscounted outcomes and one for discounted ones; model B simulates patient-level data at yearly intervals, with more granularity available to apply treatment related outcomes and costs.

5.2.4.2 Model B limitations

Accommodating the strengths of model B meant that certain practical compromises were necessary. These are described below.

- Using data for 9,211 real-world patients in the UKPDS OM1 model meant that even without bootstraps each full run of the UKPDS OM1 took 11.5-12 minutes. 40 such runs were required for each treatment arm, taking 8 hours to run. Since 6 treatment strategies were modelled (each with 2 intensifications), model B required a total of 48 hours to give a full set of results. Since introducing bootstraps would increase this time by around a factor of 3 to 4, model B was only run for non-bootstrapped analyses. By contrast, model A takes full advantage of the bootstrapping available in the UKPDS OM1. These results are reported in Section 5.2.10.
- Running the UKPDS OM1 a year at a time can lead to underestimation of the overall 40 year costs and QALYs. However, this is aligned to the approach taken by the UKPDS OM1 and OM2 team at ISIS (University of Oxford) (127), and has been validated in personal communications with a member of this team. The costs and QALYs derived from the UKPDS OM1 component for model A vs. model B have been compared in the discussion of results and demonstrate that while their magnitudes vary as expected, their directions (order of the results of different treatment strategies) are consistent. The overall impact of this is to underestimate the cost-effectiveness of empagliflozin compared with its comparators.

5.2.5 Design of the economic evaluation – common to models A and B

Models A and B share all of the following features in their design.

5.2.5.1 Patient population

Patients with type 2 diabetes for who cannot take metformin (in whom metformin is not tolerated or is contraindicated) are considered in the model as outlined in the NICE scope (52).

5.2.5.2 Intervention and comparators considered

The main intervention considered in our evaluations is empagliflozin.

The following comparators, as determined by the NICE scope, are also considered in models A and B (52):

- Dapagliflozin
- Canagliflozin
- DPP-4 inhibitors
- SU
- Pioglitazone
- Repaglinide

It is considered that all the above comparators, with the exception of repaglinide, are relevant comparators for empagliflozin, as these are widely prescribed therapies (51). However, as repaglinide appears in the NICE scope, this is included in both models A and B.

The following doses were chosen:

- Dapagliflozin: Both 5mg and 10mg doses

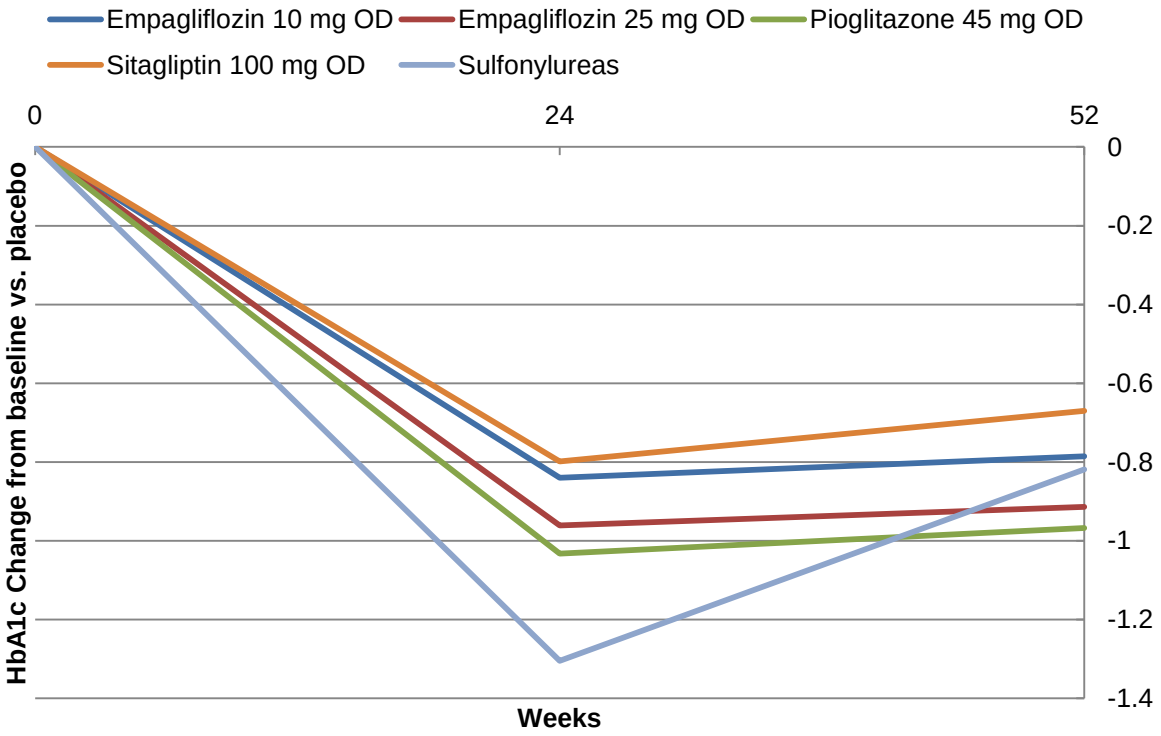
- Canagliflozin: Both 100mg and 300mg doses
- DPP-4 inhibitors: Sitagliptin 100mg OD is used as a proxy for DPP-4 inhibitors, as this is the most widely prescribed drug in the class (51)
- SU: All doses are combined together
- Pioglitazone: 45mg OD dose is used, as this is the most commonly prescribed dose (51)
- Repaglinide: 1mg OD is the only dose which has both HbA_{1c} and weight reported at 52 weeks, and therefore this dose is used as the comparator of interest. (It should be noted that in the reported NMA, the credible intervals for all repaglinide doses are very wide and caution should be applied when interpreting results of comparisons with repaglinide).

In order to make comparisons as realistic and credible as possible, the longest available duration of data was used. Although empagliflozin trials provide data up to 76 weeks, this is not the case for the other comparators and it was not possible to connect a network at 76 weeks. Data at 52 weeks of follow up were available for most comparators, with the exception of canagliflozin and dapagliflozin. It was considered that the longer term data would give a more robust analysis, and this was therefore used for all comparisons other than for the other SGLT-2 inhibitors, where 24 week data were used. Finally, 52 week data were not available for UTIs as discussed in section 4.1.4.2, and therefore 24 week data were used.

Figure 27, which demonstrates a 'treatment rebound' effect for all the treatments compared, shows that with 24 week data only, results for will be biased in favour of SU vs. all the other comparators. Although it is not possible to connect a network and show the effect at more than 52 weeks of follow up for all our comparators in this analysis, Table 30 and Table 32 suggest that there could be a similar effect for repaglinide (risk of biasing results in favour of repaglinide when 24 week results are used instead of longer term data).

Finally, as shown in Figure 7, the HbA_{1c} reduction shown by empagliflozin is maintained at least until the week 76 of follow up. Using shorter data, as used in both models (A and B) to account for a connected network of results, underestimates the benefits of empagliflozin in relation to other comparators considered in the models. This biases results against empagliflozin, suggesting that these analyses are likely to give conservative results.

Figure 27: HbA_{1c} vs. placebo at 24 and 52 weeks (taken from 24 and 52 week networks)



Abbreviations: HbA_{1c}, glycosylated haemoglobin; OD, once daily.

5.2.5.3 Perspective of the analysis

This analysis was conducted from the perspective of the NHS and personal and social services in England.

5.2.5.4 Time horizon and discounting

The time horizon considered in the model was 40 years, in line with the UKPDS OM1. Given that the mean age at baseline of the CPRD-derived real-world newly diagnosed type 2 diabetes patients is over 60 years, a time horizon of 40 years can be considered to be effectively lifetime. However given that some individual patients are considerably younger than this, there will be some patients alive at the end of the model. This means it is possible that some of the long term consequences are not fully captured. This issue is equally faced by the OHEM, and both models (A and B) in this submission.

Costs and outcomes were discounted at 3.5% in line with the NICE methods guide (120).

5.2.6 Intervention and comparators' safety and efficacy data (common to models A and B)

Safety and efficacy data used in both models (A and B) were sourced from the NMA with 52 week and 24 week data. Section 5.2.6.1.4 below sets out the first and second intensification data used in model B.

5.2.6.1 Efficacy data (model A and model B)

Efficacy data used in model A and for initial therapy in model B are shown below (Table 42–Table 48).

52-week data for model A and initial therapy in model B

Table 42: Efficacies used for HbA_{1c} for 52 week comparisons (Source: 52 week NMA)

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 1 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
SUs	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; NMA, network meta-analysis; OD, once daily; SU, sulfonylurea.
Bold results highlight those for which the 95% CrI does not cross the null value (null value=0 for continuous outcomes).

24-week data for model A and initial therapy in model B

Table 43: Efficacies used for HbA_{1c} for 24 week comparisons (Source: 24 week NMA, covariate analysis)

Treatment vs. placebo	Lower 95% CrI	Treatment difference in % HbA_{1c}	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 100 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 300 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 5 mg OD	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HbA_{1c}, glycosylated haemoglobin; NMA, network meta-analysis; OD, once daily.
Bold results highlight those for which the 95% CrI does not cross the null value (null value=0 for continuous outcomes).

Efficacy data common to both 24 and 52 week analyses (model A and initial therapy in model B)

Efficacy data for SBP changes at 24 and 52 weeks were taken from our NMA-derived data at 24 weeks, the best available such data.

Table 44: Efficacies used for SBP

Treatment vs. placebo	Lower 95% CrI	Treatment difference in SBP, mmHg	Upper 95% CrI	Source
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Canagliflozin 100 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Canagliflozin 300 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Dapagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Dapagliflozin 5 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA
Repaglinide	[redacted]	[redacted]	[redacted]	Assumed equivalent to placebo

Treatment vs. placebo	Lower 95% CrI	Treatment difference in SBP, mmHg	Upper 95% CrI	Source
SU	[redacted]	[redacted]	[redacted]	Assumed equivalent to placebo

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily; SBP, systolic blood pressure; SU, sulfonylurea
Bold results highlight those for which the 95% CrI does not cross the null value (null value=0 for continuous outcomes).

Efficacy data for 24 and 52 week treatment intensifications (up to 2) in model B

First intensification in patients not eligible for metformin left sulfonylurea (SU, more common) and sitagliptin (for initial therapy with SU only) as the only two options for first intensification in model B. Efficacy data used are presented in the tables below.

Table 45: First intensification HbA_{1c} efficacy

Treatment Regimen	Vs. Placebo	Source
SU	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy
Sitagliptin 100 mg	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy

Abbreviations: HbA_{1c}, glycosylated haemoglobin; NMA, network meta-analysis; SU, sulfonylurea.

Table 46: First intensification SBP efficacy

Treatment Regimen	Vs. Placebo	Source
SU	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy
Sitagliptin 100 mg	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy

Abbreviations: NMA, network meta-analysis; SBP, systolic blood pressure; SU, sulfonylurea.

Table 47: Second intensification HbA_{1c} efficacy vs. placebo

Treatment Regimen	Vs. Placebo	Source
NPH Insulin	-1.30	Khunti et al, 2014 (129)

Abbreviations: HbA_{1c}, glycosylated haemoglobin; NPH, Neutral Protamine Hagedorn.

Table 48: Second intensification SBP efficacy vs. placebo

Treatment Regimen	Vs. Placebo	Source
NPH Insulin	-4mmol	Yale et al, 2013 (130)

Abbreviations: NPH, Neutral Protamine Hagedorn; SBP, systolic blood pressure.

5.2.6.2 Safety data for model A and model B

Safety data used in model A and for initial therapy in model B are shown in Table 49–Table 53 below. Table 54–Table 59 sets out the first and second intensification data used in model B.

52-week data for model A and initial therapy in model B

Table 49: Data used for all hypoglycaemia for 52 week comparison

Treatment vs. SU	Lower 95% CrI	OR	Upper 95% CrI	Source
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]	52 week NMA
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]	52 week NMA
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]	52 week NMA
Repaglinide 1 mg OD	[redacted]	[redacted]	[redacted]	24 week NMA for Repa 0.5-4mg TD
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]	52 week NMA
SU	[redacted]	[redacted]	[redacted]	52 week NMA

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily; OR, odds ratio; SU, sulfonylurea.

Table 50: Data used for weight at 52 weeks (Source: 52 week NMA)

Treatment vs. placebo	Lower 95% CrI	Treatment difference in weight, kg	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Pioglitazone 45 mg OD	[redacted]	[redacted]	[redacted]
Repaglinide 1 mg OD	[redacted]	[redacted]	[redacted]
Sitagliptin 100 mg OD	[redacted]	[redacted]	[redacted]
SU	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily; SU, sulfonylurea.

24-week data – for model A and initial therapy in model B

Table 51: Data used for all hypoglycaemia at 24 weeks. (Source: 24 week NMA)

Treatment vs. SU	Lower 95% CrI	OR	Upper 95% CrI
Empagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Empagliflozin 25 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 100 mg OD	[redacted]	[redacted]	[redacted]
Canagliflozin 300 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 10 mg OD	[redacted]	[redacted]	[redacted]
Dapagliflozin 5 mg OD	[redacted]	[redacted]	[redacted]
SU	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily; OR, odds ratio; SU, sulfonylurea.

Table 52: Data used for weight at 24 weeks. (Source: 24 week NMA)

Treatment vs. placebo	Lower 95% CrI	Treatment difference in weight, kg	Upper 95% CrI
Empagliflozin 10 mg OD			
Empagliflozin 25 mg OD			
Canagliflozin 100 mg OD			
Canagliflozin 300 mg OD			
Dapagliflozin 10 mg OD			
Dapagliflozin 5 mg OD			

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily.

Safety data common to both 24 and 52 week analyses – for model A and initial therapy in model B

Safety data for urinary tract infections (UTI) at 24 and 52 weeks were taken from the NMA-derived data at 24 weeks, the best of such data available.

Table 53: Data used for UTIs for all model runs

Treatment vs. placebo	Lower 95% CrI	OR	Upper 95% CrI	Source
Empagliflozin 10 mg OD				24 week NMA
Empagliflozin 25 mg OD				24 week NMA
Canagliflozin 100 mg OD				24 week NMA
Canagliflozin 300 mg OD				24 week NMA
Dapagliflozin 10 mg OD				24 week NMA
Dapagliflozin 5 mg OD				24 week NMA
Pioglitazone 45 mg OD				24 week NMA
Sitagliptin 100 mg OD				24 week NMA
Repaglinide				Assumed equivalent to placebo
SU				Assumed equivalent to placebo

Abbreviations: CrI, credible interval; NMA, network meta-analysis; OD, once daily; OR, odds ratio; SU, sulfonylurea.

Safety data for 24 and 52 week treatment intensifications (up to 2) in model B

First intensification in patients not eligible for metformin left SU (more common) and sitagliptin (for initial therapy with SU only) as the only two options for first intensification in model B. Safety data used in the model are presented in the table below.

Table 54: First intensification hypoglycaemia efficacy relative to placebo

Treatment Regimen	Vs. Placebo	Source
SU		24 week at first intensification from revised NMA for submission for empagliflozin combination therapy
Sitagliptin 100 mg		24 week at first intensification from revised NMA for submission for empagliflozin combination therapy

Abbreviations: NMA, network meta-analysis; SU, sulfonylurea.

Table 55: First intensification weight efficacy

Treatment Regimen	Vs. Placebo	Source
SU	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy
Sitagliptin 100 mg	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy

Abbreviations: NMA, network meta-analysis; SU, sulfonylurea.

Table 56: First intensification UTI efficacy relative to SU

Treatment Regimen	Vs. SU	Source
Sitagliptin 100 mg	[redacted]	52 week at first intensification from revised NMA for submission for empagliflozin combination therapy

Abbreviations: NMA, network meta-analysis; SU, sulfonylurea; UTI, urinary tract infection.

Second intensification in patients considered in model B involved treatment with NPH insulin. Safety data used in the model are presented in the tables below.

Table 57: Second intensification hypoglycaemia, NPH Insulin

Severity	Annual risk	Source
Severe	0.118	Leese et al,2003 (128)
All hypoglycaemic events	[redacted]	52 week at pooled placebo arms from revised NMA for submission for empagliflozin combination therapy
Non-severe hypoglycaemic events	0.142	All events minus severe events

Abbreviations: NMA, network meta-analysis; NPH, Neutral Protamine Hagedorn.

Table 58: Second intensification weight efficacy vs. placebo

Treatment Regimen	Vs. Placebo	Source
NPH Insulin	+0.3kg	Khunti et al, 2014 (129)

Abbreviations: NPH, Neutral Protamine Hagedorn.

Table 59: Second intensification UTIs

Treatment Regimen	Annual risk	Source
NPH Insulin	[redacted]	52 week at pooled placebo arms from revised NMA for submission for empagliflozin combination therapy

Abbreviations: NMA, network meta-analysis; NPH, Neutral Protamine Hagedorn; UTI, urinary tract infection.

Treatment related outcomes considered in both model A and model B

The UKPDS OM1 only includes time-since first diagnosis of seven diabetes-related events, and treatment-related factors like HbA_{1c} level and systolic blood pressure (SBP). Outcomes like hypoglycaemia and weight change are missing in UKPDS OM1. UKPDS OM2 is expected to at least include weight profiles when it is released. The OHEM by GDG and NICE includes these two additional treatment effects as well as treatment dropouts in its front end. Both the models (A and B) include all these, as well as an additional effect on urinary tract infections (UTIs) as found by our recent NMA. Given the small number of events in Table 26 and the fact that there is no clear pattern favouring or not favouring empagliflozin, it is not considered that these will bias the results. These additional outcomes considered are discussed in brief below.

- **Hypoglycaemia**: Hypoglycaemic events are not considered by the UKPDS model and are considered to be a short-term, treatment related AE. Therefore they are incorporated into the 'front end' only. The credible intervals for hypoglycaemia are very wide, and this is particularly the case at 24 weeks. It is suspected that this may be because the number of hypoglycaemic events is relatively low in clinical trials. As SUs are one of the main comparators of interest, it was possible to use a real world study of severe hypoglycaemic events as the baseline for severe hypoglycaemic events. Non-severe hypoglycaemic events were obtained by calculating the total number of events in the SU arm by synthesising the trials with placebo treatment arm using a binomial likelihood. The number of severe events was then taken away from this to give the baseline number of non-severe events. Relative risks in comparison to SUs were then used to calculate the probability of a patient having an event while on treatment.
- **Weight**: Weight is an important aspect in the analysis, with 7.37 kg of variation across the regimens under consideration at 52 weeks. The long term impacts of weight are included in the UKPDS OM1 and are discussed in Paragraph 5.3.2.2. However, the immediate effect of weight on the utility of overweight patients is not included in the UKPDS OM1. It has therefore been included in both front ends.

UTIs: As discussed above, 52 week data are not available and therefore 24 week relative risks compared to placebo are taken (

Table 38). The baseline risk for the placebo arm was calculated by synthesising the trials with placebo treatment arm using a binomial likelihood, baseline random effects model with predictive effects as recommended in NICE Decision Support Unit technical support document 5 (131).

Further details on how models A and B deal with the above additional treatment-related outcomes are provided in the 'Structural Details' section for each of the models A and B below.

Assumptions related to NMA missing values

In a number of cases, trials did not report specific events which are included in the model. Each is taken on a case by case basis as described below:

- SBP: SU, pioglitazone & repaglinide at 24 weeks. These treatments are not considered to have an effect on SBP and therefore their effect is set to the same as placebo.
- SBP: all treatments at 52 weeks. It was not possible to connect a network at 52 weeks, and therefore 24 week data is used where available.
- UTIs: SU, pioglitazone & repaglinide at 24 weeks. These treatments are not considered to affect the probability of a UTI and therefore their effect is set to the same as placebo.
- UTIs: all treatments at 52 weeks. It was not possible to connect a network at 52 weeks, and therefore 24 week data is used where available.
- Hypoglycaemia: repaglinide. None of the repaglinide doses have data for hypoglycaemia at 52 weeks, and the dose for which weight and HbA_{1c} data are available does not have data for hypoglycaemic events at any other time period. The only dose which does have data is repaglinide 0.5-4mg TID which reports at 24

weeks. Unfortunately the 24 week data for hypoglycaemia for all treatments is not certain with very wide credible intervals (95% CrI relative risk to placebo of 0.003 to 261.7). This data point, being the best available for this treatment, was used in both of the models (A and B).

5.2.7 Intervention and comparator cost and utility data (common to models A and B)

The review conducted for the empagliflozin combination therapy submission was updated internally, and used data by Alva *et al*, 2015 (132) wherever possible, to ensure consistency with the definitions used in the UKPDS OM1. The patient reported in Alva *et al* was also considered to be representative of the average patient at baseline in the model (57.2% male, average age of 60.25 years). Where data were not available from this source, other sources were used in line with the empagliflozin combination therapy submission and the latest NICE guidance on Type 2 diabetes.

5.2.7.1 Cost data

Prescription costs were taken from MIMS. Testing strips and lancets were added to the cost for SU, in line with the NICE T2DM guideline, and repaglinide (for which it is considered that testing would also be required). Costs for non-severe (as opposed to severe hypoglycaemia) were assumed to be negligible.

Table 60: Summary of cost data

Cost	Value	Source
Diabetes without complications	£459	Alva et al, 2015 (132)
IHD (non-fatal)	£9,767.00	Alva et al, 2015 (132)
IHD (fatal)	£3,766.00	Alva et al, 2015 (132)
MI (non-fatal)	£6,379.00	Alva et al, 2015 (132)
MI (fatal)	£1,521.00	Alva et al, 2015 (132)
Heart failure	£3,191.00	Alva et al, 2015 (132)
Heart failure (fatal)	£3,191.00	Assumption based on Alva et al, 2015 (132)
Stroke (non-fatal)	£6,805.00	Alva et al, 2015 (132)
Stroke (fatal)	£3,954.00	Alva et al, 2015 (132)
Amputation	£9,546.00	Alva et al, 2015 (132)
Fatal amputation	£9,546.00	Assumption based on Alva et al, 2015 (132)
Blindness (one eye)	£1,355.00	Alva et al, 2015 (132)
Renal failure	£35715.00	NICE Draft DM CG (126)
Fatal renal failure	£35715.00	NICE Draft DM CG (126)
In subsequent years		
IHD	£1,215.00	Alva et al, 2015 (132)
MI	£1,154.00	Alva et al, 2015 (132)
Stroke	£1,125.00	Alva et al, 2015 (132)
Heart failure	£1,473.00	Alva et al, 2015 (132)
Amputation	£1,792.00	Alva et al, 2015 (132)

Cost	Value	Source
Blindness (one eye)	£453.00	Alva et al, 2015 (132)
Renal failure	£35631.00	NICE Draft DM CG (126)
Other variables		
Hypoglycaemic event – non-severe	0	Assumption
Hypoglycaemic event – severe	£380	NICE T2DM Draft Guideline (126)
UTIs	£36	Dapagliflozin ERG (133)
SU (Gliclazide)	£68.36	MIMS March 2015 plus assumption of 0.429 testing strips per day at 29p per strip and 4p per lancet for SU and repaglinide (NICE T2DM Draft Guideline)
empagliflozin 10mg	£477.98	
empagliflozin 25mg	£477.98	
Dapagliflozin 10mg	£477.98	
Canagliflozin 100mg	£477.98	
Canagliflozin 300mg	£608.21	
Pioglitazone 45mg	£24.25	
Repaglinide	£93.40	
Sitagliptin 100mg	£433.86	
Insulin NPH	£396.21	Burslem et al 2011 (134)
Insulin glargine	£557.55	

Abbreviations: IHD, ischaemic heart disease; MI, myocardial infarction; NPH, Neutral Protamine Hagedorn; SU, sulfonylurea; UTI, urinary tract infection.

5.2.7.2 Utility data

Table 61: Summary of utility data

Utility	Value	Source
Diabetes without complications	0.72	Alva et al, 2014 (135)
IHD	-0.028	Alva et al, 2014 (135)
MI (year before)	-0.065	Alva et al, 2014 (135)
MI (prior history)	0.008	Alva et al, 2014 (135)
Heart failure	-0.101	Alva et al, 2014 (135)
Stroke	-0.165	Alva et al, 2014 (135)
Amputation	-0.172	Alva et al, 2014 (135)
Blindness in one eye	0.033	Alva et al, 2014 (135)
Renal failure	-0.263	NICE Draft CG (126)
Hypoglycaemic event (non-severe)	-0.00355	Currie et al, 2006 divided by 4 (136)
Hypoglycaemic event (severe)	-0.012	Currie et al, 2006 divided by 4 (136)
UTIs	-0.00283	Barry et al, 1997 (137)
Weight gain/loss (per unit of BMI over 25)†	+/-0.0061	Bagust & Beale, 2005 (138)

Abbreviations: BMI, body mass index; IHD, ischaemic heart disease; MI, myocardial infarction; UTI, urinary tract infection
†Weight gain/loss is captured in both models. Since the UKPDS model works with BMIs instead of weight, patients' BMI was calculated, with the utility applied if the BMI was over the threshold value of 25.

5.2.8 Structural details of model A

Figure 25 above shows a schematic representation of model A.

5.2.8.1 Details

The model is a simple one-year decision tree, which counts the costs of treatment, the costs and disutilities related to the treatment related AEs of UTIs and hypoglycaemia, and the utility/disutility of weight loss/gain over a 1-year time period. The model assumes that patients are only treated for one year. The treatment efficacies for HbA_{1c}, SBP and weight (only if weight is gained during the treatment year) are then applied to each patient's baseline data.

The UKPDS model was then run for each treatment for a full 40 year run. Summary results of these analyses were then manually copied into the results page of the model. Although these were run separately, runs on the UKPDS model remain comparable as long as the same random number seed is used for every comparison. In effect, the total modelling approach actually results in a 41 year time horizon. However some key assumptions and simplifications have been made and are highlighted in Table 62.

Approach to uncertainty

The robustness of the model was tested using sensitivity analyses. The variables and distributions used in the sensitivity analyses are defined in Table 62.

Table 62: Distributions used in 1 year base case model sensitivity analysis

Parameter	Distribution used
Baseline BMI	Normal
Baseline Height	Normal
Baseline annual risk of hypoglycaemia	Beta
Baseline annual risk of UTIs	Beta
Utility decrements for BMI, hypoglycaemia and UTIs	Gamma
Costs of Hypoglycaemia & UTIs	Gamma
Relative risk of Hypoglycaemia	Log Normal
Relative risk of UTIs	Log Normal
Weight gain/loss	Normal

Abbreviations: BMI, body mass index; UTI, urinary tract infection.

Probabilistic sensitivity analyses (PSA) were conducted to account for parameter uncertainty. A full list of the variables subjected to PSA within model 1 is provided in Table 63. The internal functionality to generate PSA by varying risk equations using bootstraps in the UKPDS model was also used. It should be noted that this does not have the functionality to vary the input parameters. In order to maintain the integrity of the model runs and remain transparent it was decided not to 'break into' the UKPDs run in order to vary these. Therefore there is some uncertainty amongst the estimates that is not captured by the PSA. Whilst the UKPDS model has the facility to carry out 999 bootstraps, this is not possible using a 32 bit PC. Therefore following advice from the UKPDS OM technical team, 500 bootstraps were used. These were then replicated in blocks of 500 across 10,000 lines, maintaining the integrity of the random number sequences by keeping like bootstrap numbers together. Ten thousand iterations of the one year decision tree were then run, with the costs and utilities of these then added to the long-term costs and utilities from the bootstrap analyses of the UKPDS model.

Table 63: Variables subjected to PSA in model 1

Baseline height men
Baseline weight men
Baseline height women
Baseline weight women
Baseline annual risk of hypoglycaemia
Baseline risk severe hypos
Baseline annual risk of UTIs
BMI utility decrement per unit
Utility decrement severe hypo
Utility decrement non-severe hypo
Utility decrement UTI
Cost severe hypo
Cost UTI
Weight efficacy for each treatment
UTI efficacy vs. placebo for each treatment
Hypoglycaemia efficacy vs. placebo for each treatment

Abbreviations: BMI, body mass index; hypos, hypoglycaemias; PSA, probabilistic sensitivity analyses; UTI, urinary tract infection.

Structural assumptions

Table 64 below summarises the major structural assumptions/ simplifications made for model A.

Table 64: Summary of structural assumptions to model A

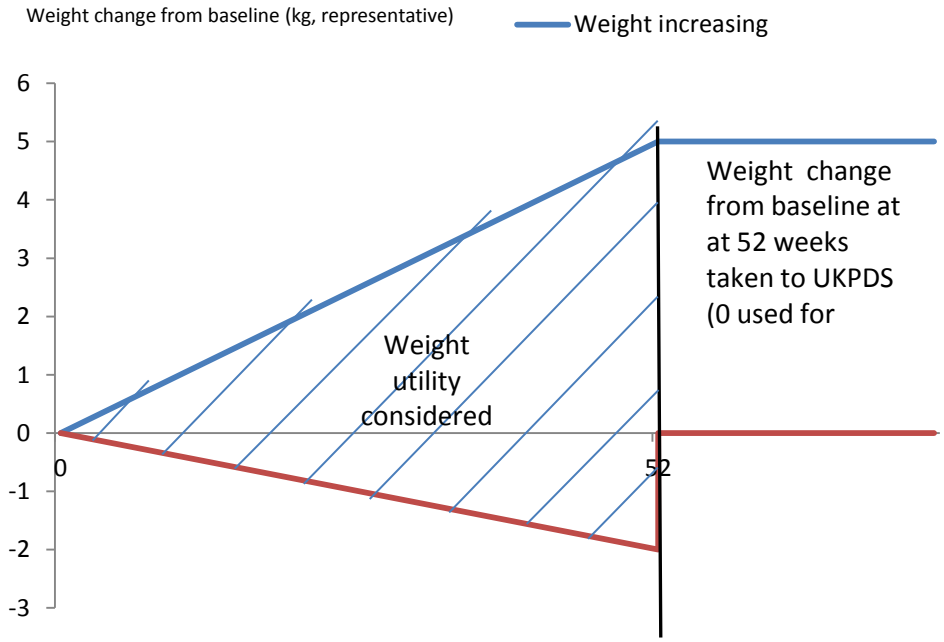
Assumption/simplification	Justification
No patients die within the first year of treatment	The treatments are all assumed to have minimal effect on immediate mortality, and that their benefits are accrued over the longer term.
No patients discontinue treatment	The model only looks at a patient being on treatment for 52 weeks. As the data in the NMA is taken from an intention to treat population and followed through to 52 weeks (24 weeks for SGLT2 comparison), the effects of discontinuation are effectively already included in the results.
Costs and quality of life not related to treatment, or treatment related AEs, are not considered in year 1	The treatments are all assumed to have minimal effect on immediate costs and quality of life other than those which are related to the treatment itself, and that their benefits are accrued over the longer term.
Patients are only treated for 1 year	This is the simplification of the model which reduced the number of assumptions required. It relies on known data from RCTs, and makes no assumption about the efficacy of the treatment in the longer term, the efficacy of subsequent line treatments and when switches take place.

Abbreviations: AE, adverse event; CPRD, Clinical Practice Research Datalink RCT; randomised controlled trial.

The following additional treatment-outcomes-related assumptions have been made for model A:

- **Hypoglycaemia**: severe and non-severe hypoglycaemic events are combined together by weighting the costs and utility decrements by the relative proportion of events at baseline. The number of hypoglycaemic events is capped at 1 per year as a simplification, and will marginally overestimate the cost effectiveness of a treatment which is more likely to result in hypoglycaemic events, such as SU. However, given the very wide credible intervals, there is a possibility of implausible results. Given that empagliflozin should have fewer hypoglycaemic events than comparators, it is considered that this is a conservative assumption, which should mean that the results marginally understate the case for empagliflozin.
- **Weight change**: a simplified approach is used for model A where weight utility is only considered during the one year of treatment. In the case of treatments where weight is reduced from baseline, as a base case, weight is considered to rebound immediately to baseline at 52 weeks (see Figure 28 below). This omits the benefits of a weight reducing therapy on long term outcomes for the period before weight rebounds to its pre-treatment level, and is therefore considered to be a very conservative approach. However, the UKPDS model only allows weight to be added into baseline, which therefore is the only option whilst maintaining a simple approach. Weight can be considered for longer periods for the utility effect by varying the 'rebound period' for weight in the base case model. By default this is set to 0 weeks, however it can be extended in order to capture some extended utility effect. The model also does not account for the utility decrement of a treatment that increases weight beyond one year. Therefore taking the example of a treatment that increases a patient's weight by 5kg, the disutility of the treatment related weight increase might be expected to continue well into the future. Given the principal comparators to empagliflozin increase weight, it is considered that this will represent a considerable reduction in the relative utility benefit of empagliflozin. Therefore, again, the cost effectiveness is expected to be underestimated.

Figure 28: Illustrative weight profile in Model A



Abbreviations: UKPDS, United Kingdom Prospective Diabetes Study Outcomes Model version 1.

5.2.9 Structural details of model B

Figure 26 shows a schematic representation of model B.

5.2.9.1 Details

Model B takes into explicit account treatment intensification as well as additional outcomes like the effects of hypoglycaemia, UTI, and weight change in its front-end to the UKPDS OM1, similar to the OHEM from the GDG and NICE.

A CPRD-derived real-world cohort of 9,211 patients is used to provide extensive, directly applicable and credible patient-level baseline data. These are then run through the UKPDS OM1 for 1 cycle without discounting. The results from the UKPDS OM1 then are taken to the front end workbook.

Here, a Kaplan-Meier (KM) approach, validated with the UKPDS OM team at Oxford (and informed by their published work) (127), is used to determine the survival as well as the occurrence of seven diabetes-related events in the UKPDS model. The default threshold chosen for both of these is a probability of 0.5; model B also allows for testing scenarios to change this threshold. For example, if the probability of mortality in year 1, derived from the UKPDS model is 0.01 and that in year 2 is 0.06, the probability of survival in year 1 is 0.99 (=1-0.01) and that in year 2 (conditional on year 1) is 0.93 (=0.99x(1-0.06)). As this probability is above the chosen threshold (0.5 as default), this particular patient is considered alive at year 2 and their costs and QALYs are counted in full (with discount applied), Similarly, for the events, the time to event is then calculated and the duration of diabetes increased by a year in preparation for the next set of extensive patient-level data to feed into the next run of the UKPDS OM1.

Additional events related to (severe and non-severe) hypoglycaemias, UTIs, and treatment discontinuations are modelled using a random number sequence. This is because the alternative KM approach could lead to a clustering of the additional events occurring towards the later runs of the model. As a more uniform but random distribution of such events was considered more plausible in real life, the random effects model was chosen for these additional events.

A treatment effect is also applied for HbA_{1c}, SBP and weight for each patient. Treatment switching to first intensification is considered based on their HbA_{1c} level as compared to a customisable HbA_{1c} lower threshold (the default in the OHEM is 7.5%).

Outcomes (QALYs) and costs from the UKPDS model and related to hypoglycaemias (severe and non-severe), weight change (based on effect on BMI), and UTIs is then calculated for that year, taking into account the survival status of each patient determined in the steps above, as well as the discount applied.

For years 2 through 40, the same steps as above are repeated with the only difference being that the treatment switches can be also for the second intensification therapy among treatment strategies considered in the model for those patients already on the second intensification therapy. Once second intensification (NPH insulin) is reached, patients are expected to stay on this therapy (aligned with the OHEM).

Outcomes and costs are accumulated over the 40 runs of the UKPDS and front end models and reported once all 6 treatment strategies considered in the model have finished running.

Approach to uncertainty

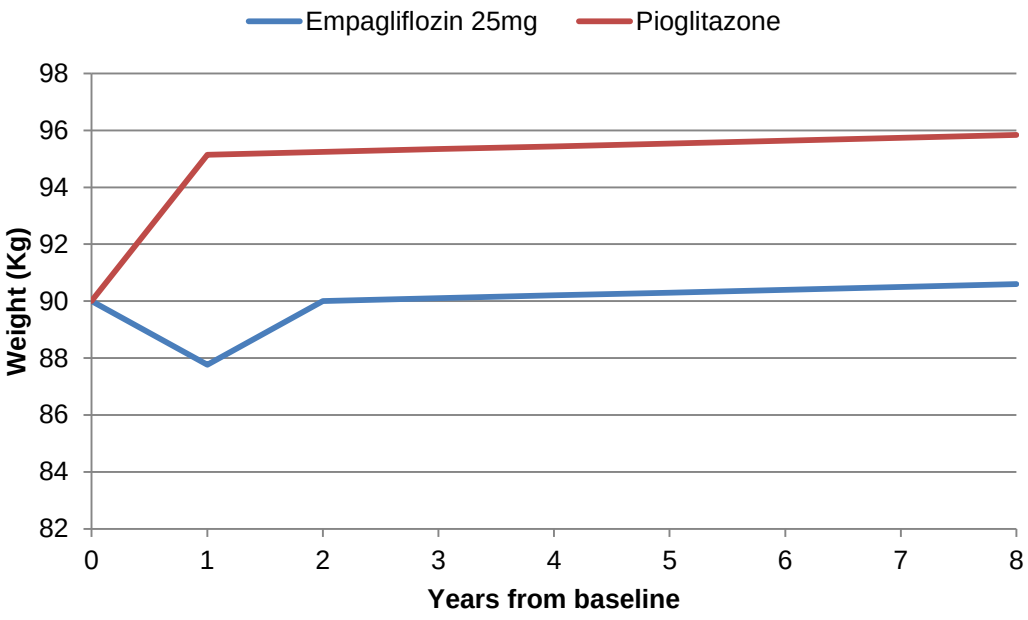
As explained in section 5.2.3.2 above on the limitations of this model, one of the difficulties in incorporating the capacity to deal with individual data from 9,211 patients and 40 1-yearly runs of the both the UKPDS OM1 and the front end for model B, was the computational load involved in incorporating bootstraps in the full analysis. Although the front end model is equipped to capture the bootstrapped results from the UKPDS OM1, this is only practical for shorter runs for the model since, as also explained above, this would increase the duration of run of the whole model by 3 to 4 fold from the existing nearly 48 hours for a full run for deterministic results. Model B, however makes full use of the internal loops (10,000 such for each patient) in the UKPDS model to reduce the Monte Carlo error as discussed above in section 5.2.1.1.

