NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Canagliflozin in combination therapy for treating type 2 diabetes

This premeeting briefing is a summary of:

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

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

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- What is the Committee's view on canagliflozin's likely place in the treatment pathway considering current NICE guidance (notably NICE clinical guideline 87 'The management of type 2 diabetes' and technology appraisal guidance 288 'Dapagliflozin in combination therapy for treating type 2 diabetes'?
- What are the main relevant comparators in clinical practice for canagliflozin in dual therapy, triple therapy and as add-on to insulin?
  - Does the Committee agree with the manufacturer's rationale not to consider the clinical effectiveness of canagliflozin in certain combinations specified in the NICE scope?
- Although pioglitazone was specified as a comparator in the NICE scope, the manufacturer and the ERG received clinical advice that it is no longer widely used because of safety concerns. Does Committee believe that pioglitazone is still a clinically relevant comparator?

- The canagliflozin trials recruited globally with limited enrolment in the UK. Does the Committee consider that the trial data are generalisable to the patient population in England?
- Is the network meta-analysis a suitable source of clinical-effectiveness data for decision-making (changes in HbA_{1c} and body mass index), rather than direct evidence from the trials?
  - Because of an absence of head-to-head trials comparing canagliflozin with some comparators in the scope (GLP-1 analogues and dapagliflozin), the clinical-effectiveness data were taken from the manufacturer's network meta-analyses. What is the Committee's view of the appropriateness, quality and reporting of these analyses?
  - The DIA3015 compared canagliflozin 300 mg and sitagliptin in triple therapy regimens with a background of metformin and a sulfonylurea, but did not include a canagliflozin 100 mg arm. Does Committee consider the meta-analysis results for the comparison of canagliflozin 100 mg and sitagliptin to be sufficiently robust for decision-making?
- Canagliflozin's European marketing authorisation recommends a starting dose of 100 mg and escalating to 300 mg if tighter glycaemic control is needed in patients with adequate renal function who tolerate canagliflozin 100 mg. What are the most likely ways that the 100 mg and 300 mg doses of canagliflozin would be used in clinical practice in England?
- The manufacturer provided evidence for canagliflozin as an add-on therapy to insulin from the DIA3008 subgroup study, which compared canagliflozin with placebo in combination with insulin and various other treatments. Patients in DIA3008 were part of the CANVAS study, which enrolled patients who had a history or high risk of cardiovascular disease. The ERG commented that DIA3008 was not relevant to the decision problem because it did not include an active comparator (although the data were used in the manufacturer's economic model). Does the Committee consider this evidence suitable for informing a decision on canagliflozin as an add-on therapy to insulin?
- Adverse events associated with canagliflozin were presented by the manufacturers as pooled safety datasets. The ERG did not agree with

manufacturer's interpretation of some of the data (for example, discontinuation rates). What is the Committee's view on the safety of canagliflozin for treating type 2 diabetes and the importance of these data to the economic modelling?

Cost effectiveness

- The manufacturer has chosen a specific comparator to represent each treatment class in the economic modelling. The ERG has described the differences between drugs in each class. Does the Committee accept the manufacturer's choices for each representative comparator?
- The manufacturer has submitted a new model that has not been critiqued in previous NICE technology appraisals. Is the Committee satisfied with the structure and functioning of the model?
- Is the Committee persuaded that the assumptions in the manufacturer's model for HbA_{1c} threshold (which is applied to the model's treatment pathways) adequately reflect clinical practice for treating type 2 diabetes in England?
- Does the Committee consider the risk equations used to estimate the probability of macrovascular complications (from the original UKPDS Outcomes Model) and the annual probabilities of experiencing worsening microvascular complications (derived primarily from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the Rochester Epidemiology Project, and the Centers for Disease Control model of chronic kidney disease) to be appropriate and correctly implemented in the model?
- The health-related quality of life and cost inputs are drawn from a range of different sources. Does the Committee consider that the values have been appropriately identified and are plausible?
- The manufacturer's sensitivity analyses show that HbA_{1c} drift is a key driver of the economic model. Does the Committee find the assumptions associated with HbA_{1c} acceptable?
- Canagliflozin's European marketing authorisation recommends a starting dose of 100 mg and escalating to 300 mg in suitable patients. However, the manufacturer's and ERG's base-case cost-effectiveness analyses (and

clinical trials) present results for 100 mg and 300 mg separately. Does Committee consider this to be appropriate?