Structural assumptions

The following treatment-outcomes-related assumptions have been made for model B:

- **Weight change**: considered to rebound to baseline after one cycle in a similar way to that considered in the OHEM. This is almost certainly a conservative assumption, because although there may be a weight rebound, it is unlikely it occurs as quickly as 1 year, particularly whilst a patient is still on a treatment. Although Figure 10 shows that the weight loss of empagliflozin relative to placebo at 76 weeks remains in line with the weight loss at 52 weeks suggesting that weight loss might at least remain whilst the patient is on treatment; in using the 52-week data and a rapid weight rebound factor, we will be underestimating the cost-effectiveness of empagliflozin. As with the OHEM, weight gained due to treatment is not considered to be lost again. For all treatments after any gain/rebound, weight is considered to rise by 0.1 kg per year (the same annual weight gain as in the NICE draft guidelines and the NICE obesity guideline) (139). Figure 29 below shows an illustrative example of a 90kg patient at baseline.

Figure 29: Illustrative weight profile in Model A (90kg patient at baseline)



5.2.10 Results from model A

5.2.10.1 Model A base case results

Table 65 presents the costs and QALYs associated with different treatments in model A, using both 52 week and 24 week data.

Table 65: Model A results – costs and QALYs

Treatment	Drug costs	Hypo Cost	UTI Cost	UKPDs Complication Cost	Total costs	UKPDS Utility	Hypo utility	UTI Utility	Weight utility	Total QALYs
52 week Comparison										
Empagliflozin 25mg	[redacted]									
Empagliflozin 10mg	[redacted]									
Pioglitazone 45mg	[redacted]									
Repaglinide 1mg	[redacted]									
Sitagliptin 100mg	[redacted]									
Sulfonylurea	[redacted]									
24 week Comparison										
Empagliflozin 25mg	[redacted]									
Empagliflozin 10mg	[redacted]									
Canagliflozin 100mg	[redacted]									
Canagliflozin 300mg	[redacted]									
Dapagliflozin 5mg	[redacted]									
Dapagliflozin 10mg	[redacted]									

Abbreviations: hypo, hypoglycaemia; QALY, quality-adjusted life year; UKPDS, United Kingdom Prospective Diabetes Study; UTI, urinary tract infection.

With 52-week data

Table 66: Model A ICERs for 52 week treatment (comparisons vs. empagliflozin 25mg)

	Incremental Costs	Incremental QALYs	ICER
Pioglitazone	£283	0.050	£5,634
SU	£278	0.042	Extendedly dominated by pioglitazone & Empa 25
Repaglinide	£253	0.041	Extendedly dominated by pioglitazone & Empa 25
Empagliflozin 10mg	-£21	0.007	Dominated by Empa 25
Sitagliptin	-£80	0.036	Dominated by Empa 25

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SU, sulfonylurea.

Table 67: Model A ICERs for 52 week treatment (comparisons vs. empagliflozin 10 mg)

	Incremental Costs	Incremental QALYs	ICER
Pioglitazone	£304	0.043	£7,015
SU	£299	0.035	Extendedly dominated by pioglitazone & Empa 25
Repaglinide	£274	0.034	Extendedly dominated by pioglitazone & Empa 25
Empagliflozin 25mg	£21	-0.007	Dominates Empa 10
Sitagliptin	-£59	0.029	Dominated by Empa 10

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SU, sulfonylurea.

With 24 week data

Table 68: Model A ICERs for 24 week treatment (comparisons vs. empagliflozin 25mg)

	Incremental Costs	Incremental QALYs	ICER
Canagliflozin 100mg	£26	-0.008	Dominates Empa 25
Empagliflozin 10mg	-£16	0.007	Dominated by Empa 25
Dapagliflozin 10mg	-£18	0.010	Dominated by Empa 25
Dapagliflozin 5mg	-£28	0.012	Dominated by Empa 25
Canagliflozin 300mg	-£38	-0.029	£1,292 (bottom left quadrant)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 69: Model A ICERs for 24 week treatment (comparisons vs. empagliflozin 10mg)

	Incremental Costs	Incremental QALYs	ICER
Canagliflozin 100mg	£43	-0.015	Dominates Empa 10
Empagliflozin 25mg	£16	-0.007	Dominates Empa 10
Dapagliflozin 10mg	-£1	0.004	Dominated by Empa 10
Dapagliflozin 5mg	-£12	0.005	Dominated by Empa 10
Canagliflozin 300mg	-£21	-0.036	£596 (bottom left quadrant)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.2.10.2 Summary of base case results from model A

By analysing the incremental costs, QALYs and ICERs (Table 66), the base case analysis shows the following:

- Using 52 week data, empagliflozin 25mg and 10mg are cost effective treatment options at a willingness to pay of £20,000 compared to pioglitazone, sulfonylurea and repaglinide.
- Empagliflozin dominates sitagliptin, which was chosen as a proxy for the DPP-4 class with both 52 week and 24 week data.
- Compared to the other SGLT-2 inhibitors dapagliflozin and canagliflozin, empagliflozin dominates both doses of dapagliflozin but is dominated by canagliflozin 100mg. However the differences within the class are very small.

The cost effectiveness for empagliflozin vs. its comparators is largely driven by the results from the UKPDS outcomes model with the additional cost of the treatment partially offset by long term reductions in complications costs from the UKPDS model. There is also an additional element of utility derived from the UKPDS model for empagliflozin in comparison to the other comparators at 52 weeks.

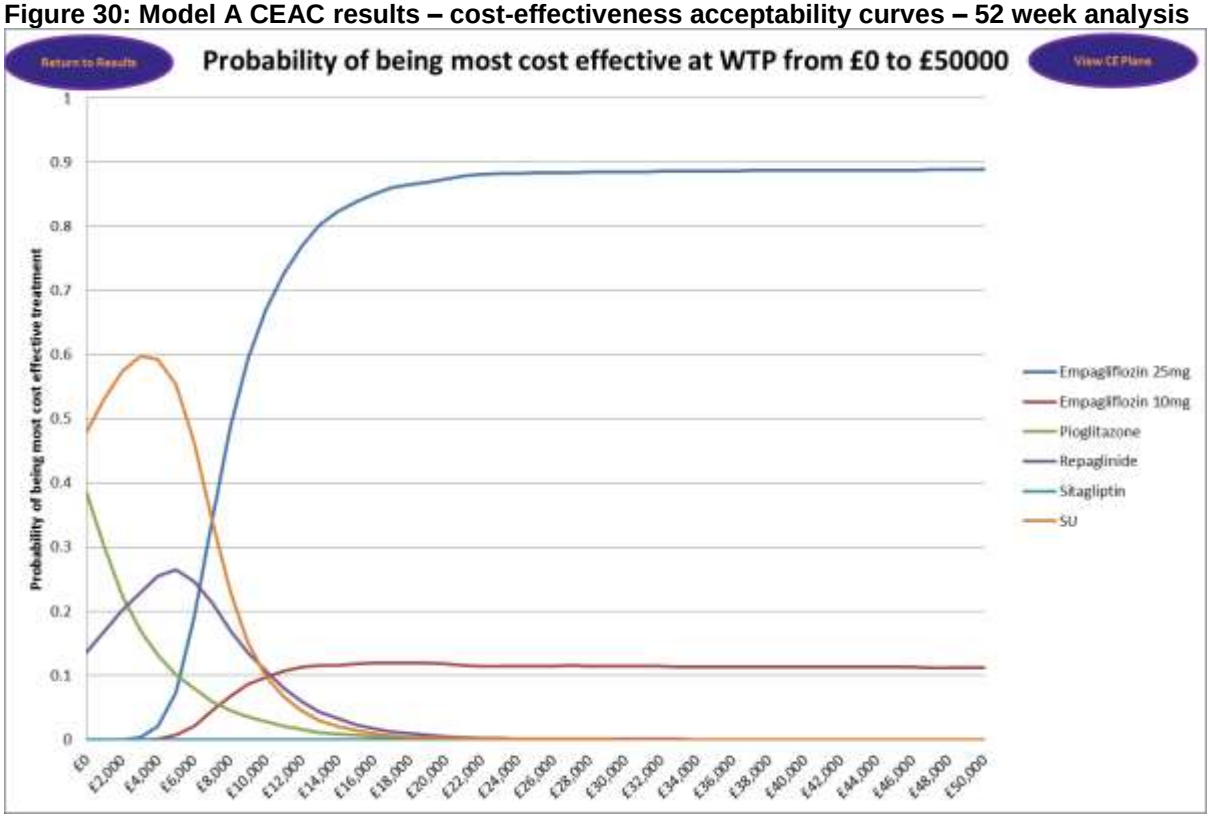
5.2.10.3 Model A probabilistic analysis results

With 52-week data

The results of probabilistic analysis in model A are presented as cost-effectiveness acceptability curves (CEACs) and cost-effectiveness planes (CEPs).

The CEAC generated for the base case analysis demonstrates that at a willingness-to-pay (WTP) threshold of £20,000, empagliflozin 25mg has an 87.5% likelihood of being the most cost effective treatment option, whilst empagliflozin 10mg has an 11.75% chance of being the most cost effective treatment (Figure 30). At a WTP threshold of £30,000, these figures change to 88.5% and 11.5% respectively.

Figure 30: Model A CEAC results – cost-effectiveness acceptability curves – 52 week analysis



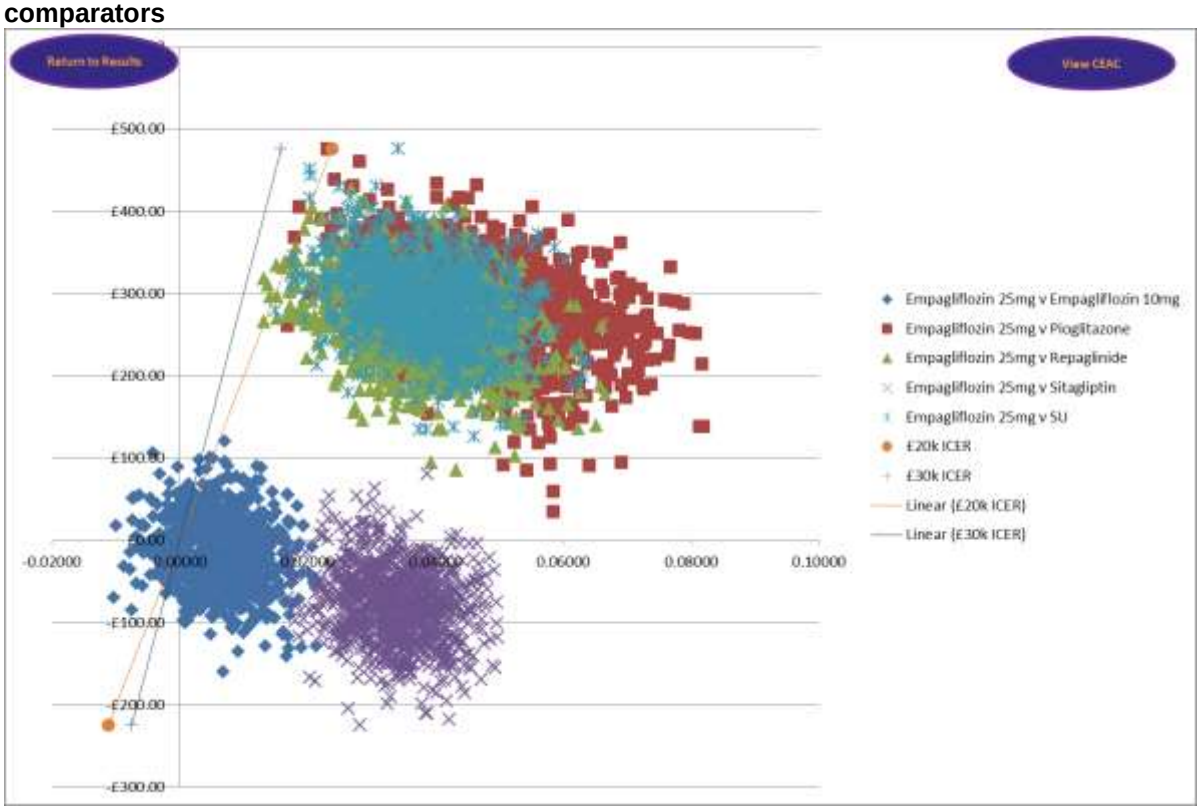
Abbreviations: CEAC, cost-effectiveness acceptability curve; SU, sulfonylurea; WTP, willingness-to-pay

The cost-effectiveness plane generated for empagliflozin 25mg vs. 52 week comparators demonstrated that in almost all simulations empagliflozin is a cost-effective treatment option at a WTP of £20,000 per QALY (Figure 31 and Table 70).

Table 70: Percentage of simulations that empagliflozin 25mg is cost effective against 52 week comparators

Comparator	%
Empagliflozin 10mg	88.2
Pioglitazone	99.8
Repaglinide	99.4
Sitagliptin	100.0
Sulfonylurea	99.6

Figure 31: Model A results - cost-effectiveness plane - empagliflozin 25mg vs. 52 week comparators



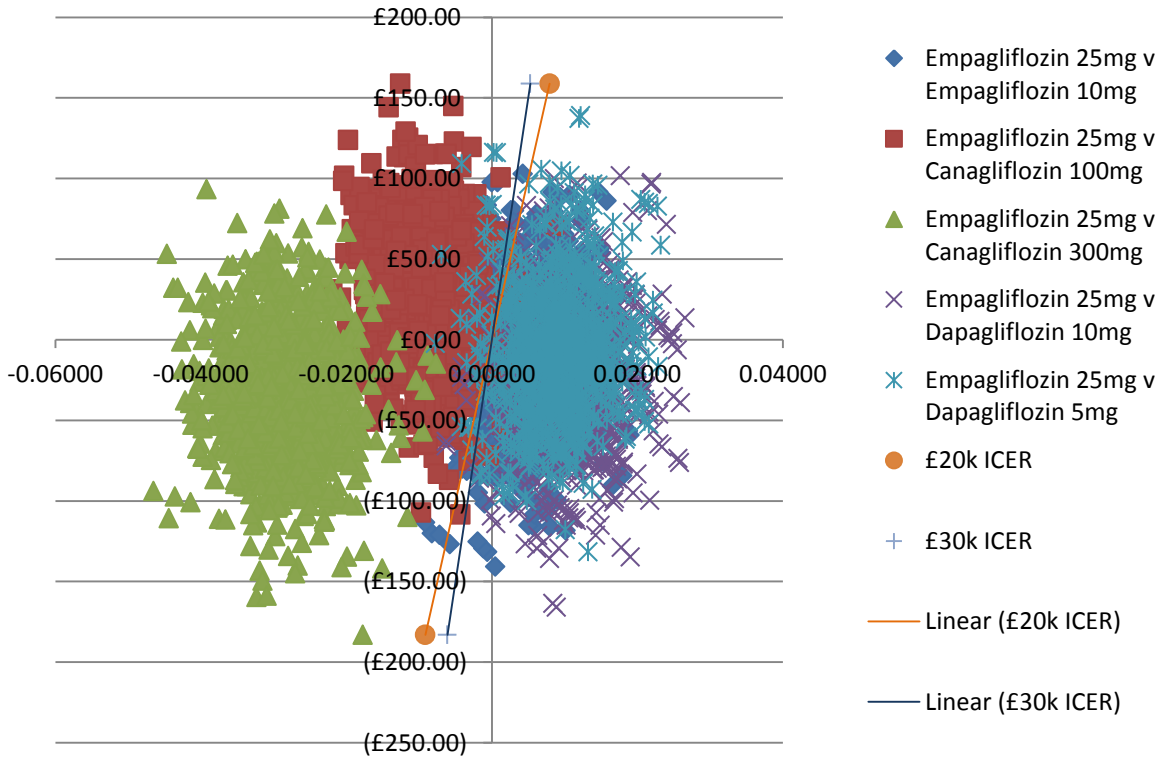
Abbreviations: ICER, incremental cost-effectiveness ratio; SU, sulfonylurea.

With 24 week data

The results are presented as CEPs and CEACs.

The CEAC generated for the base case analysis demonstrates that at a WTP threshold of £20,000, empagliflozin is not the most cost effective treatment. However, as can be seen from the CEP in Figure 32, the results are all heavily clustered, and the actual differences between treatments are very small. It could therefore be misleading to view these results on a CEAC.

Figure 32: 24 week cost effectiveness plane



Abbreviations: ICER, incremental cost-effectiveness ratio.

5.2.11 Results from model B

Costs and QALYs derived from model B are presented in Table 71 below.

5.2.11.1 With 52-week data

Model B results with 52 week data are shown in Table 72.

5.2.11.2 With 24 week data

Model B results with 24 week data are shown in Table 73.

Table 71: Model B results – costs and QALYs

Treatment			Costs						QALYs					
Initial	**1st Intns**	**2nd Intns**	**UKPDS. mn**	**Rx**	**AE.total**	**AE. HypNS**	**AE.HypS**	**AE.UTI**	**UKPDS. mn**	**Rx (BMI)**	**AE.total**	**AE. HypNS**	**AE.HypS**	**AE.UTI**
52 week results														
EMPA 25mg OD	SU	NPH Insulin	[redacted]											
EMPA 10mg OD	SU	NPH Insulin	[redacted]											
PIO 45mg od	SU	NPH Insulin	[redacted]											
REPA 1mg od	SU	NPH Insulin	[redacted]											
SITA 100mg OD	SU	NPH Insulin	[redacted]											
SU	Gliptin	NPH Insulin	[redacted]											
24 week results														
EMPA 25mg OD	SU	NPH Insulin	[redacted]											
EMPA 10mg OD	SU	NPH Insulin	[redacted]											
CANA 300mg OD	SU	NPH Insulin	[redacted]											
CANA 100mg OD	SU	NPH Insulin	[redacted]											

Treatment			Costs						QALYs					
Initial	**1st Intns**	**2nd Intns**	**UKPDS. mn**	**Rx**	**AE.total**	**AE. HypNS**	**AE.HypS**	**AE.UTI**	**UKPDS. mn**	**Rx (BMI)**	**AE.total**	**AE. HypNS**	**AE.HypS**	**AE.UTI**
DAPA 10mg od	SU	NPH Insulin												
DAPA 5mg od	SU	NPH Insulin												

Abbreviations: AE, adverse event; BMI, body mass index; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; HypS, severe hypoglycaemia; Intns, intensification; mn, mean; NPH, Neutral Protamine Hagedorn; OD, once daily; PIO, pioglitazone; QALY, quality-adjusted life year; REPA, repaglinide; RX, treatment; SITA, sitagliptin, SU, sulfonylurea; UKPDS, United Kingdom Prospective Diabetes Study; UTI, urinary tract infection.

Table 72: Model B results – 52 week ICERs

Treatment			Costs	QALYs	Incremental Costs	Incremental QALYs	ICERs
Initial	**1st.Intns**	**2nd.Intns**	**Cost.mn**	**QALY.mn**	**iCost.mn**	**iQALY.mn**	**ICER.mn**
EMPA 25mg od	SU	NPH Insulin	[redacted]	[redacted]	2834.03	0.060972714	46480.27
EMPA 10mg od	SU	NPH Insulin	[redacted]	[redacted]	2836.63	0.05573786	50892.26
PIO 45mg od	SU	NPH Insulin	[redacted]	[redacted]	Baseline	Baseline	Baseline
REPA 1mg od	SU	NPH Insulin	[redacted]	[redacted]	634.77	0.025040864	25349.33
SITA 100mg od	SU	NPH Insulin	[redacted]	[redacted]	2503.70	0.015274163	163917.49
SU	Gliptin	NPH Insulin	[redacted]	[redacted]	1526.77	0.012549491	121660.18

Abbreviations: EMPA, empagliflozin; ICER, incremental cost-effectiveness ratio; iCost,incremental cost; Intns, intensification; iQALY, incremental QALY; mn, mean; NPH, Neutral Protamine Hagedorn; OD, once daily; PIO, pioglitazone; QALY, quality-adjusted life year; REPA, repaglinide; SITA, sitagliptin, SU, sulfonylurea.

Table 73: Model B results – 24 week ICERs

Treatment			Costs	QALYs	Incremental Costs	Incremental QALYs	ICERs
Initial	**1st.Intns**	**2nd.Intns**	**Cost.mn**	**QALY.mn**	**iCost.mn**	**iQALY.mn**	**ICER.mn**
EMPA 25mg od	SU	NPH Insulin	[redacted]	[redacted]	45.98	0.021168697	2171.94
EMPA 10mg od	SU	NPH Insulin	[redacted]	[redacted]	67.89	0.006903836	9834.08
CANA 300mg od	SU	NPH Insulin	[redacted]	[redacted]	969.93	0.055863169	17362.69
CANA 100mg od	SU	NPH Insulin	[redacted]	[redacted]	1.29	0.033311031	38.85
DAPA 10mg od	SU	NPH Insulin	[redacted]	[redacted]	Baseline	Baseline	Baseline
DAPA 5mg od	SU	NPH Insulin	[redacted]	[redacted]	42.88	0.001347048	31835.82

Abbreviations: EMPA, empagliflozin; ICER, incremental cost-effectiveness ratio; iCost,incremental cost; Intns, intensification; iQALY, incremental QALY; mn, mean; NPH, Neutral Protamine Hagedorn; OD, once daily; PIO, pioglitazone; QALY, quality-adjusted life year; REPA, repaglinide; SITA, sitagliptin, SU, sulfonylurea.

5.2.11.3 Summary of results from model B

Model B results show that:

- With 52 week data, at the end of 40 years, pioglitazone is the cheapest option. Compared to this:
    - Repaglinide has the most favourable ICER, at £25,349/QALY.
    - The second and third most favourable ICERs are for empagliflozin 25mg and empagliflozin 10mg (at £46k/QALY and £50k/QALY respectively).
    - While sulfonylurea has the second highest ICER (£121k/ QALY), sitagliptin has the least favourable ICER at around £164k/QALY.
- With 24 week data, at the end of 40 years, dapagliflozin 10mg is the cheapest, but with just £1.29 difference versus canagliflozin 100mg.
    - Canagliflozin 100mg also has the most favourable ICER in this case, at just £38.85/QALY.
    - Empagliflozin 25mg and 10mg have the next most favourable ICERs at £2,172/QALY and £9,834/QALY respectively.
    - While dapagliflozin 5mg has the second highest ICER (£32k/QALY), canagliflozin 300mg has the least favourable ICER at (£172k/QALY).

In model B, as for model A, results are driven to a large extent by the outcomes and costs from the UKPDS model. However, please see the fuller discussion in section 5.2.12.2 below to provide context for these results that help interpret their significance in this decision context.

5.2.12 Discussion of results from models A and B

5.2.12.1 Model A discussion

- Using 52 week data, empagliflozin 25mg and 10mg are cost effective treatment options at a willingness to pay of £20,000 compared to pioglitazone, sulfonylurea and repaglinide.
- Empagliflozin dominates sitagliptin, which was chosen as a proxy for the DPP-4 class.
- Compared to the other SGLT-2 inhibitors dapagliflozin and canagliflozin, empagliflozin dominates both doses of dapagliflozin but is dominated by canagliflozin 100mg. However the differences within the class are very small.

Care should be taken in interpreting the results of the 24 week analysis. The differences between the treatments that are inputted into the models are minimal, and therefore the differences in outputs are also small. Unfortunately data were not available for all SGLT-2 inhibitors at 52 weeks, and results may have been different if this data was available. Notwithstanding this, it is likely that any comparison within the current treatments in the class is likely to result in clustered results.

5.2.12.2 Model B discussion

Model B illustrates two important points:

1. The results are largely consistent with those from the OHEM used by NICE in their recent evaluation of therapies for type 2 diabetes, with pioglitazone coming out as the most cost effective option.
2. The results establish more favourable ICERs for empagliflozin than most of the other comparators with 52 week data (even though the efficacy of SU is overestimated in such models, see Figure 27). Model B also demonstrates that empagliflozin is at least as cost effective as the other SGLT-2 inhibitors it was compared with using best available (24 week) data.

A few important points help validate the results from model A and explain important differences in the results seen in model B compared with the results from model A:

1. The 1-yearly runs of the UKPDS model for 40 years (in model B) yield UKPDS-related costs that are about half the magnitude of the costs of derived from 40-year composite run of the UKPDS model (in model A); £7k vs. £14k absolute values across the 6 initial treatments.
2. For the UKPDS-derived costs, the 52 week runs of models A and B are directionally consistent (i.e. the order of the results is the same). This provides an important validation of the two models.
3. Model B considers the full 40-year costs of treatment and additional costs (e.g. hypoglycaemias, weight changes, and UTIs), whereas model A only considers one-year treatment costs of a single treatment. Hence, in the final results, the treatment cost differences are between £24.25 and £477.98 for model A, whereas these costs range from £993.91 to £3,894.39 for model B using 52 week data. These also are largely directionally consistent.
4. QALYs derived from the UKPDS runs for models A and B also agree directionally, although the actual differences are very small. Weight and hypoglycaemia-related costs also lead to very small differences in QALYs.

The ICERs for empagliflozin are overestimated in model B, due to a combination of the underestimate of the UKPDS cost differences and a larger estimate of treatment cost differences in model B compared with model A, as well as the small differences in QALYs. However, this more rigorous effort to account for treatment intensification and additional treatment effects confirms the UKPDS-derived components of the results seen in model A.

5.2.13 Conclusion from pharmacoeconomic evaluations

Pharmacoeconomic evaluations of diabetes therapies are a closely contested area, with a number of comparators, close treatment costs and even closer QALYs.

Within this scenario, using a two-pronged approach, one simple (model A) and the other closer the recent OHEM from the GDG and NICE (model B) we have demonstrated that empagliflozin is cost effective and that the direction of results is consistent even with more rigorous modelling.

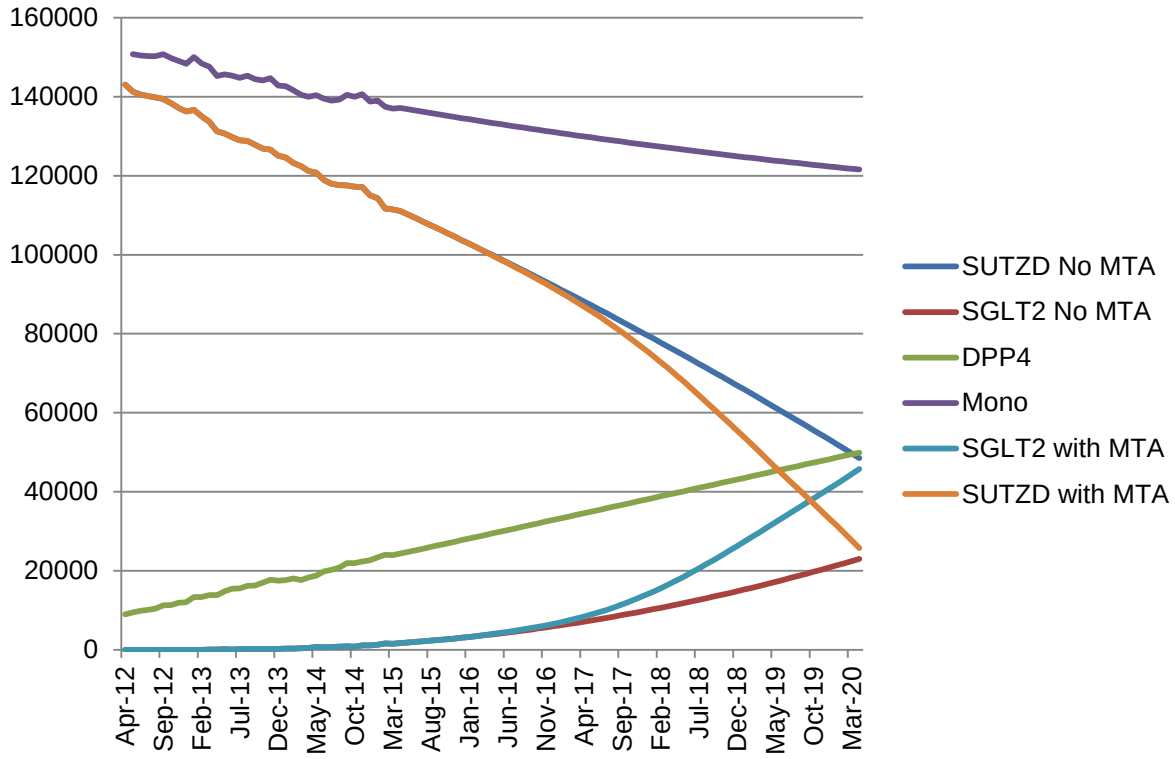
6. Wider NHS Implications

6.1 Budget Impact

6.1.1 Estimated patient numbers

Figure 33 shows the predicted uptake of monotherapy in diabetes (excluding metformin and insulin) including that of the SGLT-2 class in a world with and a world without the NICE SGLT-2 MTA. It is anticipated that the majority of this growth would come from patients who are currently on, or would otherwise be prescribed a SU or pioglitazone and who are overweight. The uptake is generated by running OLS regressions and choosing the best model by a backwards stepwise approach. It is anticipated that positive recommendation from NICE would increase the rate of this switch. The rate of increase in growth is an assumption and is based on a gradual increase from the current rate to doubling of the current rate over the duration of the analysis.

Figure 33: Predicted uptake of monotherapy in diabetes



Abbreviations: DPP4, dipetidyl-peptidase 4; mono, monotherapy; MTA, multiple technology appraisal; SGLT2, sodium-glucose co-transporter-2; SUTZD, sulfonylurea and thiazolidinedione combination.
Source (April 2012 to March 2015): Mullard M, 2015 (51).

Table 74 shows the number of patients expected to require treatment each year on monotherapy, excluding metformin and insulin. The decline follows the modelled path of decline of this population since April 2012.

Table 74: Number of patients requiring treatment each year

	2016	2017	2018	2019	2020
Monotherapy excluding metformin & insulin	133,357	129,926	126,820	124,030	121,548

Estimates of the relative market share amongst the selected monotherapy treatments are shown in Table 75.

Table 75: Estimated market share without NICE SGLT-2 MTA

Treatment	Current	Year				
		2016	2017	2018	2019	2020
SU/TZD	111,426	99,939	88,159	75,677	62,477	48,553
SGLT-2	1,548	3,940	7,172	11,431	16,722	23,047
DPP-4	23,990	29,478	34,595	39,712	44,830	49,948
Total	136,964	133,357	129,926	126,820	124,030	121,549

Abbreviations: MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; DPP-4, dipeptidyl-peptidase 4; SGLT-2, sodium-glucose co-transporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

Table 76: Estimated market share with NICE SGLT-2 MTA

Treatment	Current	Year				
		2016	2017	2018	2019	2020
SU/TZD	111,426	99,832	86,881	69,613	48,136	25,801
SGLT-2	1,548	4,047	8,449	17,495	31,064	45,800
DPP-4	23,990	29,478	34,595	39,712	44,830	49,948
Total	136,964	133,357	129,926	126,820	124,030	121,549

Abbreviations: MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; DPP-4, dipeptidyl-peptidase 4; SGLT-2, sodium-glucose co-transporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

6.1.2 Current treatment costs

Table 77 shows the estimated annual cost per patient.

Table 77: Estimated annual per-patient cost of comparators

Treatment	Cost/patient
Sulfonylurea	£68.36
Pioglitazone	£24.25
Sitagliptin	£433.86
SGLT-2 (proxy empagliflozin)	£477.98

Abbreviations: SGLT-2, sodium-glucose co-transporter-2.

Table 78 shows the estimated cost of monotherapy in England and Wales based on current market share outlined in Table 75.

Table 78: Estimated cost of monotherapy in England and Wales based on current projections

Treatment	Year				
	2016	2017	2018	2019	2020
SU/TZD	£6,390,999	£5,637,680	£4,839,468	£3,995,342	£3,104,916
SGLT-2	£1,883,241	£3,428,073	£5,463,789	£7,992,782	£11,016,005
Total	£8,274,240	£9,065,752	£10,303,258	£11,988,123	£14,120,921

NB smaller comparators excluded, DPP-4 inhibitors not predicted to change uptake so not included.
Abbreviations: DPP-4, dipeptidyl-peptidase 4; SGLT-2, sodium-glucose co-transporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

6.1.3 Impact on NHS budget

Table 79 shows the estimated overall budget impact as a result of NICE guidance on empagliflozin. However it should be noted that only treatment costs are included in this analysis, and therefore it can be expected that as demonstrated in the analysis there will be long term cost offsets.

Table 79: Estimated overall budget impact as a result of NICE guidance on the SGLT-2 class

Treatment	Year				
	2016	**2017**	**2018**	**2019**	**2020**
SU/TZD weighted combination	£6,384,157	£5,555,953	£4,451,682	£3,078,249	£1,649,948
SGLT-2 class	£1,934,385	£4,038,453	£8,362,260	£14,847,971	£21,891,484
Total	£8,318,542	£9,594,406	£12,813,942	£17,926,220	£23,541,432
Annual net budget impact	£44,301	£528,654	£2,510,684	£5,938,097	£9,420,511
Cumulative net budget impact	£44,301	£572,955	£3,083,639	£9,021,735	£18,442,247

Abbreviations: NICE, National Institute for Health and Care Excellence; SGLT-2, sodium-glucose co-transporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal (MTA)

Diabetes (type 2) - canagliflozin, dapagliflozin and empagliflozin (monotherapy) [ID756]

Janssen Submission

July 10th 2015

(Update of June 15th 2015)

Abbreviations

ABCD	Association of British Clinical Diabetologists
ACE-i	Angiotensin Receptor Blocker inhibitor
ADA	American Diabetes Association
AE	Adverse Event
AHA	Anti-Hyperglycaemic Agent
ANCOVA	Analysis of covariance
ARB	Angiotensin Receptor Blocker
AWMSG	All Wales Medicines Strategy Group
BDR	Background Diabetic Retinopathy
BID	Twice daily
BIM	Budget Impact Model
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CANA	Canagliflozin
CANTATA-M	CANagliflozin Treatment and Trial Analysis - Monotherapy
CANVAS	Canagliflozin CardioVascular Assessment Study
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CoDHY	Consensus in Diabetes, Obesity, and Hypertension
COPD	Chronic Obstructive Pulmonary Disease
CR	Clinical Study Report
CrCl	Creatinine clearance
CrI	Credible Interval
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DFI	Diabetic Foot Infection
DFU	Diabetic Foot Ulcer
DIC	Deviance Information Criterion
DMO	Diabetic Macular Oedema
DPP-4	Dipeptidyl peptidase-4
DPP-4-i	Dipeptidyl peptidase-4-inhibitor
DSA	Deterministic Sensitivity Analysis
DSP	Diastolic blood pressure
DUK	Diabetes UK
DXA	Dual-energy X-ray absorptiometry
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
FBG	Fasting Blood Glucose
FE model	Fixed Effects model
FPG	Fasting plasma glucose
FRG	Familial Renal Glucosuria
FR-MMTT	Frequently Sampled Mixed Meal Tolerance Test
GI	Gastro-intestinal
GLP-1	Glucagon-like peptide-1 agonists
GMI	Genital Mycotic Infection
GMM	Growth Mixture Model
H2H	Head-to-head
HbA1c	Haemoglobin A1c
HCP	Healthcare Professional

HRG	Healthcare Resource Group
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
IR	Immediate Release
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-To-Treat
IVRS	Interactive Web Response System
LE	Life Expectancy
LEA	Lower Extremity Amputation
LOCF	Last Observation Carried Forward
LOS	Length of Stay
LPA	Latent Profile Analysis
LS	Least Square
MAA	Market Authorisation Application
MACE	Major Adverse Cardiovascular Events
MCMC	Markov Chain Monte Carlo
MDQ	Mood Disorder Questionnaire
MET	Metformin
MET+SU	Metformin and a sulfonylurea
MET+TZD	Metformin and a thiazolidinedione
MI	Myocardial Infarction
mITT	Modified Intention-To-Treat
MMRM	Mixed Model Repeated Measures
MoA	Mechanism of action
MR	Modified release
MTA	Multiple technology appraisal
NDA	National Diabetes Audit
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NMA	Network Meta-Analysis
NPH	Neutral Protamine Hagedorn
NR	Not Reported
NYHA	New York Heart Association
OAD	Oral anti-diabetic drug
OAD	Oral Anti-Diabetic
OD	Once daily
PBO	Placebo
PbR	Payment by Results
PCI	Percutaneous Coronary Intervention
PDMS	Prediabetes and the Metabolic Syndrome Congress
PP	Per Protocol
PPG	Post prandial glucose
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcome
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral Vascular Disease
QALY	Quality Adjusted Life Year
OD	Once daily
QOF	Quality and Outcomes Framework
QW	Once weekly
RCT	Randomised controlled trial
RE model	Random Effects model

RTg	Renal Threshold for Glucose
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT	Sodium glucose co-transporter
SGLT-i	Sodium glucose co-transporter inhibitor
SLR	Systematic Literature Review
SMBG	Self-Monitoring Blood Glucose
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SU	Sulfonylurea
SUCRA	Surface Under the Cumulative Ranking
T2DM	Type 2 Diabetes Mellitus
TDS	Third Three times daily
THIN	The Health Information Network
TTO	Time Trade Off
Tx	Treatment
TZD	Thiazolidinediones
UGE	Urinary glucose excretion
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary tract infection
VVC	Vulvovaginal candidiasis
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WTP	Willingness to Pay
YLL	Years of Life Lost

1. Executive summary

Overview

Canagliflozin (Invokana®, Janssen-Cilag) is an orally administered selective sodium-glucose co-transporter-2 inhibitor (SGLT-2-i), indicated for the treatment of type 2 diabetes mellitus (T2DM) either as monotherapy or in combination with other glucose-lowering medicinal products including insulin. Canagliflozin is available in two doses, 100 mg and 300 mg given as a once daily (od) dose at an annual cost of £476.93 and £608.21, respectively (1). Due to its efficacy, tolerability and simple od dosing regimen, adherence to canagliflozin is proven to be good with a high proportion of patients remaining on treatment after one year (2).

The recommended starting dosage of canagliflozin is 100 mg od. The higher dose of 300 mg od is reserved for use in patients who tolerate canagliflozin 100 mg od, yet do not achieve target HbA1c reduction and are in need of tighter glycaemic control [redacted]. Data indicates that [redacted] of patients in the UK currently on canagliflozin are receiving the 100 mg dose, with the remainder receiving the canagliflozin 300 mg dose (3).

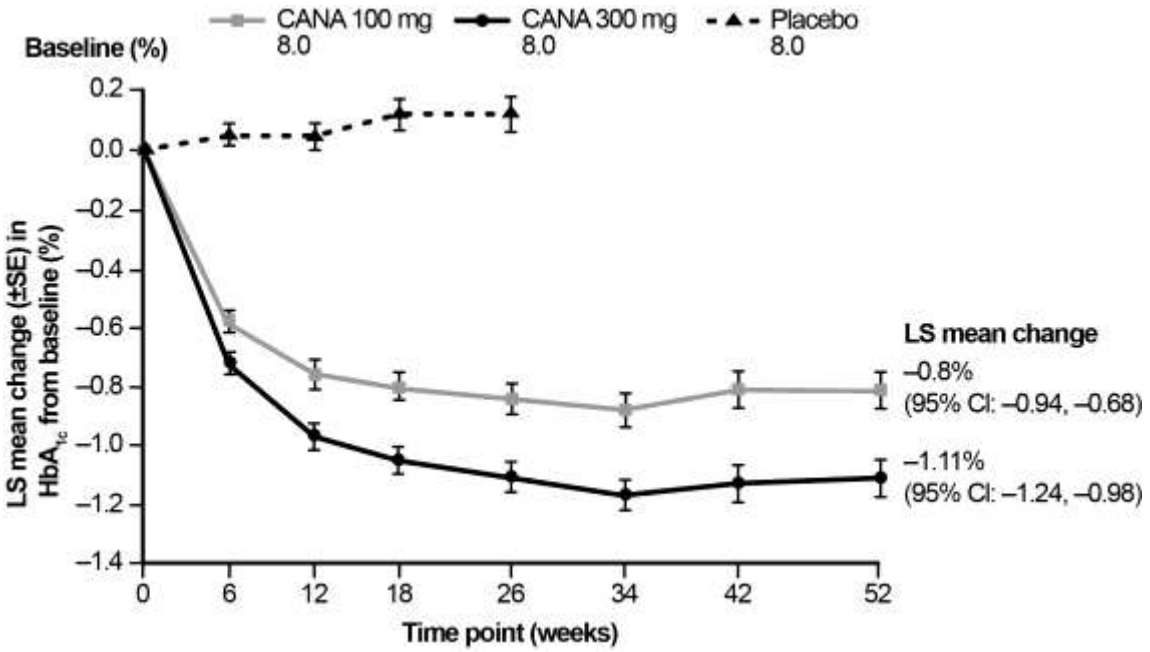
This Multiple Technology Appraisal (MTA) considers the use of SGLT-2-i as monotherapy in patients unable to take metformin (4), presenting the clinical and cost-effectiveness evidence for canagliflozin. Approximately 15% of T2DM patients are unable to take metformin due to either contraindications or intolerance, and are thus applicable to this submission (4).

Clinical Evidence

Two pivotal studies provide the clinical evidence for canagliflozin monotherapy; CANTATA-M which compared both doses (100 mg and 300 mg) with placebo for 26 weeks (5) with an extension out to 52 weeks (6) and a Japanese study comparing canagliflozin 100 mg and 200 mg with placebo for 24 weeks (7).

Both studies showed a significant reduction in HbA1c versus placebo from a mean baseline HbA1c of 8%. The Japanese study demonstrated a reduction in HbA1c (least square [LS] mean change from placebo at 24 weeks) of -1.03% with the 100 mg dose (7). A dose-dependent reduction in HbA1c with canagliflozin was demonstrated in CANTATA-M (LS mean change from placebo at 26 weeks) of -0.91% with the 100 mg dose and -1.16% with the 300 mg dose; this clinical benefit was maintained out to 52 weeks, see Figure 1 (5, 6).

Figure 1: CANTATA-M LS mean change in HbA1c at 52 weeks (adapted from Stenlof 2014) (6)



Decreases in FPG, BP and body weight were maintained, as were lipid changes. The reduction in body weight from baseline was -3.3% from baseline in the 100 mg arm and -4.4% in the 300 mg arm.

Those patients with higher baseline HbA1c achieved greater reductions in HbA1c with canagliflozin compared with those with lower baseline levels. In the high glycaemic subgroup of CANTATA-M (5),

which contained patients with a mean baseline HbA1c of 10.6%, reductions from baseline in HbA1c were -2.13% and -2.56% for the 100 mg and 300 mg dose of canagliflozin, respectively.

Clinically relevant reductions in systolic blood pressure (SBP) (-3.7 mmHg with the 100 mg and -5.4 mmHg with the 300 mg in CANTATA-M, and -5.2 mmHg with the 100 mg in the Japanese study) and body weight (2.2-3.3% loss) were seen in both clinical trials, and maintained out to 52 weeks with both the of doses of canagliflozin (5-7).

Canagliflozin results in changes to the lipid profile, resulting in a slight decrease in the LDL/HDL ratio and modest reductions in triglycerides. An interim meta-analysis of cardiovascular (CV) events in the long-term CANagliflozin cardioVascular Assessment Study (CANVAS), however, has shown no increase in CV risk with canagliflozin (8).

Canagliflozin is associated with a number of AEs related to the SGLT-2-i mode of action. The majority of these were mild to moderate in nature, managed with standard therapies and did not result in treatment discontinuation. These AEs include genital mycotic infection (GMI), urinary tract infection (UTI) and volume-related AEs. Overall, out of 482 patients treated with canagliflozin in the clinical studies, only two patients discontinued due to GMI, and only one discontinued due to osmotic diuresis. Hence canagliflozin is well tolerated, with comparably low rates of discontinuation compared to placebo at week 52 in CANTATA-M and week 24 in the Japanese study (1-3% and 1-2% for canagliflozin and placebo, respectively) (6) (7).

Of note, two additional studies confirm the results seen in CANTATA-M and the Japanese study: DIA3011, an active-comparator study of canagliflozin 100 mg and 300 mg versus metformin extended release (XR) and both doses of canagliflozin plus metformin XR (9), and an open study comparing canagliflozin 100 mg and 200 mg in Japanese patients (10). In DIA3011, the reduction in HbA1c from baseline was 1.37% and 1.42% for canagliflozin 100 mg and 300 mg respectively at 26 weeks (9). In the open study the reduction in HbA1c from baseline was 0.8% for canagliflozin 100 mg at 52 weeks (10). Clinical benefit with canagliflozin was also demonstrated in all other end-points of interest.

Network Meta-Analysis

A network meta-analysis (NMA) provides data comparing outcomes with canagliflozin to other SGLT-2-i, sulfonylureas (SUs), dipeptidyl peptidase-4 inhibitors (DPP-4-i) and pioglitazone, as per the defined scope for this MTA. Results from the NMA confirm and provide further support to the findings from the placebo-controlled studies of canagliflozin. Rigorous sensitivity analyses were carried out in order to test heterogeneity within the network and increase the validity of results and robustness of conclusions. A sensitivity analysis was also conducted to assess the impact of including trials assessing the use of repaglinide in monotherapy.

The NMA reports that:

- Canagliflozin 300 mg was ranked highest in terms of mean change from baseline in HbA1c and canagliflozin 100 mg was third highest after glipizide (data from 40 studies);
- Canagliflozin 300 mg was the second most effective agent in achieving HbA1c < 6.5%, behind pioglitazone (22 studies), and the most effective agent in lowering fasting plasma glucose (FPG) (36 studies);
- Canagliflozin 300 mg and 100 mg were ranked first and second for weight loss (19 studies), reduction in BMI (six studies) and reduction in SBP (eight studies).

It should be noted, however, that missing data for some agents meant that no results were available versus SU (weight and SBP), DPP-4-i (BMI) or other SGLT-2-i (BMI). All agents included in an analysis considering hypoglycaemia had a low risk of hypoglycaemia, with both canagliflozin 100 mg and 300 mg associated with a similarly low risk as dapagliflozin. Again, missing data meant that no results were available versus SU or empagliflozin for hypoglycaemia (11).

The clinical studies, together with the NMA, provide strong and robust evidence that canagliflozin is effective in lowering HbA1c and has the added benefits of BP lowering and weight loss with a low risk of hypoglycaemia. These results are consistent with conclusions drawn from both the clinical trials and the NMA for canagliflozin in combination therapy, appraised by NICE in 2013 (12) (13). Clinicians support the use of canagliflozin in patients in whom the additional clinical benefits will provide further clinical gain; for example, in obese patients with one or more co-morbidities such as sleep apnoea, uncontrolled hypertension, polycystic ovary syndrome and osteoarthritis.

Economic Analysis

A comprehensive economic analysis of the cost-effectiveness of canagliflozin monotherapy in treating T2DM was conducted using ECHO-T2DM, an externally validated micro-simulation model of the long-term costs and disease outcomes previously accepted by NICE (12). The results from the NMA were used to estimate treatment effects for available parameters versus all relevant comparators defined in the initial data submission.

Of note, canagliflozin 300 mg monotherapy alone is not used routinely in clinical practice. It is, however, clinically plausible that a subset of patients that tolerate canagliflozin 100 mg yet do not achieve the desired HbA1c reduction may transition to canagliflozin 300 mg. Whilst clinical data for this dose increase of canagliflozin 100 mg to 300 mg are not available, rationale for its inclusion, and method for doing so, were discussed and justified by UK clinicians (14) and acknowledged during the canagliflozin STA (12). Current experience suggests approximately [redacted] of patients' progress to the higher dosage of canagliflozin within their treatment pathway.

Results from the economic analysis show SGLT-2-i to be associated with the greatest QALY gains, with canagliflozin being the most effective intervention based on 10.039, 10.051, and 10.083 QALYs for 100 mg and 300 mg and 100 mg dose increase, respectively versus current standard of care (SU), generating a QALY gain of 9.949 over 40 years. Total costs incurred by all comparators are generally similar, with the exception of pioglitazone. Overall, results demonstrate that canagliflozin monotherapy is a pharmaco-economically justifiable treatment option for use in patients with T2DM who are contraindicated or intolerant to metformin.

As acknowledged by NICE, the use of pioglitazone in clinical practice is declining in the UK (12). Since the presence of pioglitazone in the base case analysis results in comparators being dominated and extendedly dominated in the incremental analysis, only an incremental cost-effectiveness ratio (ICER) for pioglitazone versus canagliflozin 300 mg can be derived. Given canagliflozin 300 mg is only applicable to a subset of patients, as previously mentioned, this ICER provides little insight into the relationship between alternative treatments. By excluding pioglitazone from the interpretation of results, more informative economic analyses can be expressed: ICERs for canagliflozin 100 mg, 100 mg dose increase to 300 mg, and 300 mg compared with SU (next cheapest drug to pioglitazone) are £3,377, £4,392 and £8,090 per QALY, respectively.

Extensive sensitivity analyses show the structural assumptions around the ECHO-T2DM modelling are robust and that there are few assumptions that directionally impact resulting ICERs. The variables demonstrating the most uncertainty in the ICER are HbA1c metabolic drift.

Conclusion

It is well established that treating patients with T2DM early in the course of their disease to achieve tight glycaemic control is of benefit in reducing the emergence of long-term debilitating complications (11). Canagliflozin is effective in lowering HbA1c and has the added benefits of BP lowering and weight loss, which helps to minimise the risk of long-term complications associated with the progression of T2DM. Through a robust NMA and rigorous cost-effectiveness analysis, there is compelling evidence for canagliflozin as an efficient use of NHS resources for monotherapy treatment in patients with T2DM unable to take metformin. Both the clinical and economic results generated using the NMA are consistent with results from use of canagliflozin in dual and triple therapy which further strengthens the validity of the analysis (12).

Canagliflozin has shown consistent dose dependant response across all treatment lines and can be administered in combination with pioglitazone, SUs and insulin when patients stop responding to canagliflozin monotherapy, giving patients and clinicians a wide array of treatment options from which to choose the most suitable regimen.

2. The technology

Description of the technology

Canagliflozin (Invokana, Janssen-Cilag) is an orally administered selective SGLT-2-i, available in two doses (100 mg and 300 mg), given as a once daily (od) tablet.

Canagliflozin inhibits the activity of SGLT-2 in the proximal tubule of the nephron, which blocks glucose re-absorption in the kidney and increases the amount of glucose excreted in the urine. This mode of action means that, as well as lowering blood glucose, as measured by HbA1c, canagliflozin also results in a loss of approximately 308-476 calories/day which manifests as weight reduction, predominantly due to fat loss, and lowers blood pressure (BP) due to mild osmotic diuresis (15-18). The use of canagliflozin as monotherapy has a low risk of hypoglycaemia, comparable to that observed with placebo (5).

Lowering of post-prandial glucose (PPG) and insulin contributes further to glycaemic control. Canagliflozin 300 mg given prior to a meal has been shown to limit the post-prandial excursion of glucose and insulin by delaying intestinal glucose absorption, which is thought to be due to local inhibition of intestinal SGLT-1 by canagliflozin (19). This effect is not observed with the 100 mg dose of canagliflozin, nor with dapagliflozin or empagliflozin (20, 21). In a pharmacodynamic study in healthy volunteers, canagliflozin 300 mg resulted in a 10% reduction in PPG excursion whereas dapagliflozin 10 mg had no effect on PPG (20).

Canagliflozin is also associated with improvements in model-based indices of beta-cell function (22), which suggests that canagliflozin may have the potential to slow disease progression. Longer-term studies are still required to assess the impact of sustained treatment on disease progression.

Licensed indication and dose

Canagliflozin is indicated for use in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as either monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications, or as add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (23).

This Multiple Technology Appraisal (MTA) concerns monotherapy only and therefore we will only consider evidence for canagliflozin as monotherapy. NICE have previously appraised canagliflozin as add-on therapy and recommended use in dual therapy in combination with metformin, in triple therapy when taken with either metformin and a sulfonylurea, or metformin and pioglitazone, and when added to insulin, with or without other antidiabetic drugs (Technology appraisal 315, June 2014) (12).

The recommended starting dosage of canagliflozin is 100 mg od. In patients tolerating canagliflozin 100 mg od who have an estimated glomerular filtration rate (eGFR) of at least 60 ml/min/1.73 m^2 or creatinine clearance (CrCl) of at least 60 ml/min and need tighter glycaemic control, the dosage can be increased to 300 mg od (23).

Administration and costs of the technology

Canagliflozin is taken orally with or without food, preferably before the first meal of the day. Tablets should be swallowed whole. Costs are £39.20 for 30 tablets for the 100 mg dose and £49.99 for 30 tablets for the 300 mg dose (1). The annual cost of canagliflozin is £476.93 for the 100 mg daily dosage and £608.21 for the 300 mg daily dosage. The majority of prescriptions in the UK are for the 100 mg dose; latest data reveal that 17% of patients on canagliflozin titrate to the 300 mg dose (24).

Changes in service provision and management

No additional tests or investigations are required to select patients for treatment with canagliflozin.

As canagliflozin is an oral therapy, there are no anticipated costs due to location of care, staff or administration. Patient monitoring is expected to follow largely the same schedule and in the same setting as for patients treated with other anti-hyperglycaemic agents (AHAs) including the monitoring of change in eGFR in people with T2DM. However, unlike sulfonylureas (SU) and repaglinide, canagliflozin does not require self-monitoring of blood glucose (SMBG).

Urinary tract infections (UTI) and genital mycotic infections (GMIs) are adverse events (AEs) associated with all SGLT-2-i, including canagliflozin, and result from the increased urinary glucose levels observed with this therapeutic group. Some patients may need to visit their GP for treatment, whilst others will obtain over the counter treatment, for example anti-fungal treatment in women with GMI.

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

Context

T2DM is a chronic progressive disease. Worsening glycaemia from reduced insulin sensitivity and progressive insulin deficiency is usually associated with the development of micro- and macro-vascular complications over time (25). Life-time exposure to hyperglycaemia, sometimes referred to as glycaemic legacy, drives the risk for the complications of diabetes (26).

The complications of diabetes result in considerable morbidity. People with diabetes are two- to four-times more likely to develop cardiovascular disease (CVD) than those without diabetes, indeed CVD is the leading cause of premature death and disability in people with diabetes (27). Microvascular complications result in a considerable burden; diabetes is a leading cause of blindness, renal failure and diabetic foot ulcers which could require amputation (27).

Diabetes has a significant impact on mortality: average life expectancy is reduced by 10 years in people with diabetes (28). Diabetes is extremely costly: it accounts for approximately 10% of the NHS budget and 80% of these costs are due to complications (29).

Approach to treatment

A key aim of treatment in T2DM is to prevent and/or delay the progression of complications; tight glycaemic control reduces both macro- and micro-vascular complications (30, 31).

Greatest benefit is seen when there is continual tight glycaemic control from the time of diagnosis of T2DM (32), which reduces the glycaemic legacy. Indeed, studies which enrolled people with established diabetes (8-11.5 years) and sub-optimal glycaemic control (ADVANCE, ACCORD and VADT) (33-35), failed to demonstrate the same level of benefit as UKPDS, which enrolled people with newly diagnosed diabetes (30). Given the benefit of tight glycaemic control, the latest NICE draft clinical guidelines (36), which update Clinical Guideline 87, recommend initiating treatment in newly diagnosed patients with a HbA1c above 6.5%, and intensifying treatment once patients reach a HbA1c of 7.5% or above (28, 36).

An individualised approach to diabetes care tailored to each patient is the optimal care model in T2DM (36). The latest NICE draft clinical guidelines (37) recommend individualised care: *Adopt an individualised approach to diabetes care that is tailored to the person's needs and circumstances, taking into account their personal preferences, comorbidities, risks of polypharmacy, and their ability to benefit from long-term interventions due to reduced life expectancy. Such an approach is especially important in the context of multimorbidity.*

Therefore, glycaemic control should be considered in the context of other risk factors such as co-morbidities, (e.g., obesity) and CV risk factors (e.g., BP and lipids). Interventions that reduce BP, cholesterol and glycaemia in overweight and obese people reduce the risk of CVD and stroke (38). Draft NICE clinical guidelines recommend that all people with T2DM should be supported to try to lose weight if overweight or obese, achieve and maintain blood glucose levels and BP in the normal range

or as close to normal as is safely possible and maintain a lipid and lipoprotein profile that reduces the risk of vascular disease (36).

However, despite published guidelines, the achievement of treatment targets is poor in patients with (39)diabetes in England and Wales. Data from the National Diabetes Audit 2012-2013 shows that 63% of people with T2DM did not reach all three of the key treatment targets (HbA1c 7.5% [<58 mmol/l], total cholesterol <5 mmol/l and BP <140/80 mmHg) (40). It should be noted that audit standards differ from best practice standards which are more restrictive (i.e., HbA1c<7%, BP<130/80 mmHg and total cholesterol <4 mmol/l) (36, 41). There are a number of reasons for poor glycaemic control, which include clinical inertia (lack of up-titration or intensification of treatment), side-effects of treatment, lack of patient engagement and understanding of diabetes, and poor adherence (42).

Current treatment guidelines

This MTA considers the use of SGLT-2-i as monotherapy in patients unable to take metformin (4).

NICE clinical guideline 87 recommends dietary advice and increased physical activity for all people with T2DM. If life-style interventions do not reduce hyperglycaemia, then metformin is recommended as first-line pharmacological treatment (28). However, a minority of people, around 15%, are unable to tolerate metformin due to AEs, primarily gastro-intestinal (GI) in nature, or are unsuitable for treatment due to contraindications (36). Expert opinion suggests that AE, rather than contraindications, are the main reason that patients are unable to take metformin.

For those people for whom metformin is unsuitable, draft NICE clinical guidelines which update clinical guideline 87, recommend repaglinide as the initial alternative to metformin (37). Expert opinion suggests that repaglinide may not be not the most appropriate initial alternative due to hypoglycaemia risk and weight gain, together with potential adherence problems since it is given three times daily (37, 43). Furthermore, repaglinide requires several dose titration steps necessitating additional healthcare professional (HCP) visits and SMBG, which has implications for the patient and the health economy, through added costs associated with repaglinide therapy, beyond drug acquisition costs.

According to the draft NICE clinical guidelines, if repaglinide is contraindicated or not preferred then other alternatives to metformin may be considered in the following order: pioglitazone, dipeptidyl peptidase-4 inhibitor (DPP-4-i) and SU.

Expert opinion suggests that pioglitazone and SU may not be appropriate options at this stage. Both agents cause weight gain, pioglitazone is associated with potentially serious AE (e.g. fluid retention issues, including heart failure) and SU significantly increase the risk of hypoglycaemia compared with other oral AHA (37, 43). SU also require SMBG.

Monotherapy treatment is considered to have failed when blood glucose is not adequately controlled, i.e. HbA1c rises above 7.5%. Intensification of treatment and progression to dual therapy should be considered, followed by the addition of insulin or triple therapy if required (36). When considering drug treatment, it is essential to consider the impact of drug choice on risks and benefits (36). The use of an agent that has a positive impact on other risk factors and co-morbidities, including a low risk of hypoglycaemia, allows true individualised treatment, as recommended in NICE guidelines (36) .

Two important side effects of AHA treatment are hypoglycaemia and weight gain. Of the proposed options in patients unable to take metformin, tight glycaemic control using insulin secretagogues such as SU and repaglinide is associated with an increased risk of hypoglycaemia (44) , whereas SGLT-2-i, DPP-4-i and pioglitazone have a very low hypoglycaemia risk (45, 46).

The UK Hypoglycaemia Study Group evaluated the incidence of hypoglycaemia over 9-12 months in six regions across the UK. They found that 40% of patients on SU experienced symptomatic hypoglycaemia during the study period (47). The risk of a severe hypoglycaemic episode (an episode requiring third party assistance) was 7% during the first two years of treatment with SUs (47).

Severe hypoglycaemia may significantly increase the risk of death and the complications of diabetes. In the ADVANCE study of 11,140 patients with T2DM, the mortality rate in patients who had experienced at least one severe hypoglycaemic episode was 19.5% versus 9.0% in patients without a

severe hypoglycaemic episode, p<0.001. The rates of major macro-vascular events were 16.8% versus 10.2% respectively, p<0.001 (48).

Hypoglycaemia and fear of hypoglycaemia limit adherence to treatment and glycaemic control (49). Patients report that hypoglycaemia and fear of hypoglycaemia may lead to increased levels of anxiety, deliberate overeating in order to boost blood glucose levels and failure to use anti-hyperglycaemic therapies appropriately.

Hypoglycaemia has a negative impact on all aspects of patients' lives, including social activities, travelling, driving, exercising and attendance/productivity at work regardless of the severity of the episode, which in turn impacts on quality of life (49-51). As would be expected, the impact of severe hypoglycaemia on patients' lives is significantly greater than non-severe hypoglycaemia, however, non-severe hypoglycaemia also has a considerable impact (51). In one study, patients experiencing a non-severe hypoglycaemic episode during working hours missed 11.4 hours of work and 29% of patients reported missing an appointment or not finishing a work project on time. If the non-severe hypoglycaemic episode was outside working hours, patients missed 15.1 hours of work time. In patients with nocturnal hypoglycaemia, 14.2 hours of work time were missed and 40% of patients reported missing an appointment or not finishing a work project on time (52).

The impact of hypoglycaemia is considerable in terms of cost to the NHS. Recent data from a UK-based audit reveals that patients taking a SU accounted for one-third of patients with T2DM admitted to Accident and Emergency with a hypoglycaemic episode (53). Further data published in 2015 estimates the cost of a severe hypoglycaemic episode in patients with T2DM at £407, rising to £2,152 for a severe episode requiring admission to hospital (54).

Repaglinide, SU and pioglitazone all cause weight gain. DPP-4-i are weight neutral whereas SGLT-2-i lead to a modest decrease in weight (45, 46). In terms of benefits, a reduction in BP and simplicity of the treatment regimen are important. Of the proposed options in patients unable to take metformin, SGLT-2-i are the only agents that have been shown to consistently reduce BP in clinical trials (45, 46).

SGLT-2-i have a simple od dosing regimen, which has implications for adherence. It has been estimated that around one-half of all medicines prescribed for long-term conditions, such as T2DM, are not taken as recommended (55), and adherence falls further in patients with co-morbid diseases and increased pill burden (56). AEs have a negative impact on adherence in patients with T2DM (49, 57), in particular hypoglycaemia and weight gain (58). Therefore, agents without these AEs, such as SGLT-2-i, have the potential to improve adherence. Furthermore, SGLT-2-i do not require dose titration, which avoids the need for repeated HCP visits and SMBG.

In conclusion, SGLT-2-i provide effective lowering of HbA1c with additional clinical benefits of BP lowering and weight loss with a low risk of hypoglycaemia. These agents offer clinicians an option to provide personalised treatment and are most suitable for use in those patients in whom the additional clinical benefits will provide further clinical gain, for example in patients who are overweight or obese with one or more additional co-morbidities such as sleep apnoea, uncontrolled hypertension, polycystic ovary syndrome and osteoarthritis.

In the following pages, and accompanying appendices, we present evidence for the clinical and cost-effectiveness of canagliflozin.

4. Clinical evidence

Summary of relevant canagliflozin RCTs

Four studies included canagliflozin as monotherapy were identified.

Two of these studies are not considered in detail in this submission for the reasons given below:

- DIA3011; an active-comparator study of canagliflozin 100 mg and 300 mg versus metformin extended release (XR), canagliflozin 100 mg plus metformin XR and canagliflozin 300 mg plus metformin XR. We have drawn data from an unpublished topline data report and a published poster presented at American Diabetes Association (ADA) 2015 (59). Full details of this study have not been included in this submission since draft NICE clinical guidelines do not recommend metformin XR and the study did not include a placebo arm. We have presented a summary of the study in Appendix 1 and the results have been included as a sensitivity analysis to the NMA.

- Inagaki et al. (2015); open-label, 2-arm study of canagliflozin 100 mg and 300 mg. This study did not have a comparator arm and therefore could not be included into the NMA (10).

Two trials comparing canagliflozin with a relevant comparator are included in this submission, and are presented in detail below.

- CANTATA-M (Stenlof et al.): placebo-controlled study of canagliflozin 100 mg and 300 mg. We have drawn data from both the published papers (5, 6) and the clinical study report, where required (8).

- Inagaki et al. (2014): placebo-controlled study of canagliflozin 100 mg and 200 mg. We have drawn data from both the published paper (7) and the clinical study report, where required (60). The 200 mg dose is not licenced in the UK and thus we have only presented the 100 mg data in this submission.

Of note, two additional studies confirm the results seen in CANTATA-M and the Japanese study: DIA3011, an active-comparator study of canagliflozin 100 mg and 300 mg versus metformin extended release (XR) and both doses of canagliflozin plus metformin XR (9), and an open study comparing canagliflozin 100 mg and 200 mg in Japanese patients (10). In DIA3011, the reduction in HbA1c from baseline was 1.37% and 1.42% for canagliflozin 100 mg and 300 mg respectively at 26 weeks (9). In the open study the reduction in HbA1c from baseline was 0.8% for canagliflozin 100 mg at 52 weeks (10). Clinical benefit with canagliflozin was also demonstrated in all other end-points of interest.

CANTATA-M

Study design

Randomised double-blind placebo controlled trial conducted in 17 countries (America, Canada, Austria, Estonia, Lithuania, Iceland, Poland, Romania, Spain, Sweden, Columbia, Guatemala, Philippines, South Africa, South Korea and Malaysia (8)). Study patients either had inadequate control on diet and exercise alone or on an AHA. Patients on an AHA underwent an 8-week washout/diet and exercise period followed by a 2-week placebo run-in period. Patients not on an AHA underwent a 2-week placebo run-in period.

After the placebo run-in period, patients were randomised 1:1:1 via an Interactive Voice Response System/Interactive Web Response System to canagliflozin 100 mg, 300 mg or placebo for a 26-week placebo-controlled core treatment period, followed by a 26-week double-blind extension period. Randomisation was stratified according to whether patients were taking AHA at baseline and whether they participated in the frequently sampled mixed meal tolerance test (FS-MMTT).

Glycaemic rescue with metformin was allowed if FPG >15 mmol/l up to week 6, >13.3 mmol/l week 6-12 and >11.1 mmol/l week 12-26.

At the start of the 26-week double-blind extension period, patients on placebo were switched to sitagliptin 100 mg.

See Appendix 1 for the study design diagram for the core study.

A substudy of patients with HbA1c above the inclusion range (high glycaemic substudy) was also conducted in patients with HbA1c >10 and ≤12% (108 mmol/mol) at screening or week -1 and FPG ≤19.4 mmol/l at week -1. Patients eligible for the substudy had a 1 week single blind placebo run in followed by a 26-week double-blind, active-treatment period. Patients were randomised to canagliflozin 100 mg or 300 mg and were not eligible for the 26-week extension study.

Inclusion and exclusion criteria

Inclusion criteria were as follows:

- Men and women aged 18-80 years.
- Not on an AHA at baseline with HbA1c ≥7% (53 mmol/mol) and ≤10% (86 mmol/mol).
- On AHA monotherapy or metformin plus SU dual therapy (at ≤50% of maximally effective dose) with HbA1c ≥6.5% (48 mmol/mol) and ≤9.5% (80 mmol/mol) at screening and HbA1c ≥7% (53 mmol/mol) and ≤10% (86 mmol/mol) and fasting plasma glucose (FPG) of <15 mmol/l at day 0 of the 2-week placebo run-in period.

Exclusion criteria were as follows:

- Repeated FPG >15 mmol/l during the pre-treatment phase.
- History of type 1 diabetes, hereditary glucose-galactose malabsorption, primary renal glucosuria or CVD.
- Treatment with peroxisome proliferator-activated receptor-γ (PPARγ) agonist, insulin, another SGLT-2-i within 12 weeks of screening.
- eGFR <50 ml/min/1.73 m^2 at screening.

Outcomes

The pre-specified primary end-point of the study was change in HbA1c from baseline to week 26. Secondary end-points included proportion of patients reaching HbA1c targets, changes from baseline in FPG and systolic blood pressure (SBP) and percentage changes from baseline in body weight, HDL-C, LDL-C and triglycerides.

Safety end-points included AEs, specifically UTI, GMI and hypoglycaemia. Hypoglycaemic episodes included biologically confirmed episodes (fingerstick or plasma glucose <3.9 mmol/l) and severe episodes (requiring assistance from another person or resulting in seizure/loss of consciousness).

Statistical analysis

See Appendix 1 for full details of the statistical analysis.

Participant flow

In the core study, 587 patients were randomised, and 584 received at least one dose and were included in the mITT: placebo (n=192), canagliflozin 100 mg (n=195) and canagliflozin 300 mg (n=197). All of the 91 patients who participated in the high glycaemic substudy were included in the mITT population: canagliflozin 100 mg (n=47) and canagliflozin 300 mg (n=44), see Appendix 1 for study flow diagram.

In the core study, the overall discontinuation rate was 13.1% (n=77), discontinuation was higher with placebo than with canagliflozin 100 mg and 300 mg (16.5% versus 11.7% and 11.2%). Rescue therapy was used in 22.7% of patients receiving placebo versus 2.6% and 2% randomised to canagliflozin 100 mg and 300 mg, respectively.

Patient characteristics were balanced across the three groups in the core study. Just over one-half of the patients were female (56%), mean age was 55.4 years, around two-thirds were white (68%), mean baseline HbA1c was 8% with FPG of 9.5 mmol/l, mean BMI was 31.6 kg/m^2, duration of diabetes was 4.3 years and just under one-half of patients (48%) were on an AHA at screening. See Appendix 1 for full details of patient demographics in the core study and high glycaemic substudy.

Critical appraisal

The study was of good quality, see Table 1.

Table 1: Critical appraisal of CANTATA-M

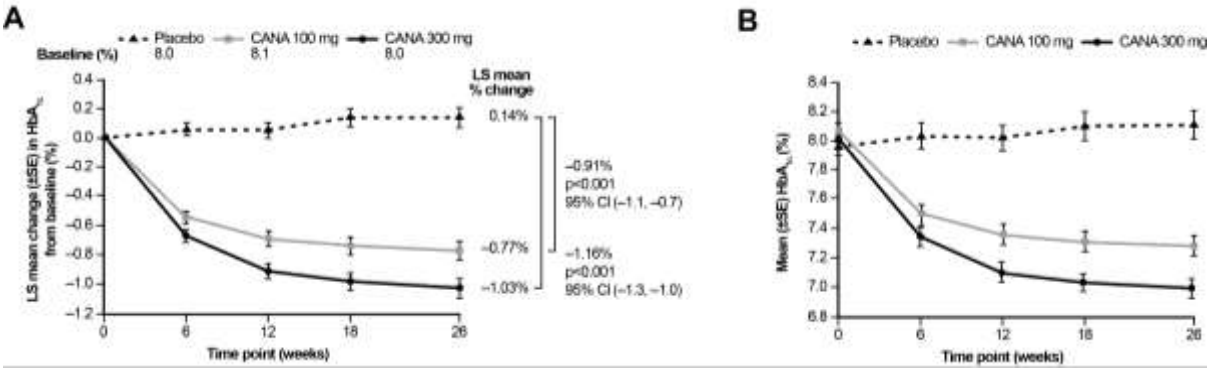
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, Yes, Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Were there any unexpected imbalances in drop-outs between groups ?	No

Primary end-point: reduction in HbA1c from baseline at 26 weeks

Both doses of canagliflozin resulted in a significant reduction in HbA1c compared with placebo (LS mean changes -0.91% with canagliflozin 100 mg and -1.16% with canagliflozin 300 mg, p<0.001), see Figure 2. Decrease in HbA1c was similar between those patients who were on an AHA at baseline and those not on an AHA.

Subgroup analyses based on baseline HbA1c revealed that reductions in HbA1c were greatest in patients with the highest HbA1c, as would be expected. In the high glycaemic subgroup, reductions from baseline in HbA1c were -2.13% and -2.56% for the 100 mg and 300 mg dose of canagliflozin, respectively.

Figure 2: CANTATA-M (A) LS mean change in HbA1c and (B) Mean HbA1c over time



Secondary end-points

Achievement of HbA1c targets

Both doses of canagliflozin resulted in greater achievement of HbA1c targets than placebo. HbA1c <7% was achieved by 62.4% of patients receiving canagliflozin 300 mg, 44.5% receiving 100 mg versus 20.6% receiving placebo, p<0.001 for both canagliflozin doses versus placebo. In the high glycaemic subgroup, 17.4% of patients receiving the 300 mg dose and 11.6% receiving the 100 mg dose achieved HbA1c <7%, despite having baseline HbA1c >10%.

HbA1c <6.5% was achieved by 28.4% of patients receiving canagliflozin 300 mg, 17.8% receiving 100 mg versus 5.3% receiving placebo. Data on the proportion of patients achieving the 6.5% goal are not available for the high glycaemic subgroup.