- The manufacturer has modelled dose escalation from canagliflozin 100 mg to canagliflozin 300 mg as a scenario analysis, based on target HbA_{1c} levels:
  - If the 100 mg dose wasn't effective at controlling HbA_{1c}, does Committee consider it reasonable to assume the same efficacy in patients who increase their canagliflozin dose from 100 mg to 300 mg as a patient in the clinical trials who received only the 300 mg dose?
  - Does the Committee believe that increasing the canagliflozin dose if glycaemic control is not achieved at 6 months reflects its likely use in clinical practice in England?
  - What is the Committee's view of using HbA_{1c} of 7.5% at 6 months as the threshold for requiring tighter glycaemic control and switching to the higher dose of canagliflozin?
- Does the Committee consider that the results from this economic model are sufficiently robust to suggest that canagliflozin is a cost-effective use of NHS resources in dual therapy, triple therapy or as an add-on treatment to insulin?

1 Background: clinical need and practice

1.1 Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. There are 2 main types of diabetes. Type 1 diabetes is caused by an absolute loss of insulin production. Type 2 diabetes is associated with obesity, and is caused by reduced tissue sensitivity to insulin (known as insulin resistance) and a failure of insulin secretion to compensate for this.

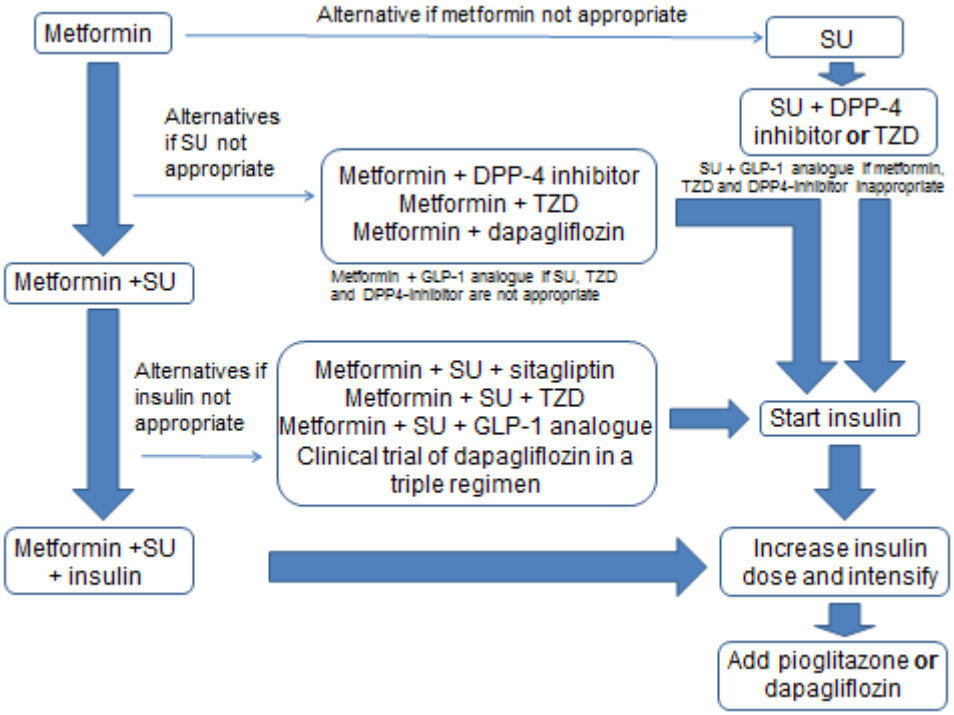
1.2 In people with untreated type 2 diabetes, symptoms include excessive production of urine (polyuria), thirst, weight loss and fatigue. Type 2 diabetes is also associated with an increased cardiovascular risk. This can manifest as coronary artery disease

(leading to heart attacks and angina), peripheral artery disease (leading to leg claudication and gangrene), and carotid artery disease (linked to strokes and dementia). If not managed effectively, diabetes can also lead to complications including kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication associated with type 2 diabetes and is the greatest cause of morbidity and premature death.

1.3 There were approximately 2.9 million people in the UK aged 17 or older with diabetes mellitus in 2011, 90% of whom had type 2 diabetes. However, there are many people with undiagnosed type 2 diabetes so the real number is likely to be higher. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin. The prevalence of type 2 diabetes in the UK is rising due to the increasing prevalence of obesity and decreased physical activity, but also increased longevity after diagnosis because of better cardiovascular risk protection. Life expectancy is reduced by up to 10 years in people with diabetes.