FPG

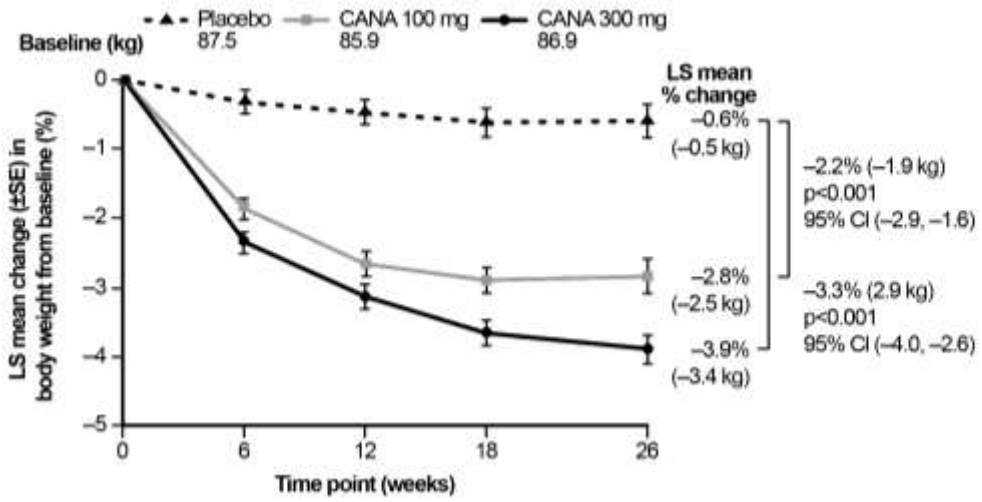
Canagliflozin resulted in significantly greater reductions in FPG versus placebo, at week 26. Differences in LS mean changes in FPG were -2.0 mmol/l and -2.4 mmol/l for canagliflozin 100 mg and 300 mg relative to placebo, p<0.001 for both. The LS mean changes from baseline in the high glycaemic subgroup were -4.5 mmol/l and -4.8 mmol/l with canagliflozin 100 mg and 300 mg respectively.

Body weight

There was a significant dose-related decrease in body weight with canagliflozin. Canagliflozin resulted in a LS mean difference of -2.2% (-1.9 kg) with the 100 mg dose and -3.3% (-2.9 kg) with the 300 mg dose, versus placebo, both p<0.001 (Figure 3). The LS mean changes in body weight from baseline in

the high glycaemic subgroup were -3% and -3.8% with canagliflozin 100 mg and 300 mg, respectively.

Figure 3: CANTATA-M Percentage change in body weight (5)



Blood pressure (BP)

There was a significant dose-related decrease in SBP with canagliflozin; LS mean difference versus placebo of -3.7 mmHg with the 100 mg dose and -5.4 mmHg with the 300 mg dose, both p<0.001. DBP was also reduced; LS mean difference of -1.6 mmHg and -2.0 mmHg, p values are not available since statistical comparison was not performed.

In the high glycaemic subgroup, the LS mean changes from baseline for SBP were -4.5 mmHg and -5.0 mmHg with canagliflozin 100 mg and 300 mg and for DBP -3.5 mmHg and -2.2 mmHg, respectively.

Please see Appendix 1 for full details of BP in the core study.

Lipids

There were significant increases in HDL-C with canagliflozin compared to placebo; LS mean differences of 6.8% (p<0.001) for the 100 mg dose and 6.1% (p<0.01) for the 300 mg dose. There were modest increases in LDL-C with canagliflozin compared to placebo; LS mean differences of 1.9% for the 100 mg dose and 6.1% for the 300 mg dose, p values are not available since statistical comparison was not performed. Overall, the LDL-C/HDL-C ratio was slightly decreased across groups. Both canagliflozin doses were associated with reductions in triglycerides compared with placebo, but these differences did not reach statistical significance.

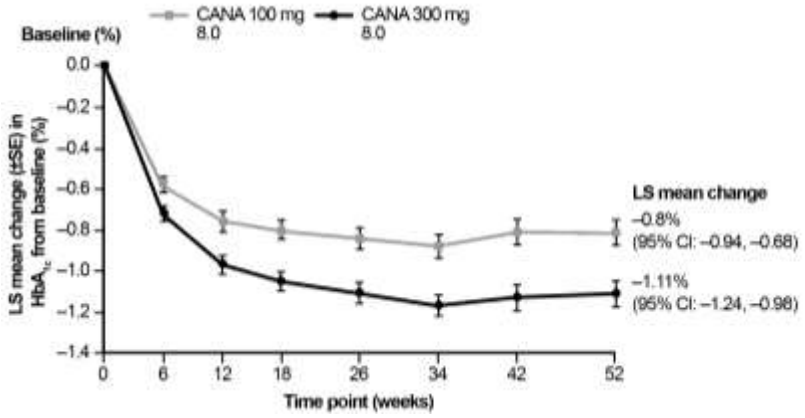
In the high glycaemic subgroup, dose related increases in HDL-C were seen with both doses of canagliflozin, there was a modest reduction in triglycerides and a small increase in LDL-C with the 300 mg dose (2.9%).

Please see Appendix 1 for full details of lipid changes in the core study.

HbA1c Results at 52 weeks

The reduction in HbA1c with canagliflozin was maintained out to 52 weeks. At week 52 the LS mean change in HbA1c from baseline was -0.81% in the 100 mg group and -1.11% in the 300 mg group (6), see Figure 4.

Figure 4: CANTATA-M LS mean change in HbA1c at 52 weeks (6)



Decreases in FPG, BP and body weight were maintained, as were lipid changes. The reduction in body weight from baseline was -3.3% from baseline in the 100 mg arm and -4.4% in the 300 mg arm.

Inagaki et al. (2014)

Study design

This was a randomised double-blind placebo controlled trial conducted in Japan. Study patients either had inadequate control on diet and exercise alone or on an AHA. Patients on an AHA underwent a 55-day washout/diet and exercise period followed by a 4-week placebo run-in period. Patients not on an AHA underwent a 4-week placebo run-in period.

After the placebo run-in period, patients were randomised using a block allocation code method 1:1:1 to canagliflozin 100 mg, 200 mg or placebo for a 24-week treatment period followed by a 2-week follow-up period. See Appendix 1 for study design diagram.

Inclusion and exclusion criteria

Inclusion criteria were as follows:

- Men and women aged >20 years.
- Not on an AHA at baseline or on AHA treatment providing that they started a washout period of ≥55 days before starting the run-in period with HbA1c ≥7% (53 mmol/mol) and ≤10% (86 mmol/mol).

Exclusion criteria were as follows:

- Repeated FPG >15 mmol/l during the pre-treatment phase.
- History of another form of diabetes, hereditary glucose-galactose malabsorption, primary renal glucosuria, CVD, inadequately controlled thyroid abnormality, anorexia or bulimia, serious liver or kidney disease, neuropsychiatric disorder, drug related shock/anaphylaxis, pregnancy/breastfeeding, unwilling to use contraception.
- Indication for insulin therapy.
- Current or history of severe complications of diabetes.
- Current or history of UTI/GMI <1 year before study entry.
- eGFR < 50 ml/min/1.73 m^2 at screening.

Outcomes

The pre-specified primary end-point of the study was change in HbA1c from baseline to week 24. Secondary end-points included proportion of patients reaching HbA1c targets, changes from baseline in FPG and SBP and percentage changes from baseline in body weight, HDL-C, LDL-C and triglycerides.

Safety end-points included AEs; UTIs and GMIs were pre-specified. Hypoglycaemic episodes included biologically confirmed asymptomatic episodes (plasma glucose <3.9 mmol/l but no symptoms) or symptomatic (symptoms present regardless of plasma glucose levels).

Statistical analysis
See Appendix 1 for full details of the statistical analysis.

Participant flow
272 patients were randomised and all received at least one dose; 90 patients received canagliflozin 100 mg and 93 received placebo. One patient in the canagliflozin 200 mg arm lacked efficacy data after starting the study, see Appendix 1 for study flow diagram.

Overall discontinuation rate was 11.4% (n=31), discontinuation was higher with placebo than with canagliflozin 100 mg (20.4% versus 6.7%).

Overall, just under one-third of the patients were female (29%), mean age was 58 years, mean baseline HbA1c was 8% with FPG of 9 mmol/l, mean BMI was 25.6 kg/m^2, duration of diabetes was 5.4 years and 75% were on an AHA at screening. The placebo and 100 mg arms were reasonably well matched. See Appendix 1 for full details.

Critical appraisal
The study was of good quality, see Table 2.

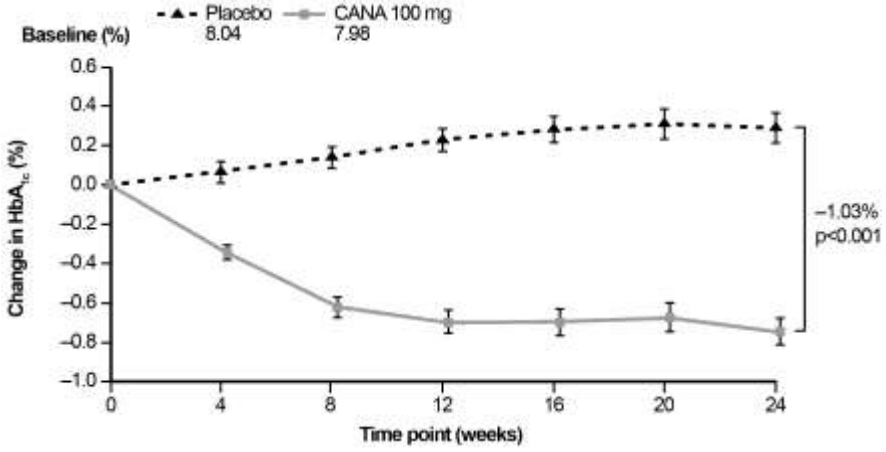
Table 2: Critical appraisal of Inagaki et al. (7)

Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Not relevant
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear
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, Yes, Unclear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Were there any unexpected imbalances in drop-outs between groups?	No

Primary end-point: reduction in HbA1c from baseline at 24 weeks
The 200 mg dose is not licenced in the UK and thus we only present the 100 mg data in this submission.

Canagliflozin 100 mg resulted in a significant reduction in HbA1c compared with placebo (LS mean changes -1.03%, p<0.001), see Figure 5.

Figure 5: Inagaki et al. change in HbA1c (7)



Subgroup analyses based on baseline HbA1c revealed that reductions in HbA1c were greatest in patients with the highest HbA1c, as would be expected.

Secondary end-points

Achievement of HbA1c targets

Canagliflozin 100 mg resulted in greater achievement of HbA1c targets than placebo. HbA1c <7% was achieved by 31.5% of patients receiving canagliflozin 100 mg versus 6.6% receiving placebo, p<0.001. [redacted].

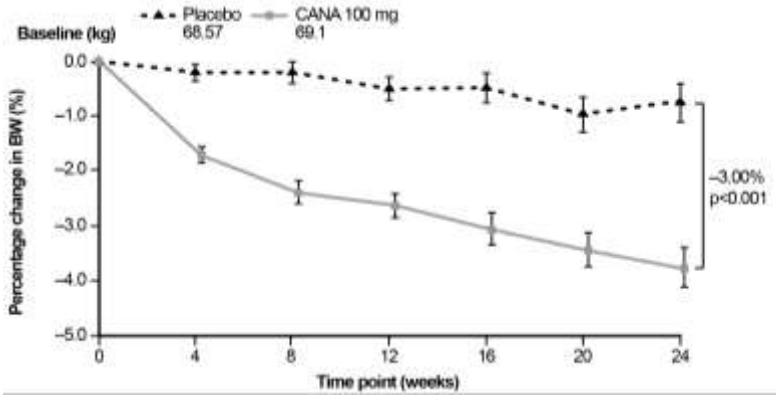
FPG

Canagliflozin 100 mg resulted in a significantly greater reduction in FPG versus placebo. At week 24 differences in LS mean changes in FPG were -2.0 mmol/l for canagliflozin 100 mg relative to placebo, p<0.001.

Body weight

There was a significant dose-related decrease in body weight with canagliflozin. Canagliflozin 100 mg resulted in a LS mean difference of -3.0%, p<0.001 versus placebo (Figure 6).

Figure 6: Inagaki et al. percentage change in body weight



Blood pressure

There was a significant decrease in SBP with canagliflozin. Canagliflozin 100 mg resulted in a LS mean difference of -5.2 mmHg, p<0.001. DBP was also reduced; LS mean difference of -2.6 mmHg, p<0.05.

Lipids

There were significant increases in HDL-C with canagliflozin 100 mg; LS mean difference of 0.18 mmol/l (p<0.001). There were modest, non-significant differences in triglyceride levels with canagliflozin. There were modest increases in LDL-C with canagliflozin 100 mg; LS mean difference of 0.13 mmol/l (p<0.05). Overall, the LDL-C/HDL-C ratio was slightly decreased in the canagliflozin 100 mg arm, although this was not significant.

Adverse events

The AEs are taken from the two RCTs described earlier: CANTATA-M (Stenlof, et al) and Inagaki et al.

CANTATA-M: 26 weeks

Canagliflozin 100 mg and 300 mg were generally well tolerated. Overall incidences of AEs were modestly higher with canagliflozin versus placebo; rates of serious AEs and AE-related discontinuations were low and similar across all three arms (Table 3). AEs leading to discontinuation occurred in 1% (n=2) of placebo patients, 3.1% (n=6) of canagliflozin 100 mg patients and 2% (n=4) of canagliflozin 300 mg patients. No single AE accounted for more than a single discontinuation.

Similar results were observed in the high glycaemic substudy; there was one discontinuation in each arm (2% for both), see Appendix 1.

There were two deaths, one in the placebo arm (intracranial haemorrhage and brain hernia) and one in the canagliflozin 100 mg arm (pneumonia, septic shock, acute renal failure and ischaemic hepatitis), neither was considered to be related to study drug. There were no deaths in the high glycaemic substudy.

Table 3: CANTATA-M summary of overall safety and selected AE (main study) at 26 weeks, n (%) (5)

	Placebo (n=192)	CANA 100 mg (n=195)	CANA 300 mg (n=197)
Any AE	101 (52.6)	119 (61.0)	118 (59.9)
AEs leading to discontinuation	2 (1.0)	6 (3.1)	4 (2.0)
AEs related to study drug	18 (9.4)	34 (17.4)	50 (25.4)
Serious AEs	4 (2.1)	8 (4.1)	2 (1.0)
Deaths	1 (0.5)	1 (0.5)	0
Selected AEs			
UTI	8 (4.2)	14 (7.2)	10 (5.1)
GMI			
Male	0	2 (2.5)	5 (5.6)
Female	4 (3.8)	10 (8.8)	8 (7.4)
Osmotic diuresis-related AEs			
Pollakiuria	1 (0.5)	5 (2.6)	6 (3.0)
Polyuria	0	0	6 (3.0)
Volume-related AEs			
Postural dizziness	0	1 (0.5)	2 (1.0)
Orthostatic hypotension	0	0	2 (1.0)

Hypoglycaemia
There were no reports of severe hypoglycaemia and the percentage of patients with documented hypoglycaemia was similar across all arms of the study (2.6% with placebo, 3.6% with canagliflozin 100 mg and 3.0% with canagliflozin 300 mg). There were no reports of hypoglycaemia in the high glycaemic substudy.

Genital mycotic infections (GMI)
The incidence of GMI was higher in patients receiving canagliflozin than those receiving placebo, particularly in women. However, such AEs were mild to moderate in severity and resolved without interruption of treatment.

Urinary tract infections (UTI)
There was a modest increase in UTIs with canagliflozin compared with placebo, however, there were no upper UTIs and all events were mild to moderate in severity and did not result in study discontinuation.

Osmotic diuresis-related and reduced intravascular volume AEs
Osmotic diuresis-related AEs (polyuria, pollakiuria [increased urinary frequency]) and reduced intravascular volume AEs (postural dizziness, orthostatic hypotension) were low (<3%) and led to few study discontinuations.

Malignancies
Data for malignancies are taken from the CSR (8). In the core study, one patient in each arm experienced ‘neoplasms benign, malignant and unspecified’, giving an incidence of 0.5% in each arm. The malignancies were uterine leiomyoma in the placebo arm, basal cell carcinoma in the 100 mg arm and breast adenoma in the 300 mg arm. The patient with basal cell carcinoma in the 100 mg arm discontinued treatment; all other patients continued in the study. There were no reported malignancies in the high glycaemic subgroup.

CANTATA-M: 52 weeks
Over 52 weeks, overall AE rates were 64.1% with placebo/sitagliptin, 67.2% with canagliflozin 100 mg and 66% with canagliflozin 300 mg; rates of serious AEs and AE-related discontinuations were low across groups. Indeed, there were no additional discontinuations after the first 26-week core study.

There was one additional death in the placebo/sitagliptin arm (pulmonary tuberculosis) which was not considered to be related to the study drug.

The incidences of documented hypoglycaemia over 52 weeks were 5.1% (n=10) with canagliflozin 100 mg, 3.6% (n=7) with canagliflozin 300 mg and 3.6% (n=7) with placebo/sitagliptin. No hypoglycaemic events led to discontinuation. Data from the CSR reveals that most (70%) patients had only one episode of hypoglycaemia during the 52 week study period, one patient receiving placebo/sitagliptin had two episodes and three had three or more episodes. One patient receiving canagliflozin 100 mg and two patients receiving canagliflozin 300 mg had three or more episodes. None of the hypoglycaemic episodes was severe in nature (16).

Compared with placebo/sitagliptin, canagliflozin was associated with higher rates of GMI and AEs related to osmotic diuresis; however the majority of such AEs were mild to moderate and only three led to discontinuation (two GMI, one in a male patient and one in a female patient and one AE related to osmotic diuresis).

Data for malignancies is taken from the CSR (14). During the extension period, two patients in the placebo/sitagliptin arm and one patient in the canagliflozin 100 mg arm experienced 'neoplasms benign, malignant and unspecified', giving incidences of 1.3% and 0.6%, respectively. The patient with prostate cancer in the 100 mg arm was the only serious AE due 'neoplasms benign, malignant and unspecified' and he continued study treatment.

Table 4: CANTATA-M summary of overall safety and selected AE (main study) at 52 weeks, n (%) (6)

	Placebo/sitagliptin (n=192)	**CANA 100 mg (n=195)**	**CANA 300 mg (n=197)**
Any AE	123 (64.1)	131 (67.2)	130 (66.0)
AEs leading to discontinuation	2 (1.0)	6 (3.1)	4 (2.0)
AEs related to study drug	23 (12.0)	44 (22.6)	53 (26.9)
Serious AEs	11 (5.7)	11 (5.6)	5 (2.5)
Deaths	2 (1.0)	1 (0.5)	0
Selected AEs			
UTI	12 (6.3)	16 (8.2)	14 (7.1)
GMI			
Male	0	5 (6.2)	8 (9.0)
Female	5 (4.8)	13 (11.4)	10 (9.3)
Osmotic diuresis-related AEs	4 (2.1)	9 (4.6)	15 (7.6)
Volume depletion AEs	1 (0.5)	3 (1.5)	4 (2.0)

Inagaki et al. (2014)

Canagliflozin 100 mg was generally well tolerated. Overall incidences of AEs were modestly higher with canagliflozin versus placebo; rates of serious AEs and AE-related discontinuations were low and similar across both arms, see Table 5. AE leading to discontinuation occurred in 2% (n=2) placebo patients and 1% (n=1) in canagliflozin 100 mg patients. No single AE accounted for more than a single discontinuation. There were no deaths during the study (7).

Table 5: Inagaki et al summary of overall safety and selected AEs at 24 weeks, n (%) (7)

	Placebo (n=93)	**CANA 100 mg (n=90)**
Any AE	55 (59.1)	59 (65.6)
AEs leading to discontinuation	2 (2.2)	1 (1.1)
AEs related to study drug	14 (15.1)	22 (24.4)
Serious AEs	2 (2.2)	1 (1.1)
Deaths	No data	No data
Selected AEs		
UTI	1 (1.1)	1 (1.1)
GMI		
Male	1 (1.7)	0
Female	0	2 (6.5)
Volume depletion-related AEs	1 (1.1)	1 (1.1)

Hypoglycaemia
Rates of hypoglycaemia were low; symptomatic hypoglycaemia was seen in 1.1% of placebo patients and 2.2% of canagliflozin 100 mg patients and asymptomatic hypoglycaemia in 2.2% and 4.4% respectively. None of the hypoglycaemic events were severe in nature.

Genital mycotic infections (GMI)
The incidence of GMI was higher in female patients receiving canagliflozin than those receiving placebo. However, such AEs did not result in discontinuation of treatment.

Urinary tract infections (UTI)
Rates of UTIs were the same with placebo and canagliflozin 100 mg at 1.1% (n=1) in both arms and did not result in discontinuation.

Osmotic diuresis-related and reduced intravascular volume AEs
Rates of AEs related to volume depletion were the same with placebo and canagliflozin 100 mg at 1.1% (n=1) in both arms and did not result in discontinuation.

Malignancies
[redacted]

5. Identification and selection of additional relevant studies

Methods
A systematic literature review was conducted in line with the NICE reference case to identify randomised controlled trials conducted in adult patients with T2DM inadequately controlled on diet and exercise assessing one intervention of interest versus an active comparator of interest or placebo on at least one study outcome (efficacy and/or safety outcomes).

Comparators included (at doses licensed and recommended in the UK):
- SGLT-2-i - canagliflozin, dapagliflozin, empagliflozin
- SU - tolbutamide, glipizide, gliclazide, glibenclamide (glyburide), glimepiride
- Pioglitazone
- DPP-4-i - vildagliptin, sitagliptin, saxagliptin, linagliptin.

A second identical search was conducted separately only considering repaglinide.

The following electronic databases were searched: Medline, Medline-in-process, Embase and the Cochrane library. Search terms were combined to capture three components of the study question: the disease of interest (T2DM), the interventions of interest and the study type of interest (randomised controlled trials).

The searches were run on March 31 2015 in four databases to identify relevant publications. Hand searches of conferences, registries and HTA websites were also conducted to capture data related to clinical trials not yet published, see Table 6, Appendix 2. Conference proceedings were searched from January 1, 2010 onwards as studies were assumed to be published within three years of a presentation at a congress. A full list of sites considered for the hand searches (i.e. conference websites, clinical trial registry and HTA websites) is reported in Table 6, Appendix 2.

For each citation, titles and abstracts (where available) of studies were reviewed by a first reviewer according to the pre-specified inclusion/exclusion criteria. A detailed list of inclusion and exclusion criteria is presented below, in Table 6. A second reviewer quality checked the assessment and any discrepancies were resolved by discussion or by a third internal reviewer if necessary. Articles identified as potentially relevant during the first phase of the screening were then reviewed in full.

Table 6: Criteria used in the trial selection process

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
Population	Adult patients Type 2 Diabetes Mellitus (T2DM) Non-Insulin Dependent Diabetes Mellitus (NIDDM)	Non-humans- animals, tissue of human No T2DM nor NIDDM Not patients inadequately controlled with diet and exercise	The population has been restricted to match the stated decision problem for the treatment of T2DM.
Intervention	Canagliflozin (100 mg/ 300 mg), dapagliflozin (5 mg, 10 mg), empagliflozin (10 mg/ 25 mg) SU (e.g. tolbutamide, glipizide, gliclazide, glibenclamide [glyburide] glimepiride) Pioglitazone (all doses) DPP-4-i (vildagliptin, sitagliptin, saxagliptin, linagliptin) Meglitinide (repaglinide)	Not monotherapy Not at least two arms of interest one intervention of interest versus. one comparator of interest	The interventions and comparators have been restricted to match the stated decision problem for the treatment of T2DM.
Comparators	Same treatments covered under the interventions plus comparison to placebo	Trial not including one treatment of interest versus another treatment of interest or placebo	Interventions have been restricted to provide an indirect comparison between canagliflozin and comparators listed in the NICE scope.
Outcomes*	HbA1c change from baseline (%) Proportion of patients reaching HbA1c <7% FPG change from baseline (mmol/l) Weight change from baseline (kg), BMI change from baseline kg/m^2) SBP change from baseline (mmHg) Proportion of patients with at least one hypoglycaemic event, “Any” hypoglycaemic events were pooled, defined as either symptomatic events (with or without biochemical confirmation) or asymptomatic events (with biochemical confirmation) Proportion of patients with at least one major hypoglycaemic event	Does not contain at least one outcome of interest.	These outcomes were chosen as these are frequently measured and reported in the trials involving patients with T2DM; and are relevant to the interventions considered in this SLR and the scope.
Trial design	Randomised controlled trials, with at least two arms. Any type of design is of interest (including crossover trials)	Single-arm trials Observational studies (prospective/retrospective)	Review includes RCTs, as these are the gold standard of clinical evidence, minimising the risk of confounding factors besides allowing a comparison of the efficacy of the interventions. Studies identified should be at least 12 weeks in duration to allow potential indirect comparison with canagliflozin.
Language restrictions	English		The restriction would not limit results substantially due to data availability in English language

Results of the systematic literature review.

A total of 4,984 unique citations were identified as part of the systematic literature search conducted in March 2015. The PRISMA diagram of summarising the total number of hits identified at each phase of the review is presented in Figure 7, Appendix 2. Full summary of the results of this systematic literature review (SLR) may be found in the study report (61).

6. Meta-analysis

Methods and outcomes of included studies

An SLR was conducted to identify RCTs conducted in adults with T2DM with inadequate glycaemic control on diet and exercise alone. While the draft NICE scope refers to the target population as "people with type 2 diabetes for whom metformin is not tolerated or is contraindicated", RCTs rarely if ever restrict their eligibility in this way. As such, studies were only excluded if the patient population was restricted to patients adequately controlled with diet and exercise. A separate pragmatic search was conducted to identify any differences in patient characteristics between patients who are intolerant and/or contraindicated to metformin and those that are not. None of the identified literature supported this hypothesis and most showed there to be no identifiable differences between these population groups (62). Therefore, it is believed that this assumption would have no significant confounding bias on the results.

In order to pool data that are comparable across trials, additional criteria were defined for inclusion into the NMA:

- Analyses were conducted at 26 weeks to match the times of assessment of the canagliflozin trials (it was not possible to conduct comparative analyses against placebo in CANTATA-M beyond 26 weeks as after this time placebo patients crossed over to sitagliptin therapy). Based on clinical expert opinion, trials reporting results at 26 weeks ± 4 weeks were included in the base case analysis and trials reporting results at 26 weeks ± 10 weeks were included in a sensitivity analysis. Trials not reporting results within these ranges were excluded from the NMA (see main assumptions below).

- Based on clinical expert opinion, nodes of the NMA were treatment- and dose-specific except for SU (see main assumptions below).

- Treatments not in common use in the UK at point of undertaking this analysis were excluded (e.g. alogliptin).

The following trials were included as part of the sensitivity analyses only: trials reporting results at 16 to 21 weeks and/or at 31 to 36 weeks, trials with results published within conference abstracts only and trials assessing repaglinide.

Methods of analysis and presentation of results

The methods of data extraction and analysis and presentation of results are described in the full study report (61), including but not exclusively: data inputs; handling of missing data; direct comparisons; model selection; inconsistency assessment; interpretation of results; main assumptions; sensitivity analysis.

Complete list of relevant RCTs

A summary of trials used to conduct the indirect/mixed treatment comparisons and sensitivity analyses is reported in Table 7 and Table 8 in Appendix 3. Forty-two trials were included in the base case analysis. The maximum duration reported in these trials was less than two years (with the exception of one with a duration of 48 months plus two weeks).

A total of twenty trials were included in the sensitivity analyses. The maximum study duration was 55 weeks, and the average study duration was 28 weeks ± 11 weeks. Among these trials, a total of 11 trials reported results at 24 weeks ± 4 weeks, and three trials reported results at 52 weeks ± 4 weeks. One trial was open-label, two were single-blinded and the remaining 15 were double-blind trials.

Outcomes of interest

The following outcomes were considered for the meta-analysis:

- Mean change in HbA1c
- Proportion of patients reaching HbA1c<7%
- Mean change in FPG
- Mean change in weight
- Mean change in BMI
- Mean change in SBP
- Proportion of patients with at least one hypoglycaemic event

Only outcomes of relevance to the economic model (i.e. change in HbA1c, weight, BMI and SBP, and incidence of hypoglycaemia) and the comparators considered in the economic simulations are presented in this submission. The full results of the SLR and the NMA including information relating to the proportion of patients reaching HbA1c <7% and FPG change from baseline (mmol/L) can be found in the NMA report (61).

Risk of bias

Sensitivity analyses excluding non-double-blinded trials were conducted as these trials are considered of lower quality.

Main assumptions (for the base case analysis)

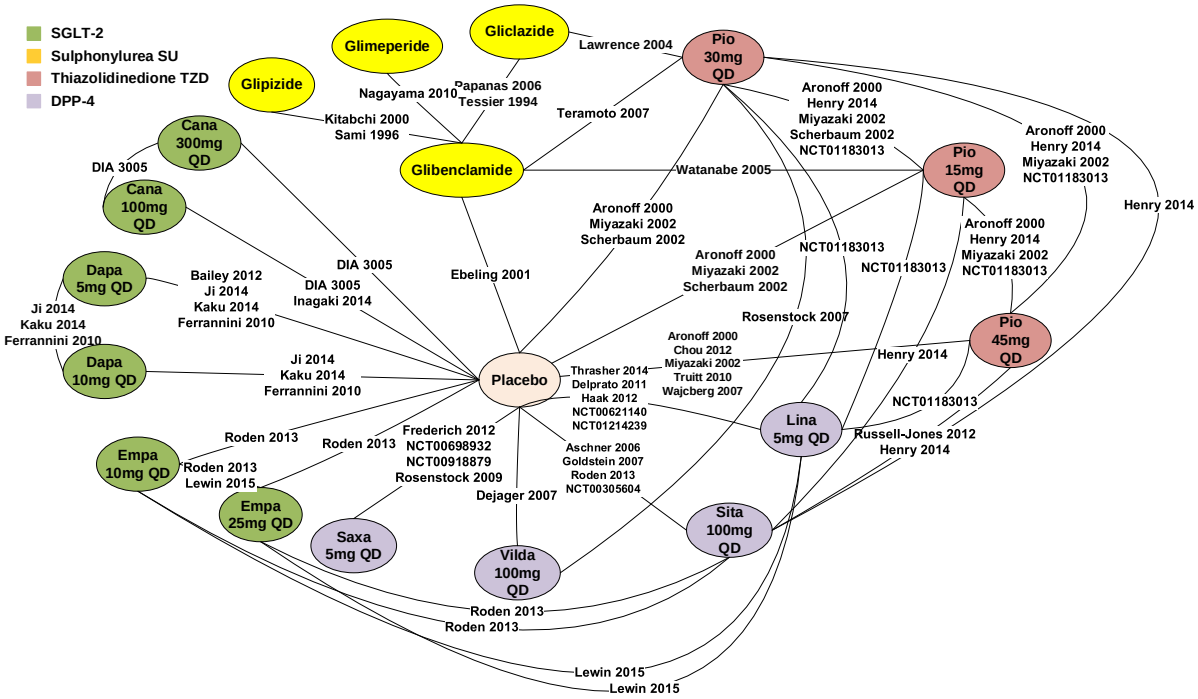
The primary and secondary endpoints for canagliflozin trials included in the NMA analysis were reported at 26 weeks. Thus, to maximise the comparability between these outcomes, and those reported in comparator trials, the primary NMA analysis only included outcomes reported at 26 weeks +/- 4 weeks.

Nodes of the NMA were treatment- and dose-specific except for sulfonylurea. Doses of sulfonylurea were pooled to reflect dose adjustments on a per-patient basis.

Results of NMA

A total of 40 studies were included in the analysis of the mean change from baseline in HbA1c. All studies were included in the analysis of the mean change in HbA1c from baseline, see Figure 7. Networks of evidence corresponding to all other outcomes reported below are shown in Appendix 3.

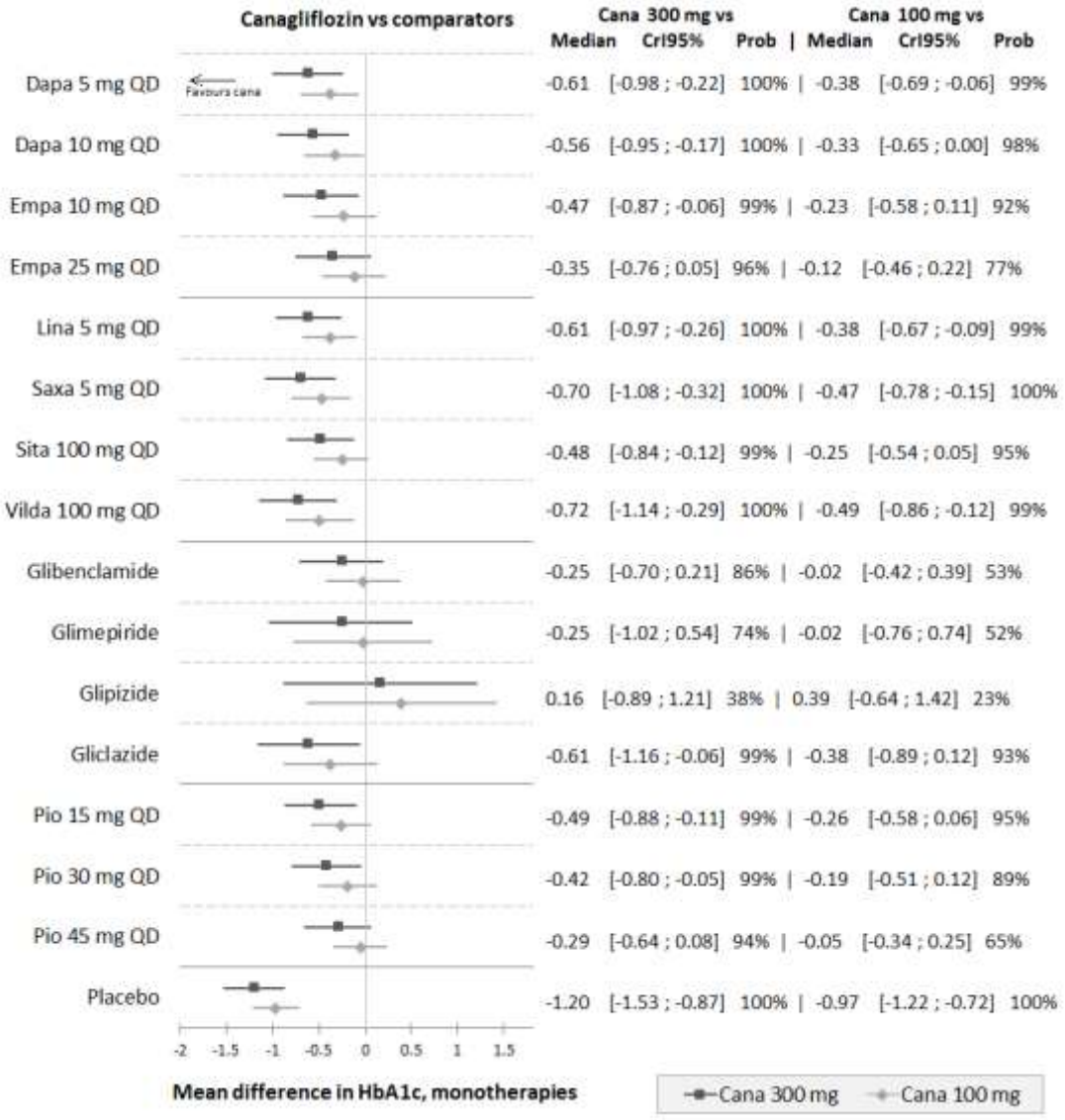
Figure 7: Network of evidence - HbA1c analysis (61)



As shown in Figure 8, greater reductions in HbA1c were observed for canagliflozin 300 mg versus other SGLT-2-i; DPP-4-i; pioglitazone; and the SUs glimepiride, gliclazide, and glibenclamide. Canagliflozin 100 mg conferred greater reductions in HbA1c versus other SGLT-2-i, DPP-4-i, pioglitazone 15 and 30 mg, and the SU gliclazide. Canagliflozin 100 mg was associated with similar HbA1c reductions compared to pioglitazone 45 mg, glibenclamide, and glimepiride. Canagliflozin 300 mg was associated with similar HbA1c reductions versus glipizide, whereas canagliflozin 100 mg was associated with lower HbA1c reductions versus glipizide.

Clinical experts reviewed the results and determined that the glipizide finding deserved further investigation, given that canagliflozin had been shown to perform favourably versus glimepiride (63), an SU with better efficacy than glipizide (64). The study by Sami (1996) included a population with high HbA1c levels at baseline (between 11% and 12% compared to <10% in other trials) (65). Given that HbA1c at baseline is an important treatment effect modifier, this could explain the results in the comparison of canagliflozin and glipizide (65).

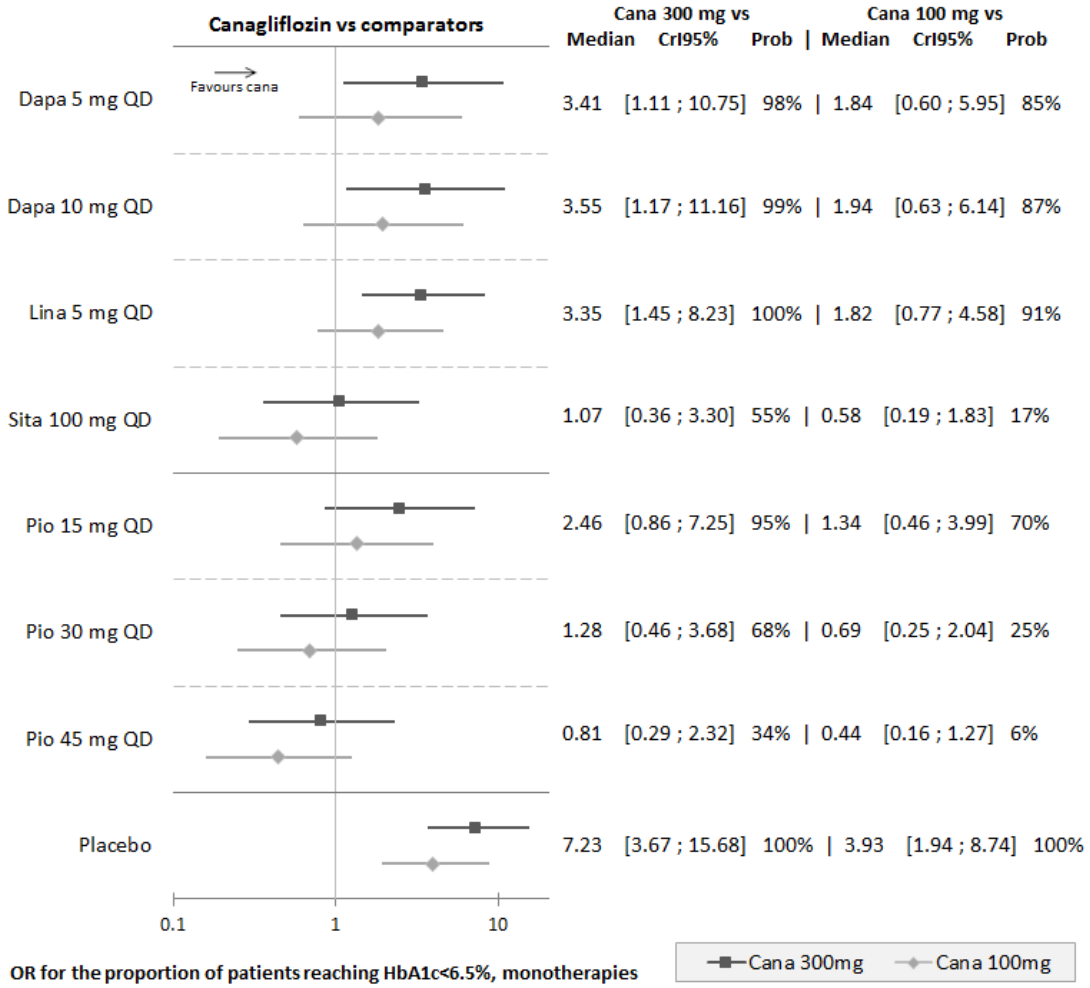
Figure 8: Mean difference in HbA1c (%) [95%CrI] at 26 weeks (RE model)



The draft clinical guideline update stipulate an HbA1c treatment target <6.5%. Thus, we have explored this outcome as part of this NMA. A total of eight studies were included in the analysis of the proportion of patients reaching HbA1c<6.5%. Canagliflozin 300 mg and 100 mg were associated with greater proportions of patients reaching HbA1c<6.5% compared to dapagliflozin 5 mg and 10 mg and linagliptin 5 mg. Canagliflozin 300 mg was associated with a comparable or greater proportion of patients reaching HbA1c<6.5% compared to pioglitazone 15 mg, 30 mg and 45 mg and sitagliptin

100 mg. Canagliflozin 100 mg were associated with a comparable proportion of patients reaching HbA1c<6.5% compared to pioglitazone 15 mg, whereas pioglitazone 30 mg and 45 mg were associated with a greater proportion of reaching HbA1c<6.5, see Figure 9. No results were available versus sulfonylureas due to missing data.

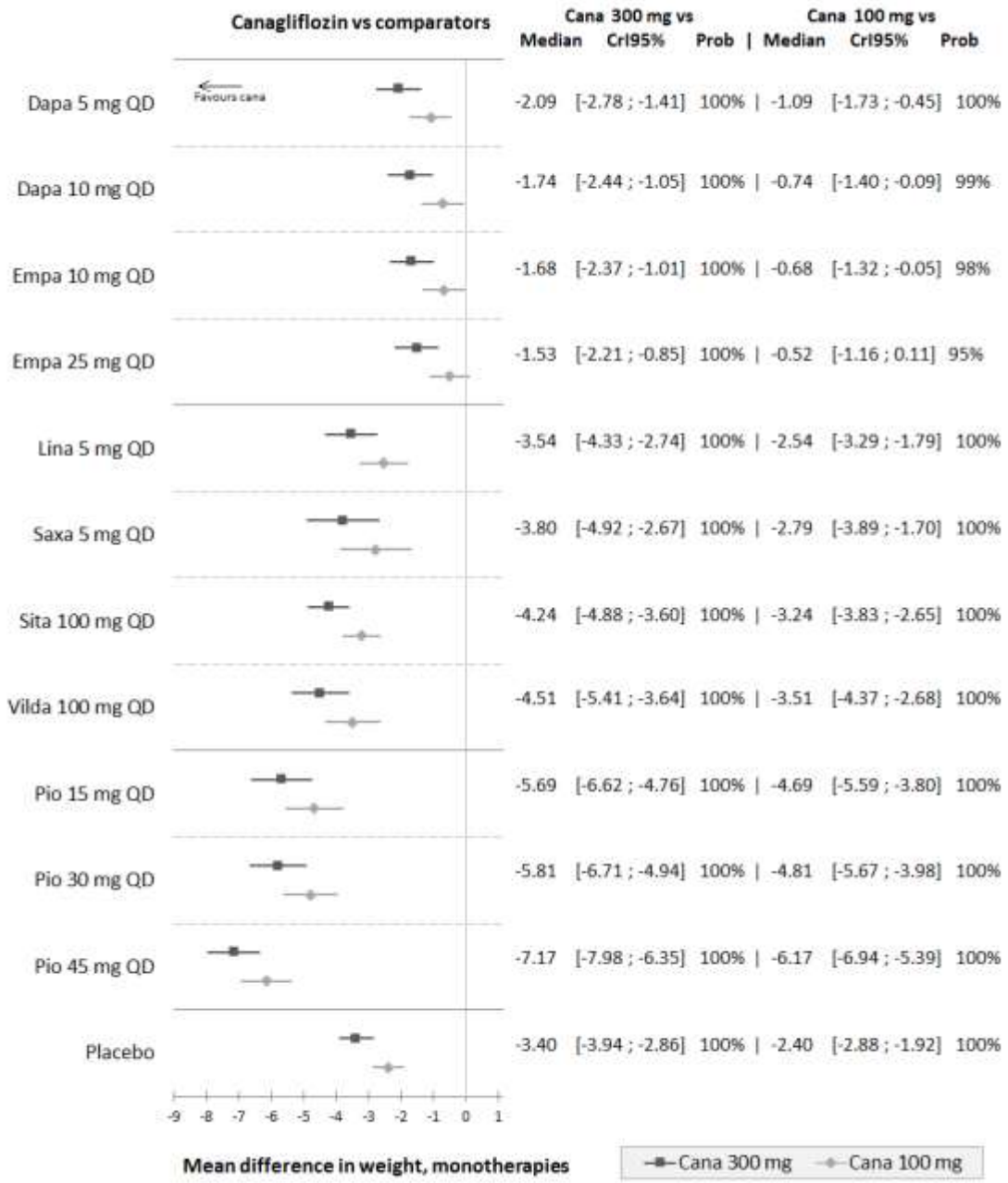
Figure 9: Odds-ratios (OR) for the proportion of patients reaching HbA1c<6.5% [95%CrI] at 26 weeks (FE model)



Eighteen studies could be included in the analysis of mean weight change from baseline, assessing agents that inhibit SGLT2, DPP-4-i, and pioglitazone. No data were available for SU. Canagliflozin provided greater reductions in weight (kg) versus all comparators, see Figure 10.

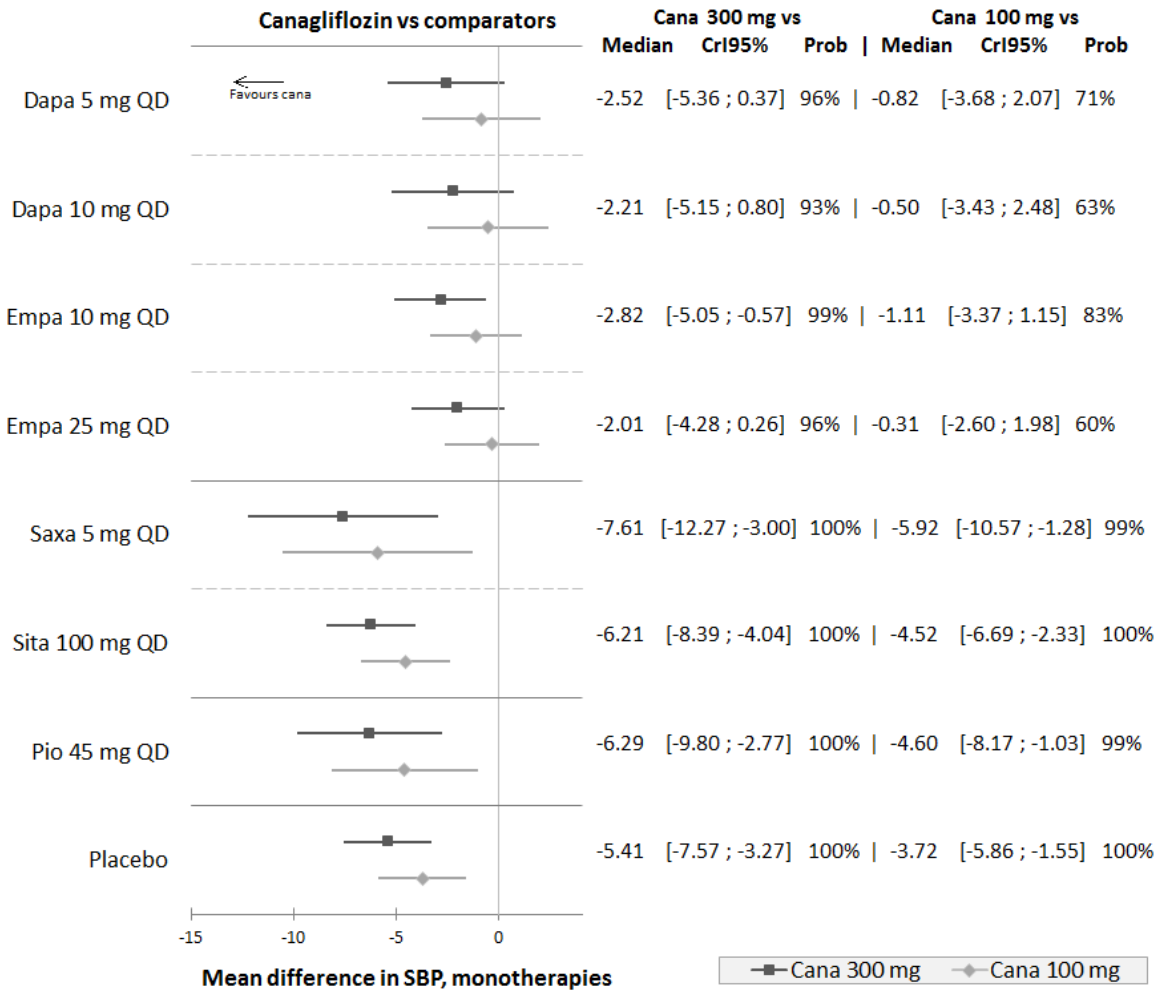
Although SU could not be evaluated in terms of weight loss, a total of six studies were included in the analysis of the mean change from baseline in BMI, which included studies for SU. Canagliflozin 300 mg and 100 mg ranked respectively first and second on the basis of the SUCRA in terms of BMI reduction from baseline see Figure 10, Appendix 3.

Figure 10: Mean difference in weight [95%CrI] at 26 weeks (FE model)



Only eight studies that assessed dapagliflozin, empagliflozin, saxagliptin, sitagliptin, and pioglitazone 45 mg could be included in the analysis of mean SBP change from baseline. The low number of trials included in the analysis of SBP led to broad credibility intervals. Canagliflozin 300 mg had greater SBP reductions versus all comparators, see Figure 11.

Figure 11. Mean difference in SBP [95%CrI] at 26 weeks (FE model)



For the analysis of the proportion of patients experiencing at least one hypoglycaemic event, several treatment arms were associated with zero events (i.e. no patient experienced hypoglycaemia at 26 weeks) and most of the studies reported less than 10% of patients with at least one hypoglycaemic episode. This small number of events led to unstable results when conducting the analysis, that is to say the uncertainty in the data meant that the results were potentially unreliable. An exploratory analysis of 17 studies was conducted; see Figure 13 and associated text, Appendix 3. For simplicity, only the rates of hypoglycaemic events reported for all studies are listed in Table 7.

WinBUGS and SAS programs are reported in Appendix 10 and the full tables of results for each endpoint are reported in Appendix 14 of the full study report (61).

Table 7: Base case analysis – Input of all hypoglycaemic events

Study name	Treatment	week	N	event	%
Aschner 2006	Placebo	24	253	2	1
Aschner 2006	Sitagliptin 100mg OD	24	238	3	1
Bailey 2012	Placebo	24	68	0	0
Bailey 2012	Dapagliflozin 5mg OD	24	68	1	1
Chou 2012	Placebo	26	137	3	2
Chou 2012	Pioglitazone 45mg OD	26	751	3	0
Delprato 2011	Placebo	24	167	1	1
Delprato 2011	Linagliptin 5mg OD	24	336	1	0
Dia 3005	Placebo	26	192	5	3
Dia 3005	Canagliflozin 100mg OD	26	195	7	4
Dia 3005	Canagliflozin 300mg OD	26	197	6	3
Ferrannini 2010	Placebo	24	75	2	3
Ferrannini 2010	Dapagliflozin 5mg OD	24	64	0	0
Ferrannini 2010	Dapagliflozin 10mg OD	24	70	2	3
Goldstein 2007	Placebo	24	176	1	1
Goldstein 2007	Sitagliptin 100mg OD	24	179	1	1
Haak 2012	Placebo	24	72	1	1
Haak 2012	Linagliptin 5mg OD	24	142	0	0
Henry 2014	Pioglitazone 15mg OD	24	183	20	11
Henry 2014	Pioglitazone 30mg OD	24	194	22	11
Henry 2014	Pioglitazone 45mg OD	24	188	20	11
Henry 2014	Sitagliptin 100mg OD	24	186	25	13
Inagaki 2014	Placebo	24	93	3	3
Inagaki 2014	Canagliflozin 100mg OD	24	90	6	7
Ji 2014	Placebo	24	132	2	2
Ji 2014	Dapagliflozin 5mg OD	24	128	1	1
Ji 2014	Dapagliflozin 10mg OD	24	133	1	1
Kaku 2014	Placebo	24	87	0	0
Kaku 2014	Dapagliflozin 5mg OD	24	86	0	0
Kaku 2014	Dapagliflozin 10mg OD	24	88	2	2
NCT01214239	Placebo	24	99	0	0
NCT01214239	Linagliptin 5mg OD	24	200	1	1
Rosenstock 2009	Placebo	24	95	6	6
Rosenstock 2009	Saxagliptin 5mg OD	24	106	5	5
Russell-Jones 2012	Pioglitazone 45mg OD	26	163	6	4
Russell-Jones 2012	Sitagliptin 100mg OD	26	163	5	3
Thrasher 2014	Placebo	24	120	1	1
Thrasher 2014	Linagliptin 5mg OD	24	106	3	3
Truitt 2010	Placebo	26	92	1	1
Truitt 2010	Pioglitazone 45mg OD	26	91	0	0

Heterogeneity and inconsistency assessments

The analysis of heterogeneity between results of pairwise comparisons led to the identification of a potential source of heterogeneity as some trials were not double-blinded or included patients with

higher diabetes duration at baseline. The analysis of inconsistency was conducted within each independent loop of the networks.

Sensitivity analyses

In a primary sensitivity analysis, two additional trials assessing repaglinide were included Jovanovic 2004 (66) and Jovanovic 2000 (67). The study by Jovanovic 2004 included a titration of repaglinide as recommended by the European Medicines Agency (68). The study by Jovanovic 2000 included two fixed doses of repaglinide (3 mg OD and 12 mg OD). Only repaglinide 12 mg was kept in the analysis and considered as equivalent to repaglinide titration, as the dose was closer to the median of the final dose (10 mg) of the repaglinide titration arm included in the trial by Jovanovic 2004.

Given the shape of this network (see figure 15, Appendix 3), the heterogeneity and inconsistency for repaglinide trials could not be assessed. It should be noted that repaglinide is not mentioned in the short guidelines by NICE from January 2015 (69). However, in the full version of the current clinical guidelines (70), a comparison of metformin and SU versus meglitinides concluded that meglitinides are not preferred to SU. This conclusion is endorsed by clinical experts who suggested that the inclusion of repaglinide should only be considered as part of sensitivity analyses (71).

All but two (excluding non-double-blind trials and including trials with results at 26 weeks +/- 10 weeks) of the other sensitivity analyses had minor impacts on the results for the mean changes from baseline in HbA1c and did not change the conclusions for the comparisons of canagliflozin 300mg versus each comparator. Results for the sensitivity analyses including repaglinide and DIA3011 results can be found in Table 9 and Table 10 in Appendix 3, respectively. Information on all sensitivity analyses conducted, an inconsistency assessment, and a heterogeneity assessment can be found in the full study report (61).

7. Interpretation of clinical evidence

Benefits of canagliflozin

Canagliflozin is an effective AHA

Evidence for canagliflozin in monotherapy comes from two studies, CANTATA-M which compared both doses (100 mg and 300 mg) with placebo for 26 weeks (5) with an extension out to 52 weeks (6) and a Japanese study comparing canagliflozin 100 mg and 200 mg with placebo for 24 weeks (7).

Both studies showed a significant reduction in HbA1c versus placebo from a mean baseline HbA1c of 8%. In CANTATA-M there was a dose-dependent reduction in HbA1c with canagliflozin (LS mean change from placebo at 26 weeks) of -0.91% with the 100 mg dose and -1.16% with the 300 mg dose, which was maintained out to 52 weeks (5, 6). The Japanese study (7) demonstrated a reduction in HbA1c (LS mean change from placebo at 24 weeks) of -1.03% with the 100 mg dose at 24 weeks.

Patients with higher baseline HbA1c achieved greater reductions in HbA1c with canagliflozin. In the high glycaemic subgroup of CANTATA-M (5), which included patients with a mean baseline HbA1c of 10.6%, reductions from baseline in HbA1c were -2.13% and -2.56% for the 100 mg and 300 mg dose of canagliflozin respectively.

Achievement of HbA1c targets was greater with canagliflozin than with placebo. In CANTATA-M HbA1c <7% was achieved by 62.4% of patients receiving canagliflozin 300 mg, 44.5% receiving 100 mg versus 20.6% receiving placebo ($p<0.001$ for both canagliflozin doses versus placebo). HbA1c <6.5% was achieved by 28.4% of patients receiving canagliflozin 300 mg, 17.8% receiving 100 mg versus 5.3% receiving placebo, despite a mean baseline HbA1c of 8%.

In the high glycaemic subgroup, 17.4% of patients receiving the 300 mg dose and 11.6% receiving the 100 mg dose achieved HbA1c <7%, despite having baseline HbA1c >10%. Data for the 6.5% goal was not available for the high glycaemic subgroup.

The results of the NMA support the findings of the placebo-controlled canagliflozin studies. The NMA provides results comparing outcomes with canagliflozin to outcomes with other SGLT-2-i, SUs, DPP-4-i and pioglitazone. A method by which to interpret these data is to consider ranking of results in terms of the surface under the cumulative ranking curve (SUCRA), which provides a summary statistic of cumulative ranking. Canagliflozin 300 mg was ranked highest in terms of mean change from baseline in HbA1c and canagliflozin 100 mg the third highest (data from 40 studies). Canagliflozin 300 mg was ranked the second most effective agent in achieving HbA1c<7% behind pioglitazone (22 studies) and the most effective agent in lowering FPG (36 studies).

Canagliflozin has additional clinical benefits

Clinically relevant reductions in BP (-3.7 mmHg with the 100 mg dose in CANTATA-M, -5.2 mmHg with the 100 mg dose in the Japanese study and -5.4 mmHg with the 300 mg dose in CANTATA-M) and body weight (2.2-3.3% loss) were observed in both clinical trials, and maintained out to 52 weeks with both the 100 mg and 300 mg dose (5-7). Rates of hypoglycaemia were low, similar to placebo, in both clinical trials and there were no severe hypoglycaemic episodes in either trial (5-7). The NMA confirms these additional benefits with canagliflozin, although there are gaps in the data due to some outcomes not being reported within the literature for some of the agents considered.

With regard to change in weight, BMI and SBP canagliflozin 100 mg and 300 mg were ranked first and second for weight loss (19 studies), reduction in BMI (six studies) and reduction in SBP (eight studies). However, missing data from some agents meant that no results were available versus SU (weight and SBP), DPP-4-i (BMI and SBP) or other SGLT-2-i (BMI). Of note, reduction in weight with canagliflozin in triple therapy (in combination with metformin and SU) is associated with an improvement in quality of life and satisfaction with health, which has been linked with an increase in healthy behaviours such as making healthy food choices and being more physically active (72).

All agents had a low risk of hypoglycaemia. Canagliflozin 100 mg and 300 mg were associated with a similar risk of hypoglycaemia to dapagliflozin. However, it should be noted that missing data for some other agents meant that no results were available versus SU or empagliflozin for hypoglycaemia. SU have a high risk of hypoglycaemia; the UK Hypoglycaemia Study Group found that 40% of patients on SU experienced symptomatic hypoglycaemia over a 9-12 month period (47). The risk of a severe hypoglycaemic episode was 7% during the first 2 years of treatment with SUs (47).

As discussed above, hypoglycaemia and fear of hypoglycaemia both limit adherence to treatment and glycaemic control. Hypoglycaemia has a negative impact on all aspects of patients' lives, including social activities, travelling, driving, exercising and attendance/productivity at work regardless of the severity of the episode, which in turn impacts on quality of life (49-51). As would be expected, the impact of severe hypoglycaemia on patients' lives is significantly greater than non-severe hypoglycaemia; however, non-severe hypoglycaemia also has a considerable impact (51). The impact of hypoglycaemia is considerable in terms of cost to the NHS. Recent data from a UK-based audit reveals that patients taking a SU accounted for one-third of patients with T2DM admitted to Accident and Emergency with a hypoglycaemic episode (53). Further data published in 2015 estimates the cost of a severe hypoglycaemic episode in patients with T2DM at £407, rising to £2,152 for a severe episode requiring admission to hospital (54). Therefore an agent with a low hypoglycaemia risk is of benefit.

The clinical studies, together with the NMA, provide strong evidence that canagliflozin is effective in lowering HbA1c and has the added benefits of BP lowering and weight loss with a low risk of hypoglycaemia. It follows that canagliflozin is most suitable for use in those patients in whom the additional clinical benefits will provide further clinical gain, for example in obese patients with one or more additional co-morbidities such as sleep apnoea, uncontrolled hypertension, polycystic ovary syndrome and osteoarthritis.

Canagliflozin is well tolerated

Canagliflozin is well tolerated, with low rates of discontinuation in the clinical trials, comparable to that seen with placebo (canagliflozin 1-3% and placebo 1-2%). However, a number of AE related to the mode of action are more common with canagliflozin than placebo. These include GMI, UTIs and volume related AEs. In the monotherapy studies detailed in this submission, most of these AEs were mild to moderate in nature, managed with standard therapies and did not result in discontinuation. Overall, only one woman and one man out of 482 treated with canagliflozin in the clinical studies discontinued due to GMI and there was one discontinuation due to osmotic diuresis.

Canagliflozin results in changes to the lipid profile, resulting in a slight decrease in the LDL/HDL ratio and modest reductions in triglycerides. Importantly, however, an interim meta-analysis of cardiovascular events in the CANagliflozin cardioVascular Assessment Study (CANVAS) has shown no increase in CV risk with canagliflozin (73).

Canagliflozin offers simplicity

Canagliflozin has a simple od dosing regimen, which can be expected to result in good adherence. It has been estimated that in patients with long-term conditions such as T2DM adherence is approximately 50% (55), and falls still further in patients with co-morbid diseases and increased pill burden (56). AEs have a negative impact on adherence (49, 57), with hypoglycaemia and weight gain having the greatest impact in patients with T2DM (58). Therefore agents without these AEs, such as SGLT-2-i and DPP-4-i, have the potential to improve adherence. Real world data from the US which analysed information from US claims databases revealed that one year after initiation of treatment significantly more patients remained on treatment with canagliflozin than with DPP-4-i (64% with canagliflozin 100 mg, 65% with canagliflozin 300 mg versus 30% [linagliptin], 31% [saxagliptin] and 50% [sitagliptin], p<0.0001) (2).

Treatment with canagliflozin is initiated at the 100 mg dose and does not require dose titration, which avoids the need for repeated HCP visits and SMBG. The canagliflozin 300 mg dose provides additional efficacy, if required.

Canagliflozin 300 mg provides additional efficacy over the 100 mg dose

Canagliflozin 300 mg is recommended for use in patients who need tighter glycaemic control and tolerate canagliflozin 100 mg od with eGFR of at least 60 ml/min/1.73 m^2 or CrCl of at least 60 ml/min (23). Thus canagliflozin 300 mg provides a treatment option in a subgroup of patients that tolerate canagliflozin 100 mg but have not achieved the desired target in terms of HbA1c reduction. This allows for individualisation of treatment in this subgroup of patients.

The clinical studies and the NMA demonstrate that canagliflozin 300 mg provides additional efficacy over the 100 mg dose, which is most pronounced in patients with a high baseline HbA1c. In the high glycaemic subgroup of CANTATA-M (5), reductions from baseline in HbA1c were -2.56% with the 300 mg dose of canagliflozin compared to -2.13% with the 100 mg dose.

There is also a dose response for the additional benefits observed with canagliflozin. In CANTATA-M, canagliflozin resulted in a LS mean difference versus placebo of -2.2% (-1.9 kg) with the 100 mg dose and -3.3% (-2.9 kg) with the 300 mg dose, both p<0.001. Larger reductions were observed in the high glycaemic subgroup (-3.0% and -3.8% with canagliflozin 100 mg and 300 mg, respectively). There was also a significant dose-related decrease in SBP; LS mean difference versus placebo of -3.7 mmHg with the 100 mg dose and -5.4 mmHg with the 300 mg dose, both p<0.001. Larger reductions were observed in the high glycaemic subgroup (-4.5 mmHg and -5.0 mmHg with canagliflozin 100 mg and 300 mg, respectively) (5).

The option of the canagliflozin 300 mg dose allows patients to remain on the same monotherapy for longer and delay intensification of treatment. This offers simplicity for the patient and for the NHS since additional healthcare visits and SMBG will not be required. At this current time, this is hypothetical since clinical studies have not been carried out using dose escalation. Clinical opinion, however, supports this approach (74). It should be noted, however, that most UK patients will remain on the 100 mg dose. [redacted].

Strengths and limitations of the evidence for canagliflozin

Strengths

The two clinical studies assessing canagliflozin in monotherapy have been published in high quality peer review journals. The key study (CANTATA-M) was a multi-centre study carried out in North America, Europe, South America, South Africa and Asia.

CANTATA-M was a two-part study, for the first 26 weeks (the core study) canagliflozin (100 mg and 300 mg) was assessed versus placebo, and for the remaining 26 weeks patients entered an extension period, with canagliflozin patients continuing on canagliflozin and placebo patients switched

to sitagliptin. This provides data on 52 weeks treatment with canagliflozin and demonstrates that the reduction in HbA1c, BP and body weight observed with canagliflozin is maintained over 52 weeks with no additional AEs. CANTATA-M also included a high glycaemia substudy in which patients had HbA1c of between 10% and 12% at baseline; patients in this substudy also showed significant clinical benefit with canagliflozin.

Canagliflozin is supported in the wider context by an extensive global clinical development programme in over 10,000 patients assessing the use of canagliflozin in dual therapy, triple therapy and as an add-on to insulin. A consistent benefit with canagliflozin has been demonstrated across the clinical study programme.

Limitations

The two clinical trials did not compare against an active comparator, however, the use of NMA helps to fill these data gaps. The Japanese study (7) considered a Japanese population and compared an unlicensed dose of canagliflozin (200 mg) and the licenced 100 mg dose with placebo over 24 weeks.

Studies have not investigated dose escalation from 100 mg to 300 mg. The clinical study design for CANTATA-M considered the 100 mg and 300 mg doses in parallel and the Japanese study considered the 100 mg and 200 mg doses in parallel.

Whilst the NICE scope (4) specifies health related quality of life as an outcome, CANTATA-M (5) and the Japanese study (7) did not include health related quality of life measures and thus no data are available from these studies.

As with all clinical studies, the use of exclusion criteria means that the clinical study population does not necessarily reflect the real world population. Although the inclusion criteria were relatively broad, patients with CVD and moderate renal impairment were excluded and therefore there is a paucity of evidence in this patient group. However, studies in the wider canagliflozin clinical study programme (CANVAS and DIA3004) did consider these patients, albeit using canagliflozin as combination treatment.

Although the duration of CANTATA-M extended to 52 weeks, T2DM is a chronic life-long condition and evidence over the longer term would be beneficial in terms of long-term durability and safety of canagliflozin.

Relevance to the decision problem

The two monotherapy studies are directly relevant to the decision problem in that they included patients who were uncontrolled on their existing treatment of diet and exercise. In both studies, the primary end-point was LS mean change in HbA1c from baseline. HbA1c is an established marker for glycaemic control and recognised as such in NICE guidance (28, 36).

Ongoing studies

None relevant.

8. Cost effectiveness evidence

Published cost-effectiveness evaluations

An update of a systematic search of published economic evaluations with relevance to the decision problem was conducted (75). Briefly, the search encompassed:

- Publically available cost-effectiveness evidence for canagliflozin, for agents in the class of SGLT-2 inhibitors (e.g., dapagliflozin), and intended comparators to canagliflozin (DPP-4-i, TZD and SU) within the scope of this appraisal. In addition, the study also included a review of economic simulation models of T2DM; see below for further detail on these results.
- Searches were conducted on Medline (PubMed Interface), Embase, Medline® In-Process, EconLIT, NHS EED, DARE, HTA (University of York's Centre for Reviews and Dissemination [CRD] Database), ISPOR and Mt. Hood Challenge conference proceedings on their

respective internet sites, and internet sites for NICE in the UK, SMC in Scotland, PBAC in Australia, and CADTH in Canada. Secondary searches of the reference lists of qualifying studies were also conducted.

- Studies were included if they:
    - Included economic evaluation that included SGLT-2-i, DPP-4-i, TZD, GLP-1 analogues, and/or SU derivatives
    - UK, Canada, or Australian setting
    - Studies published since 2013, in order to update the previous literature review which had a cut-off year at 2013. With the exception of new relevant comparators added by NICE where older publications have been added as well to fit the previous review.
- Studies were excluded if they:
    - Did not concern T2DM (e.g., T1DM)
    - Were not written in English
    - Used cost-minimisation or cost-consequence methods
    - Were limited to individual complications of T2DM (e.g., retinopathy or diabetic foot ulcers)
    - Contained insufficient information to establish whether a unique model is discussed.
- Usual methods were employed for selecting the studies for inclusion in the analysis. Specifically, titles were first reviewed by three trained health economists using a generous level of tolerance. Abstracts were then reviewed for those passing the title stage by the same three health economists. Full-length articles were then reviewed for those passing the abstract stage by two of the health economists. Finally, each qualifying study was downloaded to reference management software EndNote, where duplicate copies were removed.
- Study content—consisting of the model employed, indications and comparisons studied, perspective, key data sources, time horizon, sub-groups and sensitivity analyses, key results, and conclusions and recommendations—was extracted and entered into a data capture form consistent with that recommended by NICE. The quality of evidence was assessed using the procedure developed by Drummond and Jefferson.

The search (conducted on 1st April 2015) yielded 105 analyses of potential relevance to the UK setting, published since 2013 of which 19 were research abstracts/posters presented at ISPOR congresses, 10 were articles published in peer-reviewed journals, and 76 were HTA reviews. Eight studies of canagliflozin were found that met the inclusion criteria. For complete details, see the full report (75).

Importantly, previous HTAs assessments have raised concerns about optimistic disutility values for weight gain and hypoglycaemic events, uncertainty about the underlying clinical efficacy data (including data generated with indirect methods; these have been addressed to the extent possible in the current analysis, including use of conservative NMA and mixed treatment comparisons), and the handling of non-significant treatment effects. We have therefore used disutility weights preferred by NICE and clinical efficacy data from a comprehensive trial programme (entered into a thorough NMA to maximise consistency for scenarios where head-to-head data were unavailable).

A summary list of considered cost-effectiveness evaluations may be found in the study report (75). The quality of evidence was assessed in the 29 peer-reviewed publications and research posters. These studies were generally of acceptable quality. The main differences concerned the level of detail provided (with research posters naturally having a lower level of detail).

De novo analysis

This submission includes *de novo* economic analyses of adult patients with T2DM suitable for therapy with canagliflozin in monotherapy. This population reflects the licensed indication for canagliflozin as well as the patients recruited into the Phase 3 clinical trial programme (76).

Model Structure

In this submission, ECHO-T2DM was used to model long-term cost-benefit gains and losses to consider when treating adult patients with T2DM in monotherapy intolerant or contraindicated to metformin. The general structure is shown in Figure 17, Appendix 4. Briefly, ECHO-T2DM is a stochastic micro-simulation model in which cohorts of individual hypothetical patients are created and simulated over time using Monte Carlo (first order uncertainty) techniques. Second order (parameter) uncertainty is captured by many cohorts of patients, where each cohort is assigned unique values of the key parameters (e.g., treatment effects, risk equation coefficients, and QALY disutility weights) drawn from probability distributions; the results are aggregated. ICERs including second order uncertainty are more accurate, both because they include a greater number of patients and because they capture natural non-linearity in the disease associated with our limited understanding of a complex disease.

Choosing an adequate economic evaluation model in T2DM

An SLR of the structure, capabilities, and validity of economic evaluation models of T2DM was undertaken to assess the suitability of existing models for the purposes of an evaluation of canagliflozin in support of a submission to NICE. The search strategy was similar to that outlined above for the SLR of cost-effectiveness evaluations, details of which may be found in the study report (75).

Thirty five unique models of T2DM were identified, though only a small number are well-documented (77). There were important similarities and many differences between the models. Despite the complexity of the disease and need for modelling changing treatment paradigms over long time horizons, it was concluded that a sub-set of the models appear to be suitable for estimating the cost-effectiveness of canagliflozin in the UK treatment setting. ECHO-T2DM is one of them.

An economic evaluation model for T2DM should be capable of capturing a number of key disease features; detail of these considerations may be found in Section 4.1, Appendix 4 and in the study report (75). ISPOR and the ADA have issued general and diabetes-specific modelling best practice recommendations for economic modelling, both emphasising the importance of formal model validation (78, 79). Eight of the models have published the results of model validation in peer-reviewed journals (77, 80-84). A number of differences were found across the models, not the least in the degree of documentation reported publically. The CORE Diabetes Model (CDM) and ARCHIMEDES have been the most widely used, with CDM, ECHO-T2DM, JADE and the Cardiff Models having been used in recent T2DM submissions to NICE and other Heath Technology assessment groups (85, 86).

While a detailed justification for using the ECHO-T2DM model and its inputs for this submission is reserved for the appendix (Section 4.2, Appendix 4), a brief overview here and explanation in later sections of the submission highlight the primary reasons for this decision. Briefly, the SGLT-2-i class of drugs is relatively new in the treatment of T2DM, and class members have a MoA, therapeutic profiles and adverse event profiles that differ from traditional AHAs. As the MoA is primarily through inhibition of SGLT-2, it is important that the renal function (marked by eGFR) is accounted for in the estimation of efficacy and in the discontinuation of canagliflozin treatment when the patient's eGFR falls below 45 mL/min/1.73 m^2 or 60 mL/min/1.73 m^2 for canagliflozin 100mg and 300mg, respectively. This functionality specific to SGLT-2-i is accounted for in the ECHO-T2DM model. A number of AE's related to excretion of glucose in the urine were also included for simulations of the SGLT-2 inhibitor MoA, including upper and lower UTI's and GMI's (each allow for gender-specific rates, costs, and QALYs and there are separate event rates for the first cycle on agent and subsequent cycles). Using Monte Carlo techniques, ECHO-T2DM simulates a flexible and comprehensive AHA treatment algorithm in addition to accounting for other concomitant complications of T2DM, such as hypertension and dyslipidaemia. All health states accounted for by the model and what they capture are detailed in Section 4.2.1, Appendix 4.

Janssen recognises that the need for validation of models in T2DM is particularly high given their level of complexity and limited transparency. ECHO-T2DM has been developed accounting for the International Society for Pharmacoeconomics and Outcomes Research/Society for Medical Decision Making (ISPOR/SMDM) Modelling Good Research Practice Task Force good practice recommendations and has been through extensive review and validation exercises, including presentation at the 4th and 5th Mount Hood Challenges in 2010 and 2012. The results of a comprehensive test of predictive validity were published in Willis et al. (2013) (77), and further detail is also presented in Appendix 10.

ECHO-T2DM was used for the modelling presented in the canagliflozin NICE single technology appraisal (as well as a number of HTA submissions in other countries), and was accepted by NICE as a valid and robust model (12).