1.4 Appendix B of this document lists in full relevant recommendations in NICE guidance about the management of type 2 diabetes. A simplified version is given in figure 1 below. Briefly, NICE clinical guideline 87 recommends diet and lifestyle modifications to initially manage type 2 diabetes. For people who are overweight or obese and whose blood glucose is inadequately controlled by diet and lifestyle modifications, the oral anti-diabetic drug, metformin is recommended. A sulfonylurea (for example, gliclazide, glipizide, or glimepiride) may be considered as a monotherapy option if the person is not overweight, does not tolerate metformin or a rapid response is needed because of hyperglycaemia.

Figure 1 Simplified treatment pathway showing NICE recommendations on pharmacological treatments for type 2 diabetes (clinical guideline 87 and technology appraisal guidance 203, 248 and 288)



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SU, sulfonylurea; TZD, thiazolidinedione

1.5 If blood glucose control remains inadequate on monotherapy with metformin, a sulfonylurea should be added. A thiazolidinedione (pioglitazone) or a dipeptidyl peptidase-4 (DPP-4) inhibitor such as sitagliptin or vildagliptin can only be used as an add-on therapy to monotherapy with metformin or a sulfonylurea if the combination of metformin and sulfonylurea as dual therapy is not considered appropriate. Dapagliflozin in combination with metformin is recommended as a dual therapy regimen in NICE technology appraisal guidance 288, only if it is used as described for DPP-4 inhibitors in NICE clinical guideline 87 (see section 1.6.2 of appendix B). The glucagon-like peptide 1 (GLP-1) analogues (exenatide and liraglutide) are recommended in NICE technology appraisal guidance 203 and 248 as options for dual therapy only if metformin or a sulfonylurea is contraindicated or not tolerated and a thiazolidinedione and a DPP-4 inhibitor is contraindicated or not tolerated.

1.6 For people whose disease is not controlled on dual therapy, NICE clinical guideline 87 recommends starting insulin in preference to adding other drugs. However, if insulin is considered unacceptable (because of employment, social, recreational or other personal issues), either sitagliptin or pioglitazone are recommended as options for add-on therapy to metformin and sulfonylurea. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is only recommended in NICE technology appraisal 288 as part of a clinical trial. The injectable GLP-1 analogues (twice-daily or prolonged-release exenatide and once-daily liraglutide) may be prescribed in a triple-therapy regimen for a specific population (see section 1.6.3 in line with NICE clinical guideline 87 and technology appraisal guidance 203 and 248 in appendix B).

1.7 For people whose disease is not controlled by insulin alone, oral antidiabetic drugs may be used as add-on treatment. NICE clinical guideline 87 states that combining pioglitazone with insulin therapy may be considered for a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended in NICE technology appraisal guidance 288. Please see Appendix B for a summary of all relevant recommendations from NICE clinical guideline 87 and NICE technology appraisal guidance 203, 248 and 288.

2 The technology

2.1 Canagliflozin (Invokana, Janssen-Cilag) is an orally administered selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor, which lowers blood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine.

2.2 Canagliflozin has a European marketing authorisation for treating type 2 diabetes in adults aged 18 years and older 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.
- add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The recommended starting dosage 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/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 once daily. For patients with renal impairment, the summary of product characteristics notes that canagliflozin should not be initiated in patients with an eGFR less than 60 mL/min/1.73m^2 or CrCl less than 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, 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/min/1.73 m^2 or CrCl persistently below 45 mL/min.

2.3 The summary of product characteristics states the following adverse reactions for canagliflozin are the most commonly reported: hypoglycaemia in combination with insulin or a sulphonylurea, 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 According to the manufacturer's submission, the expected price is £39.20 for canagliflozin 100 mg (30 tablets) and £49.99 for canagliflozin 300 mg (30 tablets). The expected annual cost of canagliflozin is £477.26 for the 100 mg daily dosage and £608.83 for the 300 mg daily dosage. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of canagliflozin within its licensed indication for the treatment of type 2 diabetes.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population		
Dual therapy	Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin or a sulfonylurea.	Adults with type 2 diabetes that is inadequately controlled with metformin.
Triple therapy	Adults with type 2 diabetes that is inadequately controlled on dual therapy with either of the following: • metformin in combination with a sulfonylurea • metformin **or** a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue.	Adults with type 2 diabetes that is inadequately controlled on dual therapy with: • metformin in combination with a sulfonylurea • metformin in combination with a thiazolidinedione.
Add-on therapy to insulin	Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.	Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin and standard of care.