Inputs and assumptions required to model the main aspects of the condition and disease progression

T2DM is a chronic progressive disease characterised by marked hyperglycaemia, raised BP, changes in blood lipids and in patient body weight. Over time, there is growing insulin resistance, gradual loss of pancreatic β cells and some patients experience a deterioration of kidney function. The progression of T2DM is inexorable and as a result of these physiological changes, patients have an increasing risk of developing micro- and macro-vascular co-morbidities.

Intervention with the aim of improving blood glucose, SBP, and lipid values has been demonstrated to improve patient outcomes (87). ECHO-T2DM uses well-known risk equations to translate intervention-medicated changes in these covariates into long-run differences in patient outcomes (88).

ECHO-T2DM simulates a flexible and comprehensive AHA treatment algorithm defined by:

- treatment sequence including rescue medication(s),
- decision rules for intensification of therapy (e.g., HbA1c exceeding a threshold value, completion of a fixed duration on agent, and/or development of a contraindicating condition), and
- two types of agent-specific treatment profiles (e.g., treatment effects, durability and bio-marker evolution, stopping rules, adverse event rates, non-compliance, and contraindication), one for non-insulin agents and the other for insulin agents (which is more flexible and permits dose modification to meet HbA1c goals)

Using Monte Carlo techniques, each individual patient is assigned treatment during each cycle. ECHO-T2DM requires valid non-insulin profiles at simulation start (though one can easily simulate initiation of insulin at study baseline by inserting insulin-specific parameters into a non-insulin profile). The initial treatment effects are applied and each patient is individually evaluated for HbA1c failure, reaching a maximum duration on agent, and for contraindications and AEs that would motivate treatment discontinuation. Patients continue on this treatment as long as they survive and none of the above criteria are met. When one or more of the criteria are met, the user-defined treatment sequence will indicate which agent (if at least one is specified) will be commenced (and whether the original agent will be continued or discontinued). The process is then repeated. When there are no longer any available non-insulin agents or at the treatment line the analyst specifies, the initial insulin profile (e.g., basal insulin) is applied at the start dose and titrated up to the designated maximum dose as needed to maintain HbA1c control. When additional control is needed thereafter, the next insulin regimen (if one is specified) is started (e.g., prandial insulin on top of the long-acting insulin), again starting at an initial dose and titrating up to the designated maximum dose, as many additional insulin profiles can be added as desired.

ECHO-T2DM modelling comparisons were carried out with the specifications in Table 8. Table 9 describes the assumptions used to inform key features of the model and perform the simulations.

Table 8: Model settings

Variable	Value
Number of patient cohorts per model run: base case comparisons§	1,000
Number of patients in each cohort: base case comparisons¥	2,000
Number of patient cohorts per model run: scenario analyses and sensitivity analyses	1,000
Number of patients in each cohort: scenario analyses and sensitivity analyses	1,500
Discount Rate for Costs	3.5%
Discount Rate for Health	3.5%
Modelled time horizon	40
Maximum patient age	100

§*The number of cohorts captures parameter uncertainty; i.e. what the true value of the treatment effect is (which we parameterise with a distribution including a mean and SE). Increasing the sample size converges to the true level of uncertainty.*¥ *The number of patients in each cohort affects how much Monte Carlo uncertainty there is (i.e. whether a patient with given characteristics has an event) and the use of random numbers as well as the heterogeneity of the patients as generated initially. The larger this sample size is, the less any two different simulations would tend to differ.*

Table 9: Key features of analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (40 years)	T2DM is a chronic, progressive disease. The comorbidities resulting from hyperglycaemia make take many years to develop. T2DM and its treatments impact the patient's HRQL and incur costs over a lifetime, and a time horizon of 40 years allows the model to reflect this (89).
Cycle length	1 year	The comorbidities resulting from hyperglycaemia develop relatively slowly justifying an annual cycle length. Nearly all models of T2DM using an annual cycle length.
Half-cycle correction	No	The importance of half-cycle corrections diminished with the number of cycles simulated. In T2DM, modelling durations are typically quite long, decreasing the need for half-cycle correction.
Were health effects measured in QALYs; if not, what was used?	Yes	Consistent with previous T2DM economic models and NICE methods guide (89)
Discount of 3.5% for utilities and costs	Yes	Consistent with previous T2DM economic models and NICE methods guide (89)
Perspective (NHS/PSS)	NHS/PSS	Consistent with previous T2DM economic models and NICE methods guide (89)
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years		

As both hypertension and dyslipidaemia are major co-morbidities in T2DM, most patients are treated with anti-dyslipidaemia and anti-hypertension medications. The model allows for a proportion of patients to be receiving these medications at baseline, and also for treatment to start if treatment thresholds of lipids or BP are exceeded, and for intensification of anti-dyslipidaemia and hypertension medication to be applied. How and when these treatment algorithms are accounted for is explained in detail in Section 4.2.2, Appendix 4.

The model also incorporates heath states and events associated with pharmacological treatment, including:

- Patient weight change
- Hypoglycaemic events (separately by non-severe and severe)
- Upper and lower UTI's
- GMI, and
- Peripheral oedema.

Technology

Canagliflozin and comparator therapies are implemented in the model as per their marketing authorisations. The comparisons conducted within the economic model are shown in Table 10.

There are multiple products available in most of the comparator classes; however, comparisons were conducted against only one member of each of the classes. The rationale behind the choice of a specific comparator is also described in Table 10.

Table 10: Economic modelling comparisons conducted

Comparator	Pharmacological class member selected	Justification
SU	Gliclazide	Gliclazide is the SU with the highest level of UK prescribing (3)
TZD	Pioglitazone 30 mg	Rosiglitazone has no licence/ no other TZD available for prescribing in clinical practice in the UK. (90). 30 mg is the most commonly prescribed dose of pioglitazone in the UK. (3)
DPP-4-i	Sitagliptin 100 mg	Most commonly prescribed DPP-4-i in the UK (3)

Comparator	Pharmacological class member selected	Justification
Empagliflozin 10 mg	n/a	Proposed comparator in the NICE scope for this submission (4)
Empagliflozin 25 mg	n/a	Proposed comparator in the NICE scope for this submission (4)
Dapagliflozin 10 mg	n/a	Proposed comparator in the NICE scope for this submission (4). Dapagliflozin 10 mg is the recommended starting dose for most patients (excluding patients with severe hepatic impairment).
Meglitinides¥	Repaglinide	Proposed comparator in the NICE scope for this submission (4) Repaglinide is seldom used in the UK (3)

¥Comparator in the Scenario Analysis, only
DPP-4-i: Dipeptidyl peptidase-4 inhibitor; n/a, not applicable; SU: sulfonylurea; TZD: Thiazolidinediones

Canagliflozin dose modification intervention arm
As detailed above, the canagliflozin posology is for patients to commence treatment on the 100mg dose. In patients tolerating the 100mg dose but needing tighter glycaemic control, the dose can be increased to 300mg. The RCTs did not study the consequences of this increase from the 100mg to the 300mg explicitly; therefore, modelling techniques were employed to simulate this dose modification and its impact on the cost-effectiveness of canagliflozin versus comparators.

[redacted] the 7.5% threshold correspond with treatment review for many T2DM products in NICE guidelines (including SU, DPP-4-i's, and pioglitazone) (36).

In the model, patients are started on 100mg canagliflozin.

[redacted] Patients that are simulated to tolerate canagliflozin 100mg but that do not achieving glycaemic control < 7.5% are titrated to canagliflozin 300mg

[redacted]

In the absence of clinical data, it is assumed that a patient that switches to 300mg canagliflozin achieves the same peak HbA1c efficacy as patients treated with 300mg for the full 12 months. This 300mg treatment effect is also applied to SBP, BMI, lipid levels, and the event rate of hypoglycaemia. This is a reasonable assumption, given the clear and consistent dose-dependent response observed across the clinical trials.

Treatment intensification
The draft clinical guideline update for the treatment of T2DM suggests patients receiving monotherapy should be treated to a target of 6.5% (48 mmol/mol) and recommend treatment intensification when the patient's HbA1c rises above 7.5% (59mmol/mol) (36). The base case modelling employed an HbA1c switch threshold of 7.5% for all base case simulations. In clinical practice, the HbA1c threshold at which patients receive additional or alternative treatment may differ (91). This has been explored in a scenario analysis, see below. Further detail of the treatment intensification algorithm as well as efficacy and safety of the rescue regimens is given in Table 12 and Section 4.2.4, Appendix 4.

Treatment discontinuation
Cohorts of patients are simulated until death or the end of the designated follow-up period. In accordance with the canagliflozin SmPC, within the base case analysis canagliflozin 100 mg is

discontinued at an eGFR of <45 mL/min/1.73m^2; whereas patients treated with canagliflozin 300 mg will discontinue therapy when the patient's eGFR falls below 60mL/min/1.73m^2.

Clinical parameters and variables

Clinical expert involvement

Although NICE clinical guidelines give recommendations on how to prescribe AHAs, there is variation in the use of medicinal products in practice. Therefore, clinical experts were consulted to obtain details relating to the current use of treatments in UK clinical practice as well as the medical resources used for the administration of these treatments, and for managing AEs. The generation of these data and consensus sought is detailed in Section 5.1, Appendix 5.

Clinical data implementation into the model

Section 4.2.5, Appendix 4 details how clinical data inputs are implemented in ECHO-T2DM.

Key data sources used in the economic model

For brevity, a list of the key categories of inputs and corresponding sources used in the base case simulations appear in Table 11 along with the location of the information in the dossier, where applicable.

Table 11: Overview of key data sources used in the economic model

Parameter	Table number/location of submission	Source(s) of data
Baseline patient/ social demographic and clinical characteristics	Table 13, Appendix 5	Pooled DIA3005 and MTPC
Patient medical history	Table 14, Appendix 5	Pooled DIA3005 and MTPC
Treatment effects	Table 17, Appendix 5	Pooled DIA3005 and MTPC
Evolution of HBA1c and other clinical biomarkers	Described in Section 5.2.3, Appendix 5	(82, 85, 92)(59;140;157)
Micro-vascular, macro-vascular, and mortality risk equations	Described in Section 5.2.4, Appendix 5	(82, 87, 93-95)
Duration of treatment	Described above	(28)
Hypoglycaemia	Table 17 and described in Section 5.2.2, Appendix 5	(61) and trial data (5, 16).
Selected adverse events rates and discontinuation due to AEs	Table 17 and described in Section 5.2.2, Appendix 5	Pooled DIA3005 and MTPC
Utility decrement values	Table 30, Appendix 6	(96-99)(128;130;164;165)
Cost of diabetes-related complications and AEs	Table 34 - 37, Appendix 7	Multiple sources (1)
Drug acquisition costs, consumer costs (needles, blood glucose monitoring)	Table 31, Appendix 7	(1)

Table 12 outlines the key clinical assumptions used for the parameters to inform the economic modelling approach for the base case simulations, detail of which may be found in the appendices as outlined in Table 11, above.

Table 12: Key Assumptions for the economic modelling

Parameter	Key assumptions for Base Cases	Justification
Baseline characteristics	All values obtained from the canagliflozin clinical programme. Data was pooled from DIA3005 and MTPC to inform all base case simulations.	Baseline characteristics from the clinical programme are generalisable to patients with T2DM in the UK. Study designs as well as inclusion/exclusion criteria were very similar. Pooling data allowed for improvement in precision in terms of identifying background characteristic parameters.
Treatment effects (HbA1c, SBP, Weight, Lipids)	The NMA was the primary source of treatment effects data If data were missing, assumptions were made and either the treatment effects of the intervention or placebo arm from the pooled clinical trial dataset were used (61). Results observed at 26 weeks were assumed to be equivalent to the effects that would be observed at 52 weeks. Treatment effects associated with an agent are immediately reversed at discontinuation (i.e., at the start of the next cycle, HbA1c, SBP, weight and lipids are returned back to baseline values)	(89) See Table 16, Appendix 5 for details on data used when a treatment effect was not available in a NMA. The cycle length of ECHO-T2DM (as well as most other models in this therapy area) is 1 year. Although the canagliflozin programme includes data at 52 weeks, due to the paucity of published studies on comparators out to this time point, networks could not be constructed. Data on the residual effects of drugs post-discontinuation are unavailable
AHA Treatment algorithm	If HbA1c exceeds 7.5% when treating with monotherapy, add on a second oral AHA as described in full submission. Following first intensification, if again a threshold of 7.5% is reached patients are discontinued off their oral therapy and started on NPH insulin at 10 IU/day and titrated to a maximum of 60 IU/day as needed to maintain glycaemic control. When NPH insulin reaches its maximum dose and glycaemic control is not achieved a second regimen consisting of NPH (dose fixed at 60 IU/day) and insulin Aspart is initiated. The insulin Aspart dose is initiated at 5 IU/day and titrated to a maximum of 200 IU/day as needed to maintain control. Note that IU/day was adjusted for the weight of a patient. Discontinue canagliflozin 100 mg when eGFR<45 ml/min/1.73m^2; canagliflozin 300 mg when eGFR<60 ml/min/1.73m^2; or when a patient develops ESRD; Discontinue pioglitazone when a patient develops CHF.	Draft CG Update (36) NICE Pathways – Diabetes: Management of T2DM (41) As per the protocol. Insulin Aspart is added after patient HbA1c levels exceed 7.5% on a maximal basal insulin dose to avoid poor HbA1c control(28, 79). Insulin Aspart is the most commonly prescribed prandial-acting insulin in the UK (3). Canagliflozin SmPC (76) Pioglitazone SmPC (100)
BP and Lipid Treatment Algorithms	*Intensify BP treatment when:* SBP > 140 mmHg *Intensification sequence*: 1st ACE inhibitor (ramipril 5mg); 2nd diuretic (bendroflumethiazide 2.5mg); 3rd beta-blocker (atenolol 50mg) *Intensify dyslipidaemia treatment when:* T. Chol: ≤ 5.0 mmol/l; HDL-C: ≤ 1.4 mmol/l; LDL-C: ≤ 2 mmol/l;	(28), (41) (101)

Parameter	Key assumptions for Base Cases	Justification
	Triglycerides: ≤ 4.5 mmol/l *Intensification sequence*: 1st atorvastatin 20mg, 2nd atorvastatin 40mg, 3rd atorvastatin 80mg	
Evolution of HbA1c	HbA1c drifts upwards annually at the rates displayed in Table 18, Appendix	Values in were reviewed and endorsed with clinicians (102) (71)
Evolution of BP	BP drifts upwards annually at the rates displayed in Table 18, Appendix 5	Values in were reviewed and endorsed with clinicians (102) (71)
Evolution of Weight	Weight drifts upwards annually at the rates displayed in Table 18, Appendix 5	Values in were also reviewed and endorsed with clinicians (102) (71) (85)
Evolution of Lipids	Lipid parameters drifts upwards annually at the rates displayed in Table 18, Appendix 5	Values in were reviewed and endorsed with clinicians (102) (71)
AEs: GMI and UTI	Values obtained from the canagliflozin clinical programme. Data was pooled from DIA3005 and MTPC. Assume empagliflozin and dapagliflozin have the same AE rates as canagliflozin 100mg Assume all other AHAs have rates of these events as observed in the placebo data in the canagliflozin trials	Not available in NMA; these AEs are likely to be associated only with the SGLT-2 inhibitor MoA.
Hypoglycaemia	For all AHA, hypoglycaemic event rates are adjusted using a relative risk (RR) multiplier (for each 1 percentage point decrease in HbA1c, the relative risk of an event increases by 1.43) There are no rates of hypoglycaemia reported for SU in the NMA. Therefore, glimepiride rates from the DIA3009 study (at 26 weeks) are used and adjusted to be more reflective of the lower rates of hypoglycaemia experienced with gliclazide (RR gliclazide vs. glimepiride = 0.43 [non-sev] and 0.45 [severe]).	The risk of hypoglycaemia has been shown to be inversely related to the level of glucose control(103). Between-arm differences in the UKPDS rates of events (104). (61)
AEs: oedema	The incidence rate of oedema for pioglitazone treated patients was conservatively included in the base case analysis. Values obtained from a cost-effectiveness study informed by macrovascular event rates reported in the PROActive study were used to inform this parameter (105). Further detail is available in Section 5.2.2, Appendix 5.	A pragmatic review of the literature shows higher rates of peripheral oedema for patients treated with pioglitazone versus any other AHAs(105). See Section 5.2.2., Appendix 5 for further detail as to how this parameter has been included in the modelling.
CHF and pioglitazone	Use the 1.41 Hazard Ratio for PIO vs. the other comparators (including insulin) for the elevated risk of CHF (106).	Of the 149 PIO-treated patients investigated by Dormandy et al (2009), 5.7% were reported to have had serious heart failure (i.e. leading to hospitalization, or meeting one of the other seriousness criteria outlined in the study) compared with 4.1% (n = 108) of PBO-treated patients (HR = 1.41; 95% CI 1.10; p = 0.007). (107) Within ECHO-T2DM patients that experience CHF are discontinued off PIO treatment, as per the recommendation within the PIO SPC (100).

Measurement and valuation of health effects

Living withT2DM: patient experience and quality of life

The relationship between T2DM and HRQL has been well established. HRQL is worse for people with diabetes compared to the general population, for physical functioning and well-being (108). Poorly controlled disease leads to quicker disease progression and onset of micro- and macro-vascular complications such as nephropathy, foot ulceration, neuropathy, blindness, amputation, and stroke. HRQL declines as co-morbidities increase (108, 109). Researchers have estimated the impact of longer-term diabetes-related complications on measures of HRQL and utilities allowing individual assignment of specific utility estimates to each long-term complication (97).

People with T2DM are also at increased risk for GMI – vulvovaginal candidiasis (VVC) in women and Candida balanitis in men (110), UTIs (111-115) and depression (116). Treatment of T2DM can cause variability in glucose levels which leads to hyper- and hypo-glycaemia, and effects such as increased oedema, nausea, and changes in body weight. These impacts may influence patient behaviour and subsequently affect outcomes (117).

The opportunity to improve outcomes by recognising the important role of patients in the management of T2DM is reflected in many treatment guidelines. NICE guidelines state that T2DM "is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life (70). Accordingly, understanding of diabetes, informed choice of management opportunities, and the acquisition of relevant skills for successful self-management play an important role in achieving optimal outcomes". The more recent guidance notes that HRQL is an "important determinant of adherence to treatment." Patient-centred treatment, that is, "aligned with the perceived needs and preferences" of people with T2DM, is recommended by the NICE guidelines (28), the National Collaborating Centre for Chronic Conditions and endorsed in the 2012 ADA/EASD consensus statement (70) (36, 118).

A key determinant of HRQL in T2DM is the development of long-term complications, however, due to the difficulty of collecting data over a long enough time to observe the development of complications, most researchers have analysed HRQL cross-sectionally (119). However, a recent study that collected HRQL over 5 years was able to demonstrate a decline in HRQL over time in patients with T2DM (120).

Treatment impacts such as improved glycaemic control, low incidence of hypoglycaemia, and weight loss have been associated with an improvement in HRQL and healthy behaviours indicating a shorter-term feedback loop between HRQL and outcomes (121, 122). Researchers have proposed that patients are more likely to adhere to treatment regimens that offer benefits from the patient perspective, such as convenience, avoidance of hypoglycaemic episodes, and weight loss, vs. those regimens that do not (117, 122).

There were no measures of HRQL implemented in the trials investigating canagliflozin in monotherapy. A full patient reported outcome (PRO) report for the wider canagliflozin trial programme, including a list of the concepts measured, the instruments used, the rationale for inclusion, and the trials and time points when these measurements were implemented can be found in Appendix 6. All PROs were included in the trials as exploratory endpoints; the trials were not powered to detect differences in PRO scores between study arms. Published data sources are therefore used to populate the ECHO-T2DM model.

HRQL studies

A systematic review of the literature was conducted to identify all HRQL publications that might provide utility values for the health states incorporated in the economic model. The original search was undertaken in May 2013. Five hundred and forty-six reports met the inclusion criteria including 106 utility studies and 440 studies reporting short form outcomes. The update search was undertaken in December 2014 and retrieved 13,729 records from the database searching for the complete time period (encompassing the original search period and the update period) and 56 records through website searches and other sources. Once duplicates had been removed, including from the original search, 3,404 records remained for assessment. A PRISMA diagram is available in Figure 24, Appendix 6.2.

Over twenty databases were searched, including MEDLINE, PubMed and EMBASE. Key inclusion criteria were:

- Study participants were patients with T2DM and not Type 1 diabetes (T1DM);
- The study was not of patients who had just been hospitalised unless it was for hypoglycaemia;
- Utility values had to be derived by methods underpinned by either time trade off or standard gamble techniques.

Records identified were categorised as:

- Utility studies – papers in which the abstract implies utility values are elicited using a tool such as the EQ-5D index;
- Studies using the Short Form (SF) SF-12 and SF-36 – which can be mapped onto EQ-5D;
- Cost effectiveness/cost-utility studies – papers that may utilise utility values in cost-effectiveness or cost-utility models;
- Systematic reviews of utility values.

The reference lists of the cost-effectiveness studies and systematic reviews were then checked to identify any potential utility studies that might not have been identified by the searches. Utility studies that met the inclusion criteria were extracted with key study details, methodology and specifics on the utilities provided recorded – particularly the patient characteristic or co-morbidity that the utility represented. The full updated HRQL SLR, including the search strategy and the detailed extraction spreadsheet, can be found in the report (123).

One hundred and twenty-nine utility studies (in 130 reports) were data extracted and provided over 1,000 estimates of utility relating to patients with diabetes and their characteristics and co-morbidities. Details of the studies, including the health state utilities extracted are provided in the study report (123).

The majority of reports (96/129) reported EQ-5D utilities. Care must be taken when considering incorporating these results into a model as it is not always the case that the health states described have been elicited comparatively. Estimates may differ in many respects, with some of the most important characteristics being: (i) the methods used to solicit the estimates, (ii) the setting, (iii) the health states encompassed, (iv) any technique used to derive health-state-specific values, and (v) the sample size.

In addition, 482 studies were identified that provided quality of life (but not utility) estimates for people with diabetes. Country-specific overall utility values for patients with T2DM are available from 23 countries. The availability of utility data (absolute or incremental) by patient characteristics and co-morbidity by country is variable. Some characteristics, such as the presence of cardiovascular diseases, are well evidenced in terms of utility increments for presence of the condition. Other conditions, such as mental health problems, are less well evidenced.

The availability of key parameters in a diabetic model, such as the incremental utility from hypoglycaemia or the impact on utility from gender, age and duration of disease, have robust estimates in the literature. Due to the large number of utility values in the literature for specific characteristics, there is scope to explore the impact of different values using scenario analysis.

The impact of AEs on HRQL

A literature search was conducted to identify HRQL studies in patients with T2DM and more specifically on the nine AEs considered. A large number of studies were found identifying the impact of T2DM on patients' HRQL, but a paucity of relevant literature was available for most of the side effects (98). This was especially true, for the GI events, hypovolaemic events, and GMI in men.

As no appropriate studies in the literature were identified to provide some AE-related disutility in T2DM, a time trade off (TTO) study was conducted to capture UK societal utility values for health states associated with these events. Nine health state descriptions were developed from a literature review and supplemented with patient and clinician qualitative input to describe the burden associated the following AEs: Mild/moderate UTI; severe UTI; GMI; moderate and severe hypoglycaemic events; fear of hypoglycaemia; GI symptoms; and hypovolaemic events. The study indicates the potential importance of including information regarding AEs in economic evaluations. Although some states were rated severely in terms of utility, in reality, many of these only last a few days, therefore having a minimal quality adjusted life year (QALY) impact. For full details of the methodology for this study, please refer to the final study report (99, 124).

Quality-of-life data use and implementation in cost-effectiveness analysis
ECHO-T2DM utilises health-related utility values that were elicited from data from the CODE-2 study (97). CODE-2 was chosen as the base case because it used well-validated techniques (the EQ-5D and the UK tariff) to solicit HRQoL, it is based on patients in the European setting (including the UK as well as Belgium, the Netherlands, Italy, Spain, and Sweden), prevalence data were concomitantly captured for a large number of demographic, clinical, and health history characteristics enabling attribution of disutility to individual health complications using multivariate regression techniques and reducing the risk of the results being confounded, and the sample included more than 4,000 patients with T2DM.

In previous HTA submissions, the UKPDS equation has been used to inform utility values used (36, 86, 125); however, it is more limited for micro-vascular complications, providing estimates only for the end-stage complications of LEA and blindness. In comparison, the CODE-2 utility weights match more micro-vascular health states used in the ECHO-T2DM model, for example, by providing a wider range of estimates for different severity levels of complications. Importantly, CODE-2 includes an estimate for the disutility related to BMI, thus minimising the risks that the estimates are confounded by attributing the impact of these excluded factors to correlated but included factors. Similarly, the UKPDS dataset focuses on discrete clinical events, whereas CODE-2 estimates focus on prevalent disease states. No other study has been able to control for so many potential confounding factors (patient characteristics and health complications) simultaneously, which makes it the most exhaustive set of utility weights currently available. The CODE-2 study has also been used in previous HTA submissions and to inform utility values in the NICE clinical guidelines (12).

Although the UKPDS was a longitudinal RCT and CODE-2 a naturalistic (non-interventional) observational data collection, the patients in the UKPDS RCT are selected (relatively healthy and newly diagnosed) whereas the aim of the CODE-2 was to generate samples representative of the broader T2DM population. Alternative disutility assumptions were explored in the economic analysis for BMI and macrovascular events (modelling scenarios 4 and 19, described in Table 13 of the submission).

Other sources were used to determine disutility weights associated with AEs, as described above and in Table 29, Appendix 6.2. Where possible and appropriate, health state utilities were measured using the EQ-5D questionnaire and taken from a UK population with T2DM

Patient HRQL changes over time due to incidence of co-morbidities, AEs, change in BMI and age. ECHO-T2DM calculates over each modelling cycle the probability of the occurrence of a co-morbidity, complications and AEs, and the disutility of each is applied to the baseline utility for that year and, if relevant, for subsequent years. When multiple co-morbidities and complications are experienced, the disutilities are additive. Thus, the HRQL of simulated patients varies in the model, according to the accrual of co-morbidities and complications.

Some co-morbidities were identified through the SLR although they were not included in the economic analysis. For instance, fear of hypoglycaemia was identified in the literature and also researched in the TTO study (99, 124). Omission underestimates the disutility associated with a high rate of hypoglycaemia, such as SU and insulin. Disutility associated with patient aversion to injections was also omitted, which can be argued to underestimate disutility from injectable products such as GLP-1-a and insulin. Disutility associated with hypovolaemic events was excluded (as this was considered a minor event of short duration with very small impact on utility and NHS costs), as was minor hypoglycaemic events which are expected to have a limited impact on both utility and NHS costs.

Resource identification, measurement and valuation

NHS costs
Secondary care admissions in diabetes are classified by diagnosis codes (ICD 10), procedure codes (OPCS 4), and by Healthcare Resource Group (HRG version 4) (126). HRGs and NHS reference costs stipulate the treatment of complications associated with diabetes, such as hypoglycaemia, ketoacidosis, coma and lower limb complications (127).

Drug acquisition costs
Drug acquisition costs used within ECHO-T2DM were sourced from the BNF69 (April 2015) and are discussed and presented in Table 30, Appendix 7.1.

Drug administration and monitoring costs

No administration costs have been assumed for canagliflozin and comparators. Oral AHAs do not require supervised administration whilst insulin is self-administered. Self-monitoring of blood glucose has been accounted for within the modelling; refer to Table 31 and Table 32, Appendix 7.2 for details.

As canagliflozin is to be discontinued when eGFR is persistently below 45mL/min/1.73 m^2 or CrCl persistently below 45mL/min (see SmPC in Appendix 1), monitoring of renal function is recommended prior to initiation of canagliflozin as well as prior to initiation of concomitant medicinal products that may reduce renal function. However, diabetic patient monitoring generally includes renal monitoring and is part of routine clinical management of T2DM: prior to initiation of a new therapy and annually thereafter (28). Thus, the cost of renal monitoring has not been accounted for as an additional cost when treating patients with T2DM with an SGLT2-i-based regimen.

Health-state costs

Complications and co-morbidity costs

A comprehensive literature search was conducted to identify published peer-reviewed studies that evaluated costs associated with common diabetes-related complications or co-morbidities that were relevant for the ECHO-T2DM model. Articles that report the resource or service use or costs associated with the treatment of T2DM complications in the UK were included. Further details of the comprehensive search strategy (including databases searched, search strategies, additional screening criteria, data extraction strategy, and list of identified papers) and a summary of the coverage, methods and results of the identified studies are provided in the full SLR study report (123).

In brief, the original search was undertaken in October 2012. Ten studies met the inclusion criteria and one further study was identified from further searching. The update search was undertaken in January 2015 and retrieved 22,620 records for the complete time period encompassing the original search period and the update period. Once duplicates had been removed 21,649 records from the update search remained for assessment. A PRISMA diagram is available in Figure 25, Appendix 7.3.

In total, 15 studies were identified which reported cost estimates of patients with T2DM for major and minor complications and co-morbidities. Cost data presented in this review were reported from a variety of sources using different methods of inflation and elicitation from original source documents to derive unit costs. Regional variations in the standard of care and usual reporting in different practices make comparisons and synthesis of these data quite challenging. Some studies have derived their complication-management costs using national data sources, such as hospital care costs published by PSSRU and the latest set of Department of Health NHS National Reference Costs. Other variances in costs may be due to the definition of specific complications such as mild or acute CHF or when patients are actually diagnosed with a complication such as blindness, the definition can vary between centres.

Most costs used in the identified cost-effectiveness studies have been generated from part of the UKPDS series. These costs are well established and acknowledged due to the study size but inflated costs from the UKPDS are not considered appropriate for incorporation into the ECHO-T2DM model. Moreover, methods of treating diabetes-related complications have changed considerably since the derivations of the original UKPDS cost estimates. Since the completion of the review, a further pragmatic search of literature databases in March 2015 elicited the a publication by Alva et al., a recently published update of UKPDS, which estimates costs in the post-trial follow-up period in 1997-2007. This study is thus considered most appropriate for incorporation into the ECHO-T2DM model for this analysis (88).

Therefore, inflated values from Alva et al. (2015) have been used where possible. For those event costs not accounted for within the study by Alva et al., the costs used in the ECHO-T2DM model were derived based on treatment strategies recommended within the most recently published clinical guidelines, for example NICE clinical guidelines CG66, CG87, and CG182, and Royal Collage of Ophthalmologists' retinopathy guidelines (28, 41, 70, 128, 129). Costs were sourced from community and hospital care costs published by PSSRU and the latest set of Department of Health NHS National Reference Costs as well as the National Drug Tariff. Costs published in journals have been included when the method of costs derivation is clear and deemed representative of current UK clinical practice, and clinically validated (71). Any published costs were inflated to the most recent tax year possible using the inflation index published by the PSSRU. The annual costs of complications and co-morbidities used in ECHO-T2DM along with how cost estimates for health states have been derived are detailed in full in Table 33 to Table 35, Appendix 7.

Adverse-event costs
The AE costs considered in the economic evaluation are discussed and presented in Table 37, Appendix 7, respectively.

Miscellaneous costs
Although ECHO-T2DM has the capability to account for indirect costs, such as annual productivity of patients, these have not been assigned costs for economic comparison. ECHO-T2DM can also account for annual service use costs that are fixed, for example administration costs that do not vary with dose (pumps or syringes), which have also not been assigned costs.

Sensitivity analysis

Scenario analyses
Due to the number of comparators to the two doses of canagliflozin and the number of inputs to the ECHO-T2DM model, a very large number of theoretical sensitivity analyses are possible. The complexity of the ECHO-T2DM model means that a single comparison with a reasonable cohort size can take many hours to run. Given the finite computing resources available and limited space in which to present and discuss results, as well as recognition that there is a finite number of comparisons that are relevant to usual UK clinical practice, a pragmatic decision was made to focus the sensitivity analyses on key drivers of cost-effectiveness in the modelling of T2DM.

An exploratory analysis was conducted to identify the key drivers of cost-effectiveness and from this and consideration of the T2DM economic literature, the 17 scenario analyses were developed (Table 13). Scenario analyses were carried out either using the base case comparator data set or the dataset used in scenario 1, within which repaglinide has also been considered. When the parameter change for the scenario analysis was not considered to have direct impact on the inputs driving the repaglinide comparison, the base case comparator data set was used. Greater detail on the scenarios is provided in Appendix 8.1.

Deterministic sensitivity analysis
A total of six parameters or sets of parameters were varied by plus or minus 20%, to give a total of twelve deterministic sensitivity analyses (DSAs), conducted for each of the systematic comparisons. The parameters selected for the DSAs were based on results of preliminary modelling and consideration of the parameters explored in the scenario analyses, ensuring parameters with the greatest impact were accounted for (130). Some parameters, e.g. disutility associated with lower and upper UTIs for males and females, were grouped to reduce the number of DSAs. Tables detailing these input parameters for the eight sets of DSAs can be found in Table 39, Appendix 8.2.

Probabilistic sensitivity analysis (PSA) of the pair-wise comparisons is a default feature of the ECHO-T2DM model and was run on all simulations conducted. The values of parameters were drawn randomly from their distributions, based on their standard deviations. Table 40, Appendix 8.3 shows the stochastic variables, their distributions and limits. Further detail on PSA in ECHO-T2DM can be found in the Technical Report (131).

Table 13: Scenario analyses conducted

Number	Scenario	Base case	Alternative value
Sc1[¥]	Repaglinide included NMA results	NMA results that do not include repaglinide	Repaglinide included NMA results - multi comparison
Sc2	HbA1c metabolic drift assumption	Comparator drifts as described in Table 17, Appendix 5	Repaglinide comparison, and set HbA1c drift in comparator arm to Cana value (Base case: as per ADOPT findings, assumptions)
Sc3	Disutility values for macro-vascular complications	Currie approach	Repaglanide comparison and Evans (2013) hypo disutilities approach [U.K-reported values]
Sc4	Disutility associated with weight gain	-0.0061 per BMI >25 point gained from CODE-2	Repaglanide comparison and BMI disutility of 0.0038, adjusted Bagust value
Sc5	Patient baseline characteristics	Pooled trial data (DIA3005/MTPC (6, 7)) informed baseline characteristics	Baseline patient characteristics as in THIN + RWE HbA1c threshold (132)
Sc6	Model Comparison	Pooled trial data informed baseline characteristics, UKPDS 82 risk equation for HbA1c, 2 insulin rescue therapies, UKPDS82 macro-vascular disutility values	UKPDS baseline characteristics, UKPDS 68 risk equation for HbA1c, 1 insulin rescue therapy (NPH, only), UKPDS62 macro-vascular disutility values (133)
Sc7	Therapy weight treatment effect	NMA data treatment effect on weight, converted for those therapies w/o using weight data from trial	Run NMA data treatment effect on BMI for comparisons in which the NMA reported this data
Sc8	Time horizon	40 years	20 year time horizon
Sc9	Discount rate	3.5% for costs and outcomes	0% discount rate for costs and outcomes
Sc10			6% discount rate for costs and outcomes
Sc11[‡]	HbA1c threshold for treatment switch	7.5% (59mmol/mol)	Treat HbA1c to 7%
Sc12[§]	BMI rebound on treatment discontinuation	Full weight rebound occurs on discontinuation of treatment	Weight rebound evenly over two years following discontinuation
Sc13[⁎]	Insulin rescue therapy price	NPH INS price used	Use price of INS Glargine
Sc14	Risk equations	Linear drift in HbA1c	UKPDS 68 equation for predicting HbA1c drift (87)
Sc15	Rescue therapy insulin intensification	Basal, intensify with prandial	Include only one insulin rescue, i.e. basal insulin (NPH)
Sc16	Disutility values for macro-vascular complications	Macrovascular disutility values as in CODE-2	Macrovascular disutility values as in UKPDS62 (133)
Sc17	PIO-specific AE consideration	PIO-specific AE and management accounted for (peripheral oedema and CHF, as described in 5.2.2, Appendix 5))	No PIO-specific adjustments (CHF and PE)

[¥] *Further detail is provided in Appendix 8.1.1;* [‡]*Further detail is provided in Appendix 8.1.2;* [§] *Further detail is provided in Appendix 8.1.3;* [⁎] *Further detail is provided in Appendix 8.1.4*

Results

Comparative clinical data from CANTATA-M, the Japanese study and the NMA were extrapolated to long-term economic outcomes using ECHO-T2DM. A 40-year simulation was chosen as the base case, which is consistent with prior economic modelling in T2DM.

Base-case analysis

ECHO-T2DM normally generates pairwise comparisons, using cohorts of simulated patients that are specific for each comparison from the probability distribution of patient characteristics, thus each simulation run will generate slightly different cohorts of patients (with the expected differences decreasing with number of patients). Therefore, to more easily allow the comparison between all investigated treatments, patient cohort seed values are generated and used to inform each investigated treatment within a simulation. Of note, canagliflozin is included in the analysis to represent its three separate uses in monotherapy; canagliflozin 100 mg, canagliflozin 300 mg, and canagliflozin 100 mg dose increase. This intervention arm of canagliflozin represents the clinically plausible scenario in which patients are treated initially with canagliflozin 100 mg, tolerate it well, yet do not achieve the desired HbA1c reduction; as a result, these patients may transition to prescribed canagliflozin 300 mg, as explained in Section 8, above.

The results from the base case analysis are thus presented incrementally in Table 14. Of note, as described in Appendix 9.1, for the purposes of running the model, ECHO-T2DM requires one treatment in the analysis to be set as the defined intervention arm. Given the minimal variability in modelled outcomes, regardless of which canagliflozin treatment in the analysis is specified as the intervention, the base case analysis and all subsequent sensitivity analyses have been consistently conducted using canagliflozin 100mg as the intervention arm. The result sets generated when canagliflozin 300mg and canagliflozin dose increase are set as the intervention arm are shown in Table 41, Appendix 9.1.

Table 14: Base case incremental cost-effectiveness results for all T2DM monotherapies

	Mean Costs	Mean Utilities	Cost per QALY (ICER)
PIO	£20,264	9.998	-
SU (GLIC)	£23,220	9.949	Dominated by PIO
DPP-4I (SITA)	£23,443	9.981	Dominated by PIO
CANA 100	£23,525	10.039	Extendedly dominated by CANA 100 DOSE INCR
EMPA 25	£23,528	10.024	Dominated by CANA 100
EMPA 10	£23,580	10.010	Dominated by CANA 100
DAPA	£23,594	10.006	Dominated by CANA 100
CANA 100 DOSE INCR.	£23,669	10.051	Extendedly dominated by CANA 300
CANA 300	£24,302	10.083	£47,456

Abbreviations: CANA100, canagliflozin 100 mg; CANA300, canagliflozin 300 mg; DAPA, dapagliflozin 100 mg; DPP-4I (SITA); DPP-4i (Sitagliptin 100 mg); EMPA10, empagliflozin 10 mg; EMPA25, empagliflozin 25 mg; PIO; pioglitazone 30 mg; SU (GLIC), sulfonylurea (Gliclazide 80 mg 2x daily)

Interventions are said to be 'dominated' by an alternative if they are associated with a higher mean cost without producing higher mean QALY gains, or if they produce fewer mean QALYs without doing so at a lower mean cost. Interventions are described as being 'extendedly dominated' if using a combination of two alternatives can produce the same level of mean QALY gain for a lower mean cost. That is to say, for the same expenditure on one intervention, a combination of alternatives may be used to accrue a greater number of QALYs.

The cost-effectiveness plane (Figure 12) graphically depicts the relationship between interventions in terms of their mean total costs and mean total QALYs. Given NICE has acknowledged that the use of pioglitazone is declining and the low market share for pioglitazone in the UK (3, 12, 134), results have been presented using SU as the reference point.

Figure 12: Cost-effectiveness plane for all T2DM monotherapies, with SU at the intersection of axes

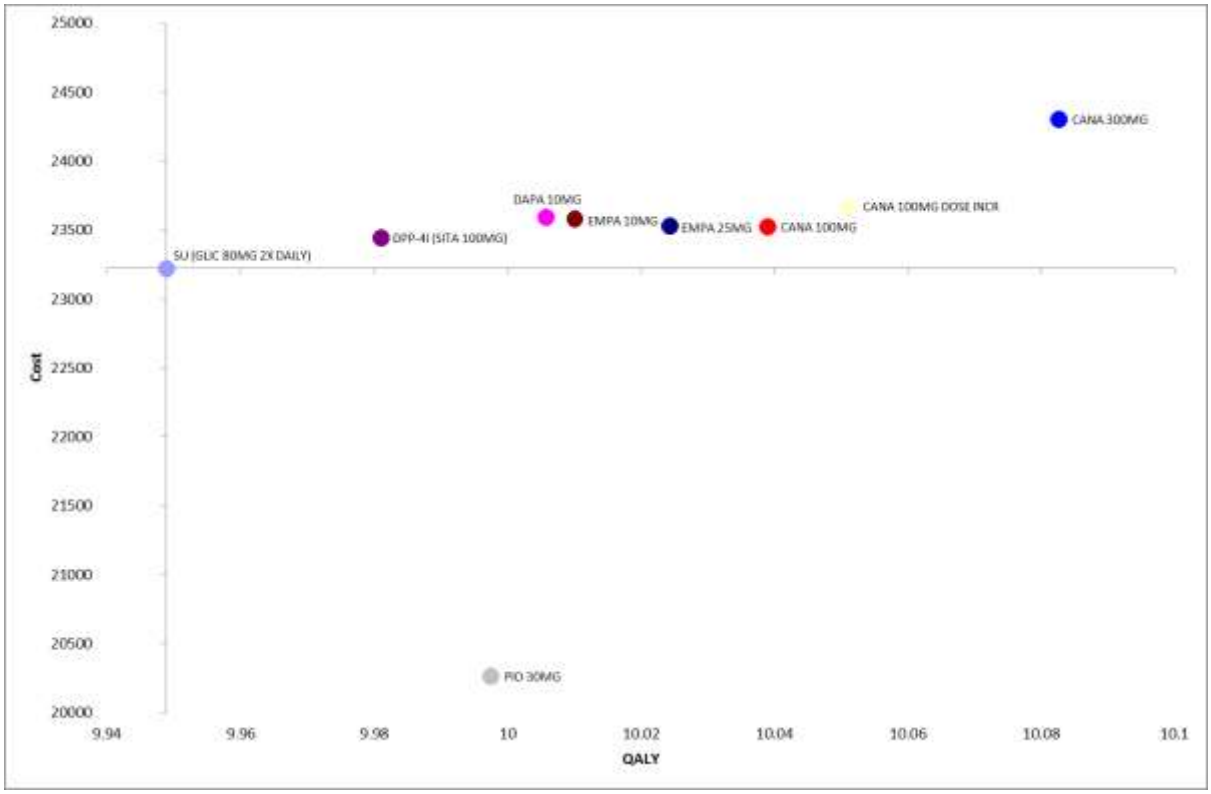


Figure 12 shows that pioglitazone is associated with the lowest mean costs out of all T2DM monotherapies. Since it also accrues a greater gain in mean QALYs compared with both SU and DPP-4-i, both comparators are dominated by pioglitazone; that is to say, both SU and DPP-4-i are more costly and less effective than pioglitazone. However, SGLT2-i are overall more costly but more effective than pioglitazone. The cost-effectiveness plane clearly depicts that canagliflozin 100mg, 300mg, and 100mg dose increase produce the greatest QALY gains of all interventions in the analysis.

Given canagliflozin 100mg is associated with lower total costs compared with dapagliflozin and both empagliflozin 10mg and 25mg doses, and yields greater QALY gains and is thus more effective, it dominates all three SGLT2-i comparators in the analysis. Whilst both canagliflozin 100mg dose increase and canagliflozin 300mg are associated with a higher QALY gain compared with canagliflozin 100mg, both comparators are more costly. Due to the presence of pioglitazone in the analysis, canagliflozin 100mg is extendedly dominated by canagliflozin 100mg dose increase, which is in turn, extendedly dominated by canagliflozin 300mg. In other words, using a combination of pioglitazone and canagliflozin 100mg dose increase can achieve comparable QALY gains as canagliflozin 100 mg alone, but at a reduced incurred cost. A similar rationale applies to the extended domination of canagliflozin 100mg dose increase.

Qualitatively this means that canagliflozin 100mg can still be considered as an alternative treatment in the appropriate patients that do not require dose escalation to canagliflozin 300mg.

Henceforth, since pioglitazone restricts the clear calculation of ICERs in the analysis and its use in the UK is known to be declining, removing it from the interpretation of results provides a more valuable insight into the relationship between alternative treatments. Results when pioglitazone has been excluded are described in Table 15.

Table 15: Incremental cost-effectiveness results for T2DM monotherapies, excluding PIO

	Mean Costs	Mean Utilities	Cost per QALY (ICER)
SU (GLIC)	£23,220		-
DPP-4I (SITA)	£23,443	9.981	Extendedly dominated by CANA 100
CANA 100	£23,525	10.039	£3,377

	Mean Costs	Mean Utilities	Cost per QALY (ICER)
SU (GLIC)	£23,220		-
DPP-4I (SITA)	£23,443	9.981	Extendedly dominated by CANA 100
CANA 100	£23,525	10.039	£3,377
EMPA 25	£23,528	10.024	Dominated by CANA 100
EMPA 10	£23,580	10.010	Dominated by CANA 100
DAPA	£23,594	10.006	Dominated by CANA 100
CANA 100 DOSE INCR.	£23,669	10.051	£12,070
CANA 300	£24,302	10.083	£20,021

Abbreviations: CANA100, canagliflozin 100 mg; CANA300, canagliflozin 300 mg; DAPA, dapagliflozin 100 mg; DPP-4I (SITA); DPP-4i (Sitagliptin 100 mg); EMPA10, empagliflozin 10 mg; EMPA25, empagliflozin 25 mg; SU (GLIC), sulfonylurea (Gliclazide 80 mg 2x daily)

Excluding pioglitazone, DPP-4-i is extendedly dominated by canagliflozin 100mg. This is because a comparable QALY gain can be achieved by using a combination of SU and canagliflozin 100mg incurring fewer costs. The ICER for canagliflozin 100mg compared with SU is £3,377 per QALY. Canagliflozin 100mg dominates dapagliflozin and both empagliflozin 10mg and 25mg.

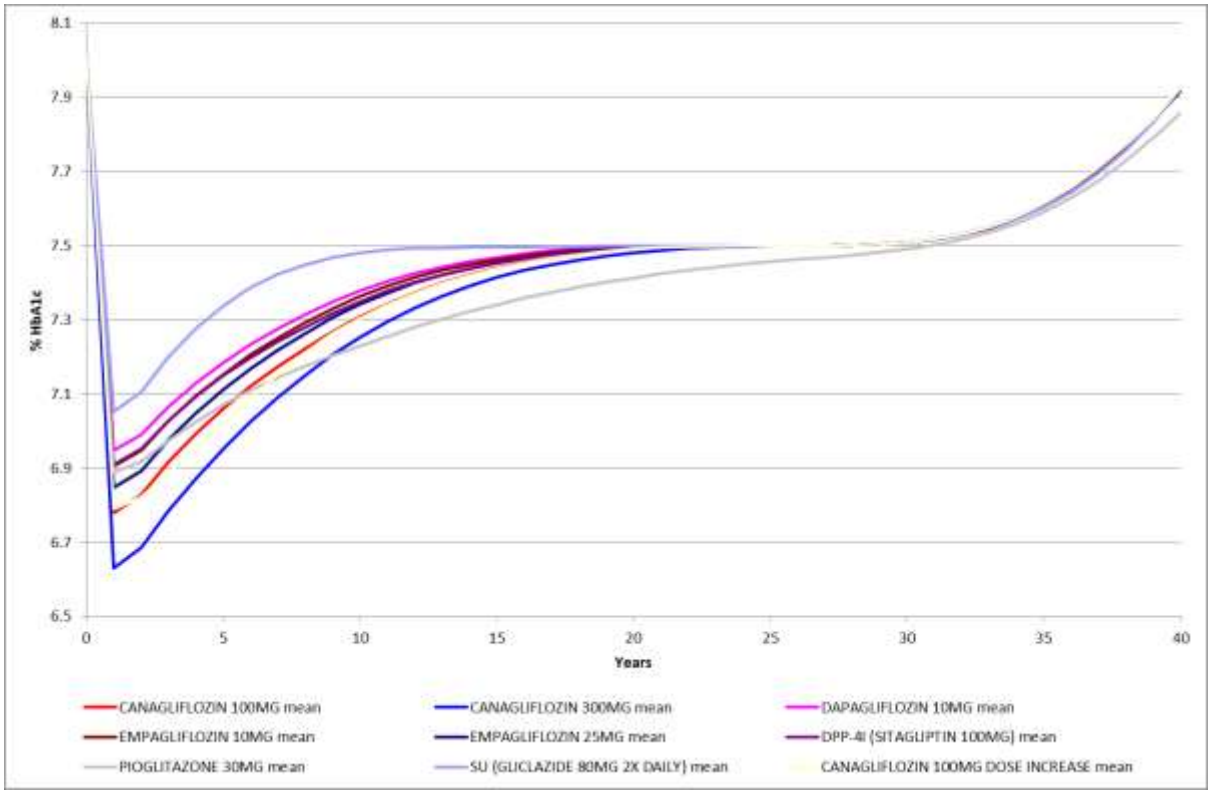
By excluding pioglitazone, canagliflozin 100mg is no longer extendedly dominated and it is possible to calculate ICERs against both canagliflozin 100mg dose increase and canagliflozin 300mg as £12,070 and £20,021 per QALY, respectively, for these interventions to replace canagliflozin 100mg.

Leaving pioglitazone aside due to its declining use in the UK, these results demonstrate that canagliflozin monotherapy can be considered a cost-effective and efficient use of health care resources in the treatment of T2DM.

Biomarker evolution

The impact of canagliflozin and the comparator on key biomarkers is modelled, with an initial effect followed by subsequent annual drift. Figure 13 show the initial impact, drift and convergence of HbA1c over the 40 year time horizon. Figures 27 and 28, Appendix 9.2 show the same for SBP and BMI, respectively. Because of differences in the timing of requirements for rescue medication, HbA1c, SBP, and lipid curves tend to converge as patients with higher values benefit from treatment-related improvements earlier. BMI tends to converge as well, even without explicit anti-obesity medication, as once the initial anti-hyperglycaemic agents are discontinued their effects on BMI are assumed to be reversed and weight gain associated with insulin is applied. Biomarker plots are available for each of the analyses conducted for the biomarkers above, but for the sake of brevity only the results from canagliflozin 100mg and 300mg base cases have been presented. Biomarker plots for other comparisons are very similar in form.

Figure 13. Mean blood glucose (% HbA1c) across all comparators over a 40 year time horizon



QALY calculations

As described previously, the model calculates the event rate each year of micro and macro-vascular events, adverse events and change in BMI. The QALY decrements are then accrued from these events, and summed over the modelled period.

Disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost

The ECHO-T2DM model does not calculate disaggregated life years but rather calculates the incidence of events and subtracts the disutility associated with these from a baseline HRQL state. The results are therefore expressed in QALY loss rather than QALY gain over the period modelled.

The summaries of QALYs lost by health state are shown in Appendix 9.3 for canagliflozin 100mg (Table 42 and 43). The summary of costs by health state and cost for predicted resource for canagliflozin 100mg are shown (Table 44 and 45) versus all comparators in the base case simulations.

Summary of base case cost-effectiveness

Canagliflozin 100mg dominates, i.e. is both less costly and more effective producing larger QALY gains, versus the other SGLT-2-i. A pairwise comparison of canagliflozin 100mg with pioglitazone results in an ICER of £78,518 per QALY due much to the assumption of slow loss of effect (low metabolic drift) with pioglitazone. The corresponding pairwise comparisons of canagliflozin 100mg with SU, DPP-4-I yield ICERs of £3,377, £1,407 per QALY, respectively. Given that canagliflozin 100 mg is cheaper yet less effective than both canagliflozin 100 mg dose increase and canagliflozin 300 mg, these comparisons yield reverse ICERs of £12,070 and £17,845 per QALY, respectively. Results hence demonstrate canagliflozin 100mg to be a cost-effective use of NHS resources when considered under standard willingness-to-pay threshold of £20,000 per QALY. Tabulated pairwise comparisons results presented in Appendix 9.1. The use of canagliflozin in clinical practice in the UK will incorporate a dose increase step in those patients requiring greater glycaemic control and therefore the dose modification scenario is of particular relevance for all comparisons in which a dose increase was applied, in monotherapy, canagliflozin was the more cost-effective option, with the exception of comparison against TZD. The conclusion of this scenario analysis is therefore that dose intensification schedule from 100mg to 300mg is a cost-effective strategy.

Deterministic sensitivity analysis

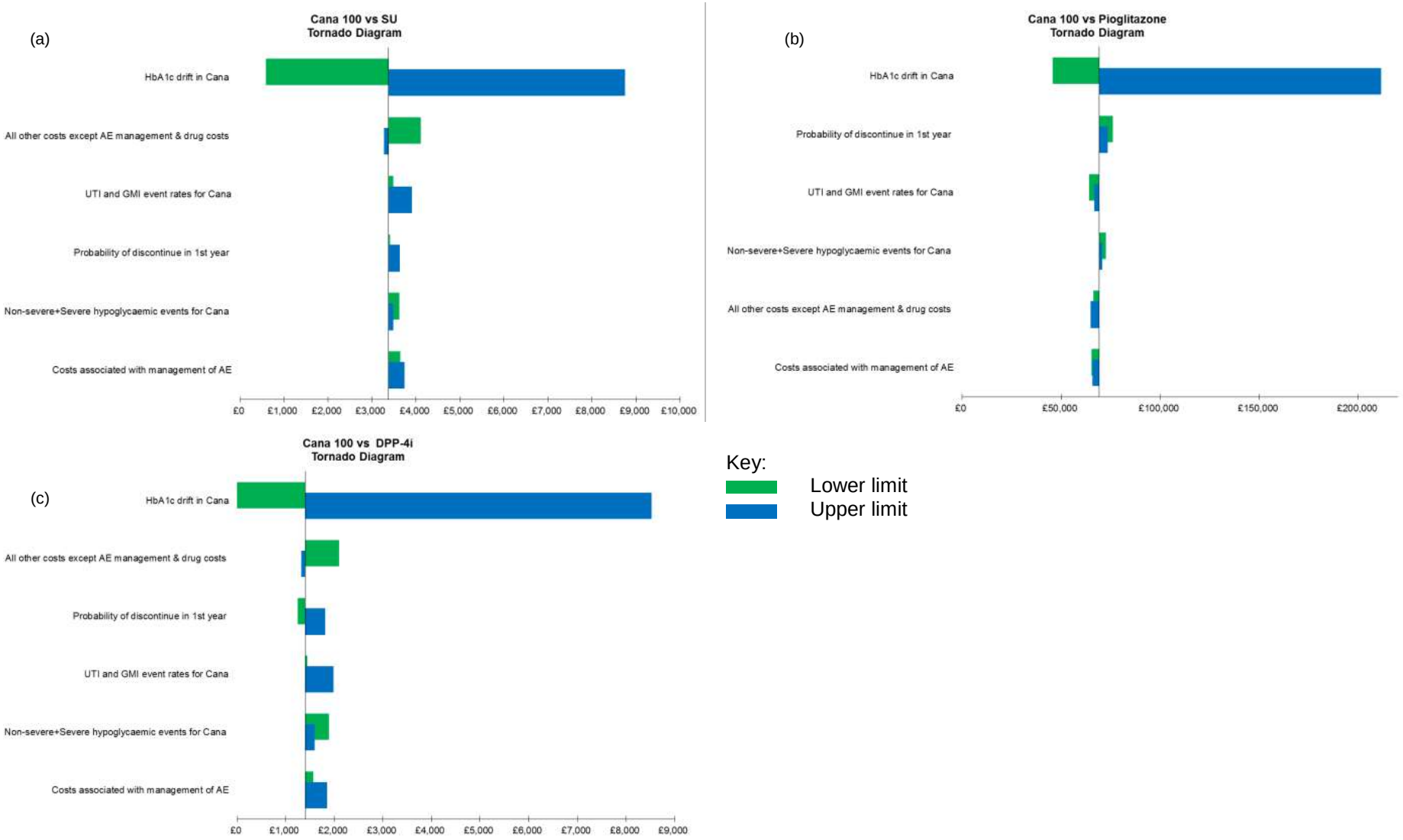
DSAs were performed for known key drivers that were not fully explored through the scenario analysis conducted. For sake of brevity, the full presentation tabulated results are presented in Table 46, Appendix 9.4, and the tornado diagrams for canagliflozin versus SU, pioglitazone, and DPP-4-i are presented sequentially in Figure 14, below.

As previously mentioned and described in Appendix 9.1, all scenario analyses have been conducted using canagliflozin 100mg as the set intervention arm in the model. Of note, given canagliflozin 100mg dominates dapagliflozin and empagliflozin 10 mg and 25 mg in the majority of DSAs, there is little value in presenting tornados for these analyses. As shown in Table 16, comparison against canagliflozin 300 mg and 100 mg dose increase consistently resulted in inverse ICERs for each DSA. This occurs when the intervention arm (canagliflozin 100 mg) is less costly and less effective than the comparator arm (canagliflozin 300mg / canagliflozin 100mg dose increase). Given these inverse ICERs, tornado diagrams were created in an inverse form to visually depict the impact of each DSA on the model outcomes, similar to those created for comparison against pioglitazone, DPP-4-i and SU.

Changes in incremental costs and incremental QALYs were small therefore minor changes in either, or both, could have large impact on the ICER under DSA. Nevertheless, the pairwise ICERs are shown to be relatively stable across the DSAs and in comparisons against the other SGLT-2-i, DPP-4-i and SU, without any qualitative change in the ICERs. Of note, in numerous cases, the base case ICER does not lie within the ICER range of the Upper and Lower parameter estimates for the DSA. This is because of stochastic variability and the small changes observed in the incremental costs and QALYs. In none of these cases were the results qualitatively reversed.

Tornado diagrams indicate that canagliflozin HbA1c drift consistently has the largest impact on the ICER across all comparisons, whilst cost of AE management and the occurrence of hypoglycaemic events have much smaller influence on model outcomes.

Figure 14. DSA Tornado diagrams for CANA 100 mg versus SU (a), PIO (b), and DPP4-i (c)



Probabilistic sensitivity analysis

Canagliflozin 100mg for use in monotherapy to treat T2DM

All appropriate data have been included in PSA (see Table 40, Appendix 8.3). Figure 15 shows the cost-effectiveness plane of pairwise comparisons for canagliflozin 100mg versus all comparators in the base case. Given the difficulty in interpreting point clouds shown on a scatterplot, the mean point estimate and 95%-confidence ellipses are presented for each intervention in Figure 30, Appendix 9.6. Monte Carlo error results for each intervention in the analysis have been calculated and are detailed in Table 49, Appendix 9.6. The 95% CI for the upper and lower 95% CIs are shown in Table 16, below. Generally the uncertainty is greater around the incremental QALYs than the incremental costs, due to the small increments achievable over a 40 year time horizon. Whilst comparison against pioglitazone is generally shown to be associated with higher incremental costs, the uncertainty related to cost associated with pioglitazone use is greater than for all other regimens assessed in this analysis. With regards to all other comparisons, there is very little variation in incremental costs, which is to be expected given the similar drug costs of SGLT-2-i, SU and DPP-4-i.

Figure 15. Cost-effectiveness plane: Differences for canagliflozin 100mg vs. all comparators

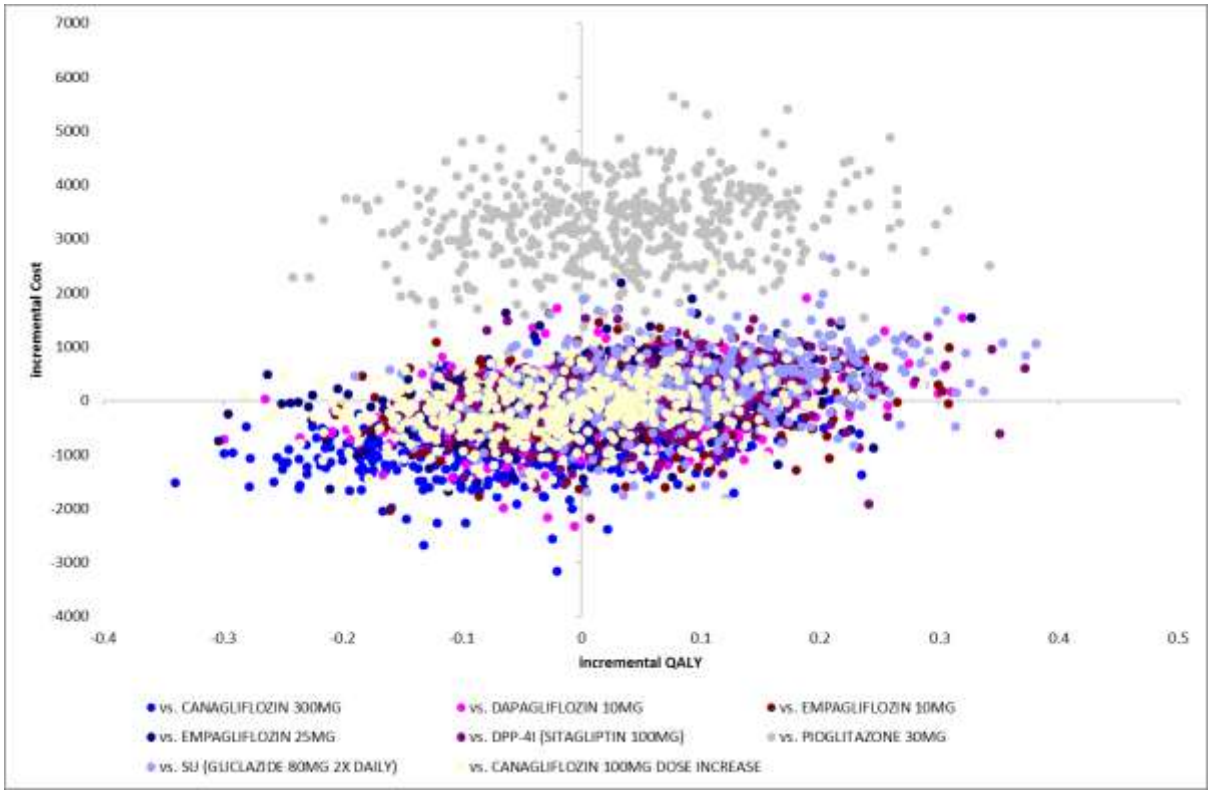


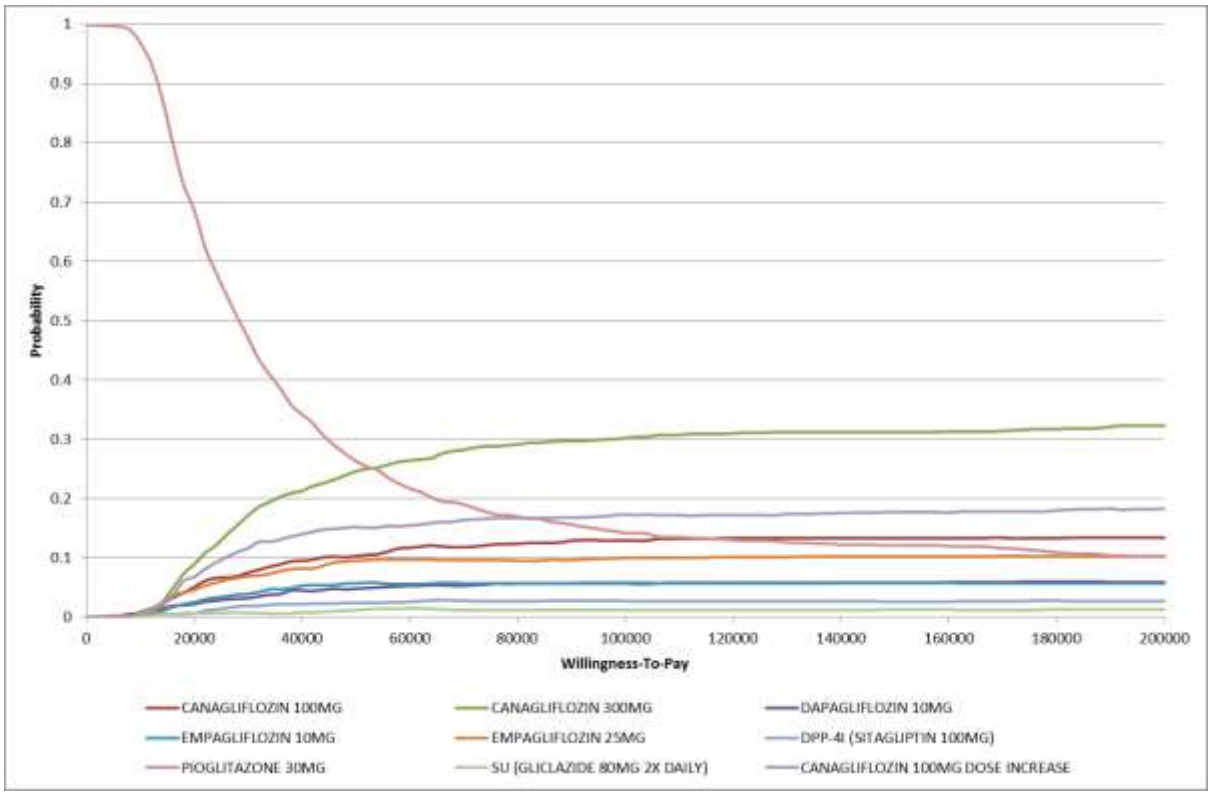
Table 16: Results of the PSA: 95% CI around incremental QALYs and costs; canagliflozin 100mg vs. all comparators in the base case

		Outcome	
		Δ QALYs	**Δ Costs**
CANA 300 mg	Point estimate	-0.04	-777
	LL 95% CI	-0.24	-1,920
	UL 95% CI	0.15	310
CANA 100 mg DOSE	Point estimate	-0.01	-144
	LL 95% CI	-0.20	-1,326
	UL 95% CI	0.18	947
DAPA 10 mg	Point estimate	0.03	-69
	LL 95% CI	-0.16	-1,196
	UL 95% CI	0.23	998
EMPA 10 mg	Point estimate	0.03	-55
	LL 95% CI	-0.16	-1,261
	UL 95% CI	0.22	962

		Outcome	
		Δ QALYs	**Δ Costs**
EMAP 25 mg	Point estimate	0.01	-3
	LL 95% CI	-0.19	-1,069
	UL 95% CI	0.22	1,130
TZD (PIO 30mg)	Point estimate	0.04	3,261
	LL 95% CI	-0.16	1,774
	UL 95% CI	0.25	4,615
SU (Gliclazide 80mg bd)	Point estimate	0.09	305
	LL 95% CI	-0.11	-929
	UL 95% CI	0.28	1,452
DPP-4i- (SITA 100mg)	Point estimate	0.06	82
	LL 95% CI	-0.12	-1,159
	UL 95% CI	0.25	1,152

Figure 16 summarises the cost-effectiveness acceptability curves for all comparisons including pioglitazone.

Figure 16. Acceptability curve for canagliflozin 100mg vs. all comparators



Scenario analysis

Selected scenario analyses were conducted using the data set used to inform scenario analysis 1, within which repaglinide is considered as a comparator. When the parameter change within a scenario analysis was considered to not have a direct impact on the inputs driving the repaglinide comparison, the scenario was conducted using the base case comparator data set, excluding repaglinide.

Only the incremental results from Scenario 1 have been presented in Table 17 and visually represented Figure 31, Appendix 9.7.

Table 17: Results of scenario analysis 1 (i.e. inclusion of repaglinide) for canagliflozin 100mg vs. all comparators

	Mean Costs	Mean QALYs	Cost per QALY (ICER)
PIO	£20,528	10.007	-
REP	£22,170	9.967	Dominated by PIO
SU (GLIC)	£23,381	9.960	Dominated by PIO
DPP-4I (SITA)	£23,758	9.987	Dominated by PIO
CANA 100	£23,833	10.046	Extendedly dominated by CANA 100MG DOSE INCR.
EMPA 25	£23,869	10.031	Dominated by CANA 100
DAPA	£23,908	10.017	Dominated by CANA 100
EMPA 10	£23,909	10.016	Dominated by CANA 100
CANA 100 DOSE INCR.	£23,981	10.054	Extendedly dominated by CANA 300
CANA 300	£24,594	10.087	£50,291

Abbreviations: CANA100, canagliflozin 100 mg; CANA300, canagliflozin 300 mg; DAPA, dapagliflozin 100 mg; DPP-4I (SITA); DPP-4i (Sitagliptin 100 mg); EMPA10, empagliflozin 10 mg; EMPA25, empagliflozin 25 mg; PIO; pioglitazone 30 mg; REP, repaglinide (2 mg 3x daily); SU (GLIC), sulfonylurea (Gliclazide 80 mg 2x daily)

Table 18: Results of the scenario analysis 1 for canagliflozin 100mg, without pioglitazone

	Mean Costs	Mean QALYs	Cost per QALY (ICER)
REP	£22,170	9.967	-
SU (GLIC)	£23,381	9.960	Dominated by REP
DPP-4I (SITA)	£23,758	9.987	Extendedly dominated by CANA 100
CANA 100	£23,833	10.046	Extendedly dominated by CANA 100MG DOSE INCR.
EMPA 25	£23,869	10.031	Dominated by CANA 100
DAPA	£23,908	10.017	Dominated by CANA 100
EMPA 10	£23,909	10.016	Dominated by CANA 100
CANA 100 DOSE INCR.	£23,981	10.054	Extendedly dominated by CANA 300
CANA 300	£24,594	10.087	£12.952

Abbreviations: CANA100, canagliflozin 100 mg; CANA300, canagliflozin 300 mg; DAPA, dapagliflozin 100 mg; DPP-4I (SITA); DPP-4i (Sitagliptin 100 mg); EMPA10, empagliflozin 10 mg; EMPA25, empagliflozin 25 mg; PIO; pioglitazone 30 mg; REP, repaglinide (2 mg 3x daily); SU (GLIC), sulfonylurea (Gliclazide 80 mg 2x daily)

As shown in the cost-effectiveness plane for this scenario analysis, including repaglinide does not qualitatively change the cost-effectiveness results. Since the trials used in the NMA to inform the efficacy repaglinide were considerably different to the trials used for all other comparators in the analysis, the uncertainty associated with these results is greater than that of the base case.

The pairwise comparison results of scenario analyses from 2-17 for canagliflozin 100mg compared with all comparators are presented in Table 19 below, and select results of the scenario analyses have been presented in incremental form in Appendix 9.7.

Summary of sensitivity analysis

When compared to the other SGLT-2-i, canagliflozin 100mg continues to be cost-effective or dominant, with the exception of Scenario 14 (alternative metabolic drift assumptions for canagliflozin). This finding is consistent with the DSA, which identified the metabolic HbA1c drift as one of the key drivers of cost-effectiveness.

When compared to pioglitazone, canagliflozin 100mg remains not cost-effective across all scenarios. Compared to SU, canagliflozin 100mg remains cost-effective, except for Scenario analyses 14, as above, and for Scenarios 2 and 6. Against the DPP-4-i, canagliflozin remains cost-effective across all scenarios.

The consistency of the results of the scenario analyses demonstrates the robustness of the model and gives some confidence to the base case ICERs.

Table 19. Results of the scenario analysis for canagliflozin 100mg versus all SGLT-2 inhibitors

Scenario analysis	vs. CANA 300mg			vs. CANA 100mg Dose Increase			vs. DAPA 10 mg			vs. EMPA 10 mg			vs. EMPA 25 mg		
	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)
Base case	-777	-0.044	17,845	-144	-0.012	12,070	-69	0.033	Dominates	-55	0.029	Dominates	-3	0.015	Dominates
ScA 1	-761	-0.042	18,334	-148	-0.009	17,266	-75	0.029	Dominates	-76	0.030	Dominates	-36	0.014	Dominates
ScA 2	-728	-0.040	17,977	-121	-0.017	7,255	-54	0.030	Dominates	-7	0.025	Dominates	0	0.014	Dominates
ScA 3	-761	-0.060	12,587	-148	-0.011	13,318	-75	0.037	Dominates	-76	0.036	Dominates	-36	0.019	Dominates
ScA 4	-761	-0.035	21,987	-148	-0.007	21,051	-75	0.023	Dominates	-76	0.025	Dominates	-36	0.011	Dominates
ScA 5	-541	-0.023	23,906	-80	-0.003	26,693	200	0.049	4,094	220	0.040	5,541	282	0.031	9,094
ScA 6	-542	-0.001	480,444	-68	-0.001	128,398	204	0.022	9,244	202	0.019	10,837	169	0.018	9,376
ScA 7	-784	-0.042	18,645	-129	-0.010	12,768	-	-	-	-	-	-	-	-	-
ScA 8	-802	-0.029	27,437	-138	-0.011	12,116	-82	0.030	Dominates	-52	0.025	Dominates	-24	0.017	Dominates
ScA 9	-938	-0.054	17,425	-83	-0.002	39,087	-65	0.070	Dominates	-111	0.056	Dominates	-23	0.028	Dominates
ScA 10	-686	-0.027	25,291	-102	-0.004	28,811	-51	0.033	Dominates	-60	0.027	Dominates	0	0.016	Dominates
ScA 11	-630	-0.031	20,387	-179	-0.014	12,489	-91	0.028	Dominates	-31	0.025	Dominates	-38	0.011	Dominates
ScA 12	-778	-0.038	20,290	-166	-0.015	10,970	-32	0.039	Dominates	-14	0.032	Dominates	-11	0.015	Dominates
ScA 13	-565	-0.035	16,166	8	-0.003	Dominated	-382	0.044	Dominates	-327	0.035	Dominates	-142	0.020	Dominates
ScA 14	-660	-0.007	89,006	-119	-0.007	16,695	198	0.003	71,395	150	0.003	50,826	65	-0.004	Dominated
ScA 15	-791	-0.040	19,786	-65	-0.007	9,431	-54	0.033	Dominates	-19	0.035	Dominates	18	0.014	1,332
ScA 16	-776	-0.036	21,382	-101	-0.004	25,716	-56	0.045	Dominates	-75	0.037	Dominates	-5	0.020	Dominates
ScA 17	-751	-0.033	22,807	-136	-0.013	10,217	-66	0.028	Dominates	-72	0.023	Dominates	-4	0.019	Dominates

N.B Coloured cells represent inverted ICERs, where the intervention is both less costly but less effective than the comparator

Incr., incremental; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 20. Results of the scenario analysis for canagliflozin 100mg versus TZD, SU, DPP-4-I, and repaglinide

Scenario analysis	vs. TZD (Pioglitazone 30 mg)			vs. SU (Gliclazide 80 mg 2x daily)			vs. DPP-4-I (Sitagliptin 100mg)			vs. Repaglinide		
	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)	Incr. Costs (£)	Incr. QALY	ICER (£/QALY)
Base case	3,261	0.042	78,518	305	0.090	3,377	82	0.058	1,407			
ScA 1	3,304	0.039	84,048	452	0.086	5,260	74	0.059	1,254	1,663	0.079	20,982
ScA 2	2,247	0.093	24,233	1,143	0.039	29,186	117	0.056	2,073	2,750	0.014	189,670
ScA 3	3,304	-0.201	Dominated	452	0.167	2,701	74	0.065	1,154	1,663	0.200	8,308
ScA 4	3,304	0.023	146,376	452	0.072	6,286	74	0.045	1,658	1,663	0.063	26,378
ScA 5	3,515	0.112	31,291	1,117	0.122	9,140	-37	0.076	Dominates			
ScA 6	2,440	0.080	30,346	1,592	0.043	36,670	97	0.044	2,196			
ScA 7	3,229	0.057	56,386	306	0.092	3,331	-	-	-			
ScA 8	2,958	0.049	60,368	405	0.080	5,073	84	0.052	1,615			
ScA 9	4,709	0.050	93,727	222	0.148	1,506	157	0.101	1,548			
ScA 10	2,704	0.048	56,554	376	0.071	5,302	100	0.053	1,880			
ScA 11	2,284	0.032	72,494	62	0.053	1,174	89	0.041	2,192			
ScA 12	3,343	0.046	72,532	305	0.091	3,355	117	0.061	1,913			
ScA 13	3,661	0.050	72,639	-394	0.093	Dominates	-94	0.067	Dominates			
ScA 14	1,389	0.043	31,945	744	0.006	133,274	212	0.022	9,428			
ScA 15	2,991	0.074	40,435	386	0.077	5,020	121	0.063	1,927			
ScA 16	3,306	0.059	56,238	344	0.096	3,580	115	0.071	1,630			
ScA 17	3,390	0.009	357,471	318	0.089	3,582	87	0.061	1,427			

N.B Coloured cells represent inverted ICERs, where the intervention is both less costly but less effective than the comparator

Incr., incremental; TZD, thiazolidinedione; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

PSA confirmed that comparisons where the incremental changes in costs and QALYs were small (e.g., canagliflozin 100mg versus PIO) naturally exhibited greater uncertainty. Estimates were spread across all four quadrants of the cost-effectiveness plane.

The multiple comparisons of canagliflozin 100mg against other alternative treatments do show that canagliflozin brings incremental value to the treatment of these patients, and all sensitivity analyses (DSA, scenario analyses and PSA) show that this incremental gain is consistent across a broad set of assumptions.

There are a number of assumptions within the base case that might be considered conservative. Due to a lack of clinical data for comparators, 26 week NMA data has been used to inform the analysis. [redacted] Secondly, it is assumed that patient bodyweight immediately returns to baseline upon discontinuation of canagliflozin. This immediate regain of weight is less plausible than a gradual weight gain, as explored in Scenario 12. Lastly, resource use associated with the initiation of insulin and oral agents with high hypoglycaemia risk that require regular GP visits to slowly increase the dose to an optimal dose at the start of treatment have not been accounted for. Consequently, the base case assumption is more conservative than may be the reality.

Key drivers of the cost-effectiveness results councillor

The relative contribution of parameters to the cost-effectiveness differed across the different comparisons. Some factors were universally important (e.g., therapeutic effects on biomarkers and their change over time), whereas other factors only gained prominence in comparisons where there was a significant difference in that factor between the two therapies compared (e.g., weight assumptions had far more impact in comparisons of canagliflozin to SU and repaglinide than to other SGLT-2 inhibitors).

A consistent finding across DSA and scenario modelling was the paramount importance of HbA1c drift on cost-effectiveness, as this has a direct influence on the duration of effectiveness of a therapy (i.e. time to reach the threshold of HbA1c of 7.5%).

Greater HbA1c lowering with canagliflozin combined with lower metabolic drift versus SU generated QALYs and cost offsets, both due to reductions in micro- and macro-vascular co-morbidities. It also led to a lengthening of the time to insulin rescue and associated weight gain and increases in hypoglycaemic events. As these events often occur after many years, however, their impact is greatly lessened by discounting.

In many comparisons, especially for the canagliflozin 300mg dose, cost-savings are derived from the delay to start of insulin therapy. The disutility from weight gain and hypoglycaemic events associated with insulin therapy also contribute to the delay to insulin as a driver of cost-effectiveness. For comparisons versus canagliflozin 300mg the disutility of retinopathy and stroke associated with alternative AHAs also contributes significantly to cost-effectiveness.

Model validation

Naturally, the usefulness of a model depends upon its ability to predict accurately the actual health and economic outcomes of patients in a real-life treatment setting. Appendix 10 details the steps taken to validate the ECHO-T2DM model.

Of key note, the ECHO-T2DM was used to model the use of canagliflozin in the STA and thus the model has been vigorously reviewed through the NICE process (12). [redacted]

Subgroup analysis

No subgroup analyses have been conducted as part of this submission. Due to the paucity of data on the efficacy of other AHAs in subgroups of potential interest, analysis and economic modelling could not be conducted.

Interpretation of economic evidence

The systematic review of the literature described above identified only one previously published cost-effectiveness analysis for canagliflozin, namely the one conducted in support of the first submission to NICE for the use of canagliflozin in combination therapy. A de novo economic analysis was conducted, as is

standard practice for economic evaluations of chronic and progressive diseases such as T2DM and was largely based on this previous submission in terms of economic input. The drivers of cost-effectiveness identified in the current modelling application were consistent with previous modelling exercises for other therapies, in particular the magnitude of improvements in HbA1c, SBP, BMI and hypoglycaemic events.

The canagliflozin economic analyses can be considered relevant for the patients identified within the scope of this submission.

Modelling the application of dose increase of canagliflozin 100mg to 300mg increased QALY gains so that a strategy of starting patients on 100mg canagliflozin and switching to 300mg during the first year if tighter glycaemic control was required was demonstrably cost-effective when compared to SU, DPP-4-i and other SGLT-2-i.

Strengths of the evaluation

A validated and previously published model was used for the canagliflozin modelling analysis. XA comprehensive set of modelling analyses were conducted against six different agents, with a large number of DSAs and scenarios conducted, allowing for a broad assessment of the cost-effectiveness of canagliflozin monotherapy in T2DM.

The unit costs, resource use and disutility weights used are consistent with previous models and relevant for the UK setting. Where there were data gaps, for example, disutility for GMI and UK-specific baseline patient characteristics, research was conducted to identify input values. Scenario analyses were conducted where alternative data were available.

From the perspective of canagliflozin, the analyses were intentionally conservative in a number of aspects. In particular, a number of arguably minor AEs specific to the class of SGLT-2 inhibitors were included, but most AEs tied to other drug classes were excluded from the base case.

Collectively, these strengths suggest a high likelihood that the benefits and cost-effectiveness of canagliflozin have not been overestimated and that the modelling results for both doses are credible and robust.

Limitations of the evaluation

As with other economic evaluations of T2DM interventions, the main limitation is the need to extrapolate short-term trial data over a 40 year time horizon using economic modelling techniques. In particular, assumptions must be made about drug durability and the consequences (bio-marker rebound) of discontinuing agents.

Due to the lack of direct comparative trial data, an NMA was performed to address these data gaps and ensure consistency across the different comparisons.

An additional limitation is the lack of direct evidence supporting dose increase from canagliflozin 100mg to 300mg._The RCTs were designed to have 100mg and 300mg arms running in parallel. None of the studies, examined efficacy when 100mg was up titrated to canagliflozin 300mg, so assumptions have been made [redacted]

Furthermore, the use of exclusion criteria means that the clinical study population does not necessarily reflect the potential real UK population. In this case there is limited evidence in patients with baseline HbA1c >9%.

9. Assessment of factors relevant to the NHS and other parties

Patients eligible for treatment in England and Wales

In 2013, there were 3.2 million people diagnosed with diabetes in the UK, however, it was estimated that roughly 630,000 of people with the disease remain undiagnosed (135, 136). With an average prevalence of 6.0%, it is anticipated that, by 2025, five million people will have diabetes in the UK (137). Approximately 90% of adults currently diagnosed with diabetes have T2DM (138), and its incidence and prevalence has increased markedly, and consistently, in the UK for over a decade (139). The proportion of very early onset T2DM continues to increase as a proportion of those diagnosed, who have a greater opportunity to develop long-term complications (140).

Not all patients receive anti-diabetic therapy immediately after diagnosis. Initial management of T2DM typically involves lifestyle interventions, although as the condition progresses glucose-lowering agents may be required to control blood glucose levels. It is estimated that 80% of diagnosed patients with diabetes receive anti-diabetic therapy (138).

As described above, the majority of patients with T2DM commence treatment on a monotherapy, and once blood glucose can no longer be adequately controlled, it is recommended that a second AHA is added (28).

Canagliflozin is indicated for use as monotherapy, when diet and exercise alone do not provide adequate glycaemic control, in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Of the 2,096,417 patients with T2DM estimated to receive pharmacological intervention, it is predicted that approximately 0.08% of these patients would be eligible for canagliflozin monotherapy. This figure of 0.08% is based on the number of patients estimated to be receiving any monotherapy that is not metformin (3).

National population data were taken from the Office of National Statistics Annual Mid-year Population Estimates (2013) (141). The estimated number of adult patients with T2DM eligible for treatment with canagliflozin monotherapy is shown in Table 21. Prevalence data that has been used to inform these projections were sourced from the Quality and Outcomes Framework (QOF) for 2012-13, in which 84.26% of people with diagnosed diabetes in England and around 173,000 in Wales are included. Diabetes prevalence in England and Wales is estimated at 6.0 % and 6.7%, respectively (91). A prescribing report by Cegedim (November 2014) was consulted to derive the proportion of patients receiving monotherapy (3).

Table 21: Adult T2DM Patient population in England and Wales eligible for pharmacological intervention

	2016	2017	2018	2019	2020
Total Population in England and Wales	**58,105,137**	**58,496,088**	**58,889,724**	**59,286,062**	**59,685,121**
Adult Diabetes population in the England and Wales	2,911,690	2,931,208	2,950,860	2,970,647	2,990,569
Adult T2DM population in the England and Wales	2,620,521	2,638,087	2,655,774	2,673,582	2,691,512
Adult Patients with T2DM receiving pharmacological intervention	2,096,417	2,110,470	2,124,619	2,138,866	2,153,210
Adult Patients with T2DM receiving monotherapy	1,179,016	1,186,919	1,194,877	1,202,889	1,210,956
Adult Patients with T2DM receiving non-metformin monotherapy	176,852	178,038	179,231	180,433	181,643
Adult Patients with T2DM starting a non-metformin monotherapy potentially eligible for canagliflozin	44,213	111,125	145,178	162,806	172,225

Abbreviations: T2DM, type 2 diabetes mellitus

Current assumed treatment options and uptake of technologies

The budget impact of current treatment is based on 80% of diagnosed patients with T2DM receiving anti-diabetic therapy (126).

The proportion of patients receiving monotherapy was estimated for five years using the Cegedim prescribing report (November 2014), and patient numbers were projected forward using a constant inflation rate of 0.7% (3).

Patient uptake of treatment has been adjusted to account for uptake of treatment throughout the year and it is assumed that patients will remain on treatment for an average of three years within this budget impact model.

Market share assumptions

Estimates are based on the assumption of canagliflozin receiving positive NICE guidance for use in monotherapy, at the start of Q3 2016. Market share was estimated based on existing monotherapies used in this disease setting; including SU, DPP-4-i and TZD (insulin, metformin and GLP-1 treatments were not considered). Of note, the uptake trend of sitagliptin was considered as a relevant model in the projection process.

The resource impact for England and Wales will differ depending upon the comparator chosen. This is complicated in the case of canagliflozin given there are a range of existing therapies that could be displaced.

For simplicity the proportion of patients in a given treatment class was assumed constant across a five year period in the scenario when canagliflozin is not considered. The predicted displacement by the SGLT-2-i class was applied to these values, of which canagliflozin gains a percentage in the scenario considering positive canagliflozin recommendation by NICE.

For monotherapy, it was anticipated that the drugs displaced by canagliflozin would primarily be those from the SU class (gliclazide), the TZD class (pioglitazone) and the DPP-4-i class (sitagliptin), with estimated displacement rates at year five of [redacted] (3).

Estimates of the uptake of canagliflozin, and thus displacement of existing monotherapies, are presented in Table 22. These figures are based on company estimates and were derived through internal discussion within Janssen. Of note, repaglinide has not been included in the base case budget impact analysis as expert clinical opinion states there is minimal use of repaglinide in UK clinical practice.

Table 22: Estimates of the uptake of canagliflozin over 5 years

	2016	2017	2018	2019	2020
% displacement of SU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% displacement of TZD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% displacement of DPP-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other significant costs associated with treatment

Costs of treatment and monitoring associated with canagliflozin are outlined in Appendix 7.2. No additional costs related to AEs are included, as canagliflozin is assumed to have no incremental impact on the cost of treating AEs in this patient population when compared to other AHAs.

Unit costs

Costs of treatments have been taken from the BNF February 2015. No other costs have been considered for incorporation into the BIM. Unit costs for treatment and monitoring can be found in Appendix 7.1.

[redacted]

Estimates of resource savings

It was assumed that the introduction of canagliflozin for the treatment of T2DM would not be associated with any resource savings that would be suitable for inclusion into this budget impact review. All resource use and service implications have been identified and explored in the economic analysis.

Estimated annual budget impact for the NHS in England and Wales

Assuming NICE guidance is available in Q3 2016, and that canagliflozin achieves market shares as presented above, [redacted]. These calculations are presented in detail in Table 23, below.

Opportunity for resource savings or redirection of resources not quantified

The below service use and associated costs have been considered for inclusion into the BIM, however, on the grounds that there is a paucity of cost data on such services it has been assumed that they are not expected to be significant in terms of budget impact nationally and all costs have sequentially been discounted from inclusion into the BIM.

- SMBG strips for insulin, SU and pioglitazone treated patients
- SGLT-2 specific AEs; i.e. less hypoglycaemia is expected versus SU, and no additional monitoring is required compared to current used treatment.

Table 23: Budget Impact by treatment line for the NHS in England and Wales, Monotherapy

		2016	2017	2018	2019	2020
Adult Patients with T2DM starting a non-metformin monotherapy potentially eligible for canagliflozin		44,213	111,125	145,178	162,806	172,225
Current Practice without canagliflozin						
SU	% of patients	78.74%	78.74%	78.74%	78.74%	78.74%
	No. of patients	34,814	87,502	114,316	128,196	135,613
	Annual cost	£1,367,558	£3,437,229	£4,490,525	£5,035,760	£5,327,091
TZD	% of patients on	3.79%	3.79%	3.79%	3.79%	3.79%
	No. of patients	1,676	4,213	5,504	6,172	6,529
	Annual cost	£34,924	£87,778	£114,677	£128,601	£136,040
DPP-4	% of patients	13.42%	13.42%	13.42%	13.42%	13.42%
	No. of patients	5,935	14,917	19,488	21,854	23,118
	Annual cost	£2,554,239	£6,419,843	£8,387,123	£9,405,478	£9,949,609
Total Current Budget		**£3,956,721**	**£9,944,850**	**£12,992,325**	**£14,569,839**	**£15,412,741**
Future Practice with canagliflozin						
SU > CANA	% of patients	1.08%	1.08%	1.08%	1.08%	1.08%
	No. of patients	376	944	1,233	1,383	1,463
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZD > CANA	% of patients on	0.59%	0.59%	0.59%	0.59%	0.59%
	No. of patients	10	25	32	36	38
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DPP-4 > CANA	% of patients	2.56%	2.56%	2.56%	2.56%	2.56%
	No. of patients	152	383	500	560	593
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CANA, canagliflozin; DPP-4, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones; T2DM, type 2 diabetes

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes [ID756]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they 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, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

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 length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Diabetes UK
Your position in the organisation: Senior Policy Officer
Brief description of the organisation: Diabetes UK is the leading charity that cares for, connects with and campaigns on behalf of every person affected by or at risk of diabetes. We help people manage their diabetes effectively by providing information, advice and support. We campaign with people with diabetes and with healthcare professionals to improve the quality of care across the UK's health services. We fund pioneering research into care, cure and prevention for all types of diabetes. We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Type 2 diabetes is a lifelong condition. It develops when the body can still make some insulin, but not enough, or when the insulin that is produced does not work properly (known as insulin resistance). It usually appears in people over 40 and accounts for around 90% of people with diabetes. In some cases it can be treated with a healthy diet and increased physical activity. Otherwise, tablets and/or insulin are required.

Type 2 diabetes is not easy to live with and has a big impact on the day-to-day lives of people with the condition, their carers and families. People have told us that they face frequent misconceptions about Type 2 diabetes and how to manage the condition, which can affect their ability to self-manage.

Type 2 diabetes is a progressive condition and people have told us their concern is the condition developing – meaning they will need to move to insulin injections or that they will develop complications. This causes significant anxiety which impacts on their management of their diabetes. This anxiety is further increased when people feel their blood glucose levels are not well controlled.

Many people with diabetes are living with diabetic complications, which can significantly affect their ability to self-manage. Deteriorating eye sight or painful neuropathy, for example, can make it harder for people to take their medication, to manage their blood glucose levels or to stay active.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Lowering blood glucose levels, with minimum side-effects. As well as an ability to take the treatment without it negatively impacting on the day-to-day life of the person living with diabetes.

Lowering blood glucose levels and achieving good diabetes control minimises the risk of developing complications. It also reduces the likelihood that someone will need to inject insulin to manage their Type 2 diabetes. Maintaining good control can help to reduce anxiety and depression caused by the stress of managing diabetes. People told us that when they were able to maintain good control any anxiety they previously had about HbA1c results reduced.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition?

Diabetes UK has experience of the different treatments currently available to treat Type 2 diabetes. This experience has been gained through:

- Conversations with people living with Type 2 diabetes
- Reading published research.

How acceptable are these different treatments and which are preferred and why?

4. What do patients or carers consider to be the advantages of the treatment(s) 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 patients or carers expect to gain from using the treatment(s) being appraised.

People with diabetes reported the following advantages of taking dapagliflozin within its current TA:

- lowered blood glucose levels, leading to increased self-confidence in overall diabetes management (due to diminished concerns about potentially needing to take insulin of about developing complications). This also impacted positively on general management – for example confidence to exercise regularly.
- Tablets are easy to swallow
- No need to take the tablets with food
-

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

- One person reported that dapagliflozin causes less stomach upset than other medication.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

- Although some people taking dapagliflozin noted lowered blood glucose levels, some people taking it reported no change.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) 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

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment(s) being appraised.

- Severe thrush

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

- As above, in some cases positive effect reported on blood glucose levels but not in all cases. This resulted in increased or alleviated anxiety (depending whether it was effective or not).

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

This treatment has been shown to have positive effects on weight management, so may be of increased benefit to people with Type 2 diabetes who are overweight.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences 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 the

assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised 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 (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

Personal statement Type 2 Diabetes – Canagliflozin , Dapagliflozin , Empagliflozin Monotherapy for Treating Type 2 Diabetes (ID 756)

[redacted]

I have been a clinical academic (consultant level) in the field of diabetes since 1993. I previously acted as clinical expert for the NICE Technology Assessment of liraglutide (TA203) as well as several new medicines assessments for the All-Wales Medicines Strategy Group.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice?

The management of hyperglycaemia in people with type 2 diabetes is outlined by NICE clinical guideline 87 (2009), with the addition of several TAs for medicines which were licenced for use following its publication. The vast majority of cases are managed within primary care but the National Diabetes Audit shows significant geographical variation in care processes and outcomes. There is strong evidence that early control of blood glucose reduces the development and progression of microvascular complications, affecting the eyes, kidneys and nerves. The evidence that tight blood glucose control reduces large vessel complications (heart attack, stroke and peripheral vascular disease) is less robust.

Are there differences of opinion between professionals as to what current practice should be?

The current NICE guidance (CG87) and the latest draft of a new guideline for type 2 diabetes, which was due to be published in August 2015 are seen to have cost as their dominant driver. Many clinicians feel that there has been a failure to embrace individualisation of therapy, as is supported by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement (2015).

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Metformin (MF) is the standard first-line pharmacotherapy in type 2 diabetes in all western guidelines. In patients who are intolerant of MF or for whom it is contraindicated, the options are:

- Sulphonylurea (SU) drugs (but with caution due to risk of hypoglycaemia, plus weight gain as side-effects). Also, there is a requirement for self-monitoring of blood glucose in patients receiving SUs, mandated in law for those who drive motor vehicles.
- Metiglinides (such as repaglinide and netaglinide) are only mentioned here as repaglinide was recommended as a monotherapy option in the first draft of the updated NICE guidelines. The use of this drug is uncommon in the UK (and it has issues of hypoglycaemia, weight gain and requires thrice-daily dosing).

- Pioglitazone (recognised side-effects include fluid retention, weight gain, congestive cardiac failure & bone fracture). The side-effects of pioglitazone and the withdrawal of the related thiazolidinedione, rosiglitazone, means that it is much less frequently used in primary care than was the case before 2010.
- Acarbose (not used to any extent in the UK, due to common bowel side-effects).
- Gliptins: Sitagliptin, linagliptin and vildagliptin are all recommended as monotherapy in patients who either do not tolerate MF or for whom it is contra-indicated. These agents can be used in patients with chronic kidney disease (CKD) and have a good tolerability and safety profile.
- Insulin (side-effects of weight gain & hypoglycaemia, along with issues of patient education, increased self-monitoring etc.). Insulin is rarely used as monotherapy in the UK.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Patients with type 2 diabetes and existing large vessel disease (cardio- and cerebro-vascular disease) and are at particularly high risk of premature morbidity and mortality. However, the first completed cardiovascular safety study for a member of the SGLT2I class (empagliflozin) showed a significant benefit in such a population.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by SGLT2I therapy?

Patients with recurrent genital fungal infections (especially females) may have an increased frequency of infection.

Subjects with stage CKD3 will respond less well to this class of therapy.

Patients on diuretics or at risk of intravascular volume depletion may be at greater risk of hypovolaemia and postural hypotension .

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

The commonest setting for initiation of this class as monotherapy therapy is primary care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

No

If the technology is already available, is there variation in how it is being used in the NHS?

Uptake of SGLT2I has been variable and this probably reflects the piecemeal uptake of new diabetes therapies, dependent upon having the involvement of more than 200 clinical commissioning groups. Following on from their NICE TAs, all three SGLTIs are available in Wales but not as a monotherapy option.

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.

The SGLT2I class were not available when CG87 was published but have been added as TAs were published by NICE in 2013 (dapagliflozin), 2014 (canagliflozin) and 2015 (empagliflozin).

The latest draft of the new NICE guideline for type 2 diabetes mentions the SGLT2I class only as a footnote in two algorithms, and refers to the TAs above. Ommission of a class of oral antidiabetic agents which have been licenced for use in Europe for over three years, is widely seen as a weakness in the current iteration of the new NICE guideline.

The ADA/EASD position statement (2015) places the SGLT2I class as a second-line option following MF and as an alternative first-line agent where MF is not tolerated.

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?

Metformin (MF) is the first-line pharmacotherapy recommended for treatment of T2DM after failure of diet and lifestyle changes. A proportion of patients are unable to tolerate MF, largely due to gastrointestinal upset, and up to 30% develop chronic kidney disease (CKD) which, depending on the formulation of MF, can exclude its use. The use of an SGLT2I as monotherapy would only be feasible in those with MF intolerance, since it is not licenced for initiation in patients with stage 3 CKD (estimated glomerular filtration rate less than 60 mLs/min).

Because the SGLT2I class has an insulin-independent mode of action, the risk of hypoglycaemia is extremely low. In addition, there are the additional benefits of weight reduction and blood pressure lowering.

SGLT2I medicines are single dose, oral therapies with no requirement for meal-time dosing. They have at least equivalent glucose-lowering to all other oral classes of anti-diabetic agents and, in empagliflozin, have the best evidence for cardiovascular and all-mortality reduction of all the glucose-lowering classes (including insulin).

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.

The same stopping rule as applied to the gliptins might be appropriate (a fall in HbA1c of at least 5 mmol/mol (0.5%) over the first six months of treatment)

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?

The main side-effect of the SGLT2I class is genetic fungal infection, typically see as a one-off early in the therapy and which resolves with over-the-counter self-medication. The side-effects are generally mild and patients are willing to tolerate these when they see benefits of good glycaemia control and weight loss.

Personal statement Type 2 Diabetes – Canagliflozin , Dapagliflozin , Empagliflozin Monotherapy for Treating Type 2 Diabetes (ID 756)

I have been a consultant diabetologist for 22 years and have previously been an invited expert for NICE TAs on dapagliflozin and empagliflozin TAs .

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice?

Type 2 diabetes is extremely common - affecting at least 6% of the adult population , with a projected prevalence of 10% by 2020. The vast majority of cases are managed within primary care. Recent National Diabetes audit shows significant geographical variation in care processes and outcomes. There is a clear evidence base demonstrating that early effective control of blood glucose can reduce the development and progression of microvascular (and potentially macrovascular) complications. Over-intensive glucose control with established Type 2 diabetes and large vessel complications in older patients has been linked to increased mortality.

Are there differences of opinion between professionals as to what current practice should be?

The algorithm for placement of different therapies in Type 2 diabetes is consensus rather than evidence based . Although the American Diabetes Association and the European Association for the Study of Diabetes have produced broad guidance to help selection of therapy for diabetes , this is not synonymous with the anticipated (released) NICE guidelines for type 2 diabetes . All guidelines place metformin as initial therapy for type 2 diabetes. Although earlier NICE TAs placed gliflozins alongside gliptins in the treatment cascade they are not distinctively placed alongside 2nd-3rd line in the draft new NICE T2 guidelines . The early use of injectable (insulin and GLP-1 analogue) therapy and the relative risks of weight gain and hypoglycaemia versus the established evidence base for the beneficial impact of glycaemic control with older sulfonylurea agents remains an area of contention amongst opinion leaders in diabetes .

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Type 2 diabetes can be treated with a range of oral and injectable therapies . The broad categories either enhance or replicate endogenous insulin action or enable more effective use of endogenous insulin. Considerations as to selection of different classes of agent may reflect cost , impact on weight , hypoglycaemia risk , efficacy and safety in renal disease , impact on established micro and macrovascular complications , risk of specific side effects such as pancreatitis . Key longer term safety-efficacy in respect of cardiovascular and cancer outcomes requires longer term large scale prospective surveillance.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Patients with a family history of diabetes with adverse outcomes, those with the 'full house' of features of metabolic syndrome , renal disease (assessed by albuminuria and eGFR) , smokers , early onset T2, consistent poor control all carry a worse prognosis

.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by SGLT2I therapy?

Patients with CKD3-4 will respond less well to this class of therapy.
Patients with established bladder dysfunction or other bladder pathology or recurrent genitourinary infections – including fungal infections may be more likely to display the more common side effects .
Patients on diuretics or at risk of intravascular volume depletion may be at greater risk of hypovolaemia and postural –blood pressure lowering effects .

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

The commonest setting for initiation of this class as monotherapy therapy will be primary care .

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Monitoring of patients initiated on other therapies such as diuretics or antibiotic-antifungal agents whilst on this agent could be highlighted by dispensing pharmacists .

If the technology is already available, is there variation in how it is being used in the NHS?

Uptake of SGLT2I has varied as with any new class of therapy , awaiting outcome safety studies . The recent EMPA-reg study demonstrated changes in CV outcomes within 6 months and in some patients with CVD apparently with monotherapy

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.

NICE –Type 2 – recently published
ADA-EASD best practice guidelines for T2DM 2012

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?

Initial therapy in current NICE type 2 guidelines recommends metformin as first line therapy . In practice 15-20% of patients will not tolerate either standard or sustained release metformin and this would be considered for the proposed option of SGLT2I or other licensed monotherapy . However in distinction to other alternative oral therapies for single agent use when metformin not tolerated , the class of SGLT2I has insulin independent mode of action making risk of hypoglycaemia extremely low . in addition additional benefits of weight and blood pressure reduction can be anticipated

<u>Use of SGLT2I as monotherapy</u>

The placebo controlled monotherapy studies with canagliflozin demonstrate important glycaemic lowering efficacy with weight loss and BP lowering .

The network meta analysis also demonstrate efficacy of at least a comparable degree to all active comparitors with greater clinical utility than the use of titrated repaglinide recommended by NICE in the draft T2 DM guidlines

The recent EMPA-reg study raises the option of considering monotherapy for patients with established CVD and eGFR > 30 assuming no other contraindications .

Whereas metformin is not recommended when eGFR < 30 the same preclusion would apply for SGLT2I , although on grounds of reduced efficacy as opposed to safety.

Haematocrit , urate and renal function measures are likely to be considered with initial use especially if already at risk of dehydration , GU infection. Sterile urine without haematuria should be established at baseline given the potential impact of sustained marked glycosuria on urothelial cells and the need to avoid any concern regarding bladder cancer risk .

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.

Recurrent GU infections , hypovolaemia , acute kidney injury , newly developed haematuria requiring investigation .

Sick day rules important for temporary withdrawal given risk of hypovolaemia compounding patients with vomiting , diarrohea and starvation and the very infrequent reported euglycaemia ketoacidosis reported with SGLT2I class .

Efficacy over 6 months evidenced by drop in HbA1c of at least 5 mmol/mol as basis for continued treatment .

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?

Unclear whether recurrent urinary bacterial and fungal infections – impact of urine volume-nocturia would preclude longer term use although evidence from trials suggest these effects are modest and reduce over time course of therapy .

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Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Thank you for agreeing to give us a statement on your organisation's 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:

Name of your organisation : ABCD (Association of British Clinical Diabetologists) and RCPL (The Royal College of Physicians of 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)? 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.)? Yes – Clinical Director in East and North Herts NHS trust
- other? (please specify) Member of executive of ABCD and Secretary of RCPL Joint Speciality Committee in Diabetes and Endocrinology

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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? **Type 2 diabetes is extremely common - affecting 5-7% of the adult population , with a projected prevalence of 10% by 2020. The vast majority of cases are managed within primary care. Recent National Diabetes audit shows significant geographical variation in care processes and outcomes. There is a clear evidence base demonstrating that early effective control of blood glucose can reduce the development and progression of microvascular (and potentially macrovascular) complications. Over-intensive glucose control with established Type 2 diabetes and large vessel complications in older patients has been linked to increased mortality.**

Are there differences of opinion between professionals as to what current practice should be?
The algorithm for placement of different therapies in Type 2 diabetes is consensus rather than evidence based . Although the American Diabetes Association and the European Association for the Study of Diabetes have produced broad guidance to help selection of therapy for diabetes , this is not synonomous with the older NICE guidelines for type 2 diabetes . The early use of injectable (insulin and GLP-1 analogue) therapy and the relative risks of weight gain and hypoglycaemia versus the established evidence base for the beneficial impact of glycaemic control with older sulfonylurea agents remains an area of contention amongst opinion leaders in diabetes .

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Type 2 diabetes can be treated with a range of oral and injectable therapies . The broad categories either enhance or replicate endogenous insulin action or enable more effective use of endogenous insulin. Considerations as to selection of different classes of agent may reflect cost , impact on weight , hypoglycaemia risk , efficacy and safety in renal disease , impact on established micro and macrovascular complications , risk of specific side effects such as pancreatitis . Key longer term safety-efficacy in respect of cardiovascular and cancer outcomes requires longer term large scale prospective surveillance.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Patients with a family history of diabetes with adverse outcomes, those with the 'full house' of features of metabolic syndrome , renal disease (assessed by albuminuria and eGFR) , smokers , early onset T2, consistent poor control all carry a worse prognosis

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Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with CKD3-4 may respond less well to this class of therapy. Patients with established bladder dysfunction or other bladder pathology or recurrent genitourinary infections – including fungal infections may be more likely to display the more common side effects .

Patients on diuretics or at risk of intravascular volume depletion may be at greater risk of hypovolaemia and postural –blood pressure lowering effects .

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

The commonest setting for initiation of this therapy will be primary care although use alongside insulin may be more likely in specialist care .

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Monitoring of patients initiated on other therapies such as diuretics or antibiotic-antifungal agents whilst on this agent could be highlighted by dispensing pharmacists .

If the technology is already available, is there variation in how it is being used in the NHS?
Not currently available

Is it always used within its licensed indications? If not, under what circumstances does this occur?

Therapy could have place in patients with type 1 diabetes especially if overweight-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.

NICE –Type 2 – under review

ADA-EASD best practice guidelines for T2DM 2012

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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?

Patients with obesity and/or at risk of hypoglycaemia may currently be considered for gliptins or GLP-1 analogues . Dapagliflozin could be considered an agent which may also be placed alongside these newer agents although patients with CKD3 -4 would be less likely to respond to dapa in contrast to gliptins .

Haematocrit , urate and renal function measures are likely to be considered with initial use especially if already at risk of dehydration , GU infection. Sterile urine without haematuria should be established at baseline given the potential impact of sustained marked glycosuria on urothelial cells and the need to avoid any concern regarding bladder cancer risk .

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.

Recurrent GU infections , hypovolaemia , acute kidney injury , newly developed haematuria requiring investigation .

Efficacy over 6 months evidenced by drop in HbA1c of at least 5 mmol/mol as basis for continued treatment .

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?

Glycaemic benefits key outcome .

Unclear whether exclusion of those at highest risk of GU infections , use of diuretics would mean that the study patients were representative of wider

general practice based population. Long term efficacy and safety (CVD and cancer incidence) would require long term surveillance outwith initial phase II studies. Longer term outcome studies should be planned that evaluate all small and large vessel outcomes especially incidence of diabetic nephropathy, along with CVD and cancer 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?

Unclear whether recurrent urinary bacterial and fungal infections – impact of urine volume-nocturia would preclude longer term use although evidence from trials suggest these effects are modest and reduce over time course of therapy

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Single Technology Appraisal (STA)

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.

Updated published abstracts and presentations at recent international speciality meetings at – ADSA and EASD + papers published within last few months that might not have been included in systematic review if undertaken prior to meeting in January

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

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Single Technology Appraisal (STA)

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)?

Education of primary health care teams of a new class of therapy would be important as well as enabling placement of the class of therapy within upcoming Type 2 DM guidelines .

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Patient/carer expert statement (MTA)

Canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes [ID756]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they 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(s).

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. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to specify which treatment (s) you are commenting on.

1. About you

Your name: [redacted]
Name of your nominating organisation: Diabetes UK
Do you know if your nominating organisation has made a submission?

☐√ Yes ☐ No

Do you wish to agree with your nominating organisation's submission?

☐√ 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 (s) being appraised (that is, those included in the title)?

☐√ Yes ☐ No

If yes, please tell us which one(s)

Dapaglifozin

If you wrote the submission from the patient organisation 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 hungry and feeling a bit light-headed and needing something to eat.

- Sometimes, it is difficult in getting some people to understand I have diabetes due to a high family history and not because I ate too many sweet, sugary and inappropriate meals. I have never been overweight.

- It is frustrating when I receive poor advice/mixed messages from those involved with my diabetes care 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.

DAPAGLIFOZIN

- Better blood sugar control which reduces my risk of complications.

- Minimum side effects from medication.

- Not having to take insulin.

- Feeling more confident and healthier when blood glucose levels are improved.

- Greater flexibility in my lifestyle.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

- Some HCP's have more knowledge than others about diabetes and the medications available which makes it difficult to discuss or find out about newer medications which might be more suitable or appropriate.

- 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.

4. What do you consider to be the advantages of the treatment(s) 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(s) 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.
- It is easy to take.
- Feel healthier
- Better quality of life.

Please explain any advantages for the treatment(s) being appraised compared with 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.
- 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(s) being appraised, please tell us about them.

- Have not discussed this with others.

5. What do you consider to be the disadvantages of the treatment(s) 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

Please list any concerns you have about current NHS treatments in England.

- Are GP/HCP's giving the correct drug as a priority to the patient or looking at costs first.

Please list any concerns you have about the treatment(s) being appraised.

- Drug might be withdrawn due to costs.
- Other health risks yet unknown.
- Making sure that patients drink enough to avoid dehydration due to the way the drug works.

- HCP not giving person enough information about the treatment and how it works.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

- Not discussed.

6. Patient population

Do you think some patients might benefit more from the treatment(s) 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.

Do you think some patients might benefit less from the treatment(s) 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.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment(s)?

☐ 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(s) 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 the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with the treatment(s) being appraised 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.

- None that I can think of.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐√ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

- 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.

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.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your statement.

- Improved blood glucose levels
- Lead a healthier lifestyle
- More confident
- No longer stressed about blood glucose levels
- Seem to have a more flexible lifestyle