When evaluating dual therapy regimens, the manufacturer advised that adults with type 2 diabetes that is inadequately controlled with a sulfonylurea would not be considered. The manufacturer's reasons for excluding this population were a relatively high rate of hypoglycaemia associated with the combination

of canagliflozin and sulfonylurea, and the high proportion of patients receiving sulfonylurea-based dual therapy who would be ineligible for treatment with canagliflozin (because metformin use is restricted in people with impaired renal function). Although the ERG agreed that most patients treated with dual therapy would receive an add-on to metformin, it noted that the manufacturer's rationale was not justified and commented that excluding patients treated with a background of a sulfonylurea was not reasonable because this was a significant number of people with diabetes treated in the NHS (because of the high prevalence of diabetes). It further noted that these people would be eligible for treatment with canagliflozin in line with its European marketing authorisation.

When evaluating triple therapy regimens, the manufacturer stated that a combination of canagliflozin with metformin and a DPP-4 inhibitor or a GLP-1 analogue would not be considered because it believed that

[redacted]

The ERG noted that the manufacturer did not specifying how many agents are used as part of 'standard of care' when evaluating canagliflozin as an add-on therapy to insulin.

The manufacturer presented subgroup analyses for change in HbA_{1c} according to baseline HbA_{1c} and baseline body mass index, which had been requested in the final scope.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Canagliflozin (in combination with oral anti-diabetic agents and/or insulin)	Canagliflozin 100 mg or 300 mg once daily (in combination with oral anti-diabetic agents and/or insulin)

The ERG stated that the use of canagliflozin specified in the manufacturer's decision problem was narrower than defined in the licensed indication and may not reflect all the potential uses of canagliflozin in clinical practice.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators		
Dual therapy	For the combination of canagliflozin and metformin, the comparators are: • sulfonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin) • dapagliflozin (with metformin). For the combination of canagliflozin and sulfonylurea, the comparators are: • pioglitazone (with a sulfonylurea) • DPP-4 inhibitors (with a sulfonylurea) • GLP-1 analogues (with a sulfonylurea).	For the combination of canagliflozin and metformin, the comparators are: • sulfonylureas (with metformin) • thiazolidinediones (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin) • dapagliflozin (with metformin).

Triple therapy	For the combination of canagliflozin, metformin and a sulfonylurea, the comparators are: • pioglitazone (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea) • insulin (with metformin and a sulfonylurea) For the combination of canagliflozin, metformin and pioglitazone, the comparators are: • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • insulin (with metformin and pioglitazone). For the use of canagliflozin in any other triple therapy regimen, the comparator is: • insulin (alone or in combination with one or more oral anti-diabetic agents).	For the combination of canagliflozin, metformin and a sulfonylurea, the comparators are: • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea) • insulin (with metformin and a sulfonylurea) For the combination of canagliflozin, metformin and pioglitazone, the comparator is: • DPP-4 inhibitors (with metformin and pioglitazone)
Add-on therapy to insulin	• One or more oral anti-diabetic agents (in combination with insulin).	Canagliflozin in combination with insulin with or without metformin, will be compared to: DPP-4 inhibitors (with insulin with or without metformin) GLP-1-analogues (with insulin with or without metformin) Dapagliflozin (with insulin with or without metformin)

The manufacturer reported that it would not compare the dual therapy combination of canagliflozin and a sulfonylurea with other oral antidiabetic

agents in combination with a sulfonylurea because of the reasons stated above in the population section. It added that several triple therapy combinations would not be evaluated because insufficient clinical data were found to populate a network meta-analysis:

- Metformin, a sulfonylurea and canagliflozin compared with metformin, a sulfonylurea and either pioglitazone or insulin.
- Metformin, a thiazolidinedione and canagliflozin compared with metformin, a thiazolidinedione and either a GLP-1 analogue or insulin.

The manufacturer advised that no efficacy data were available to allow an indirect comparison of canagliflozin and a thiozolidinedione as add-on therapy to insulin, and confirmed that using canagliflozin in any other triple therapy regimen would not be assessed. The ERG stated the comparators outlined in the manufacturer's decision problem were appropriate for the NHS and were generally those recommended in NICE guidance. The ERG indicated that the combination of canagliflozin, metformin and thiazolidinedione may be of limited relevance to clinical practice because the use of thiazolidinediones in England is declining.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	The outcome measures to be considered include: • HbA_{1c}/glycaemic control • frequency and severity of episodes of hypoglycaemia • change in cardiovascular risk factors (including blood pressure and/or serum lipids) • weight change • complications of diabetes (for example, cardiovascular, renal and eye) • mortality • adverse effects of treatment (including genitourinary tract infection) • health-related quality of life.	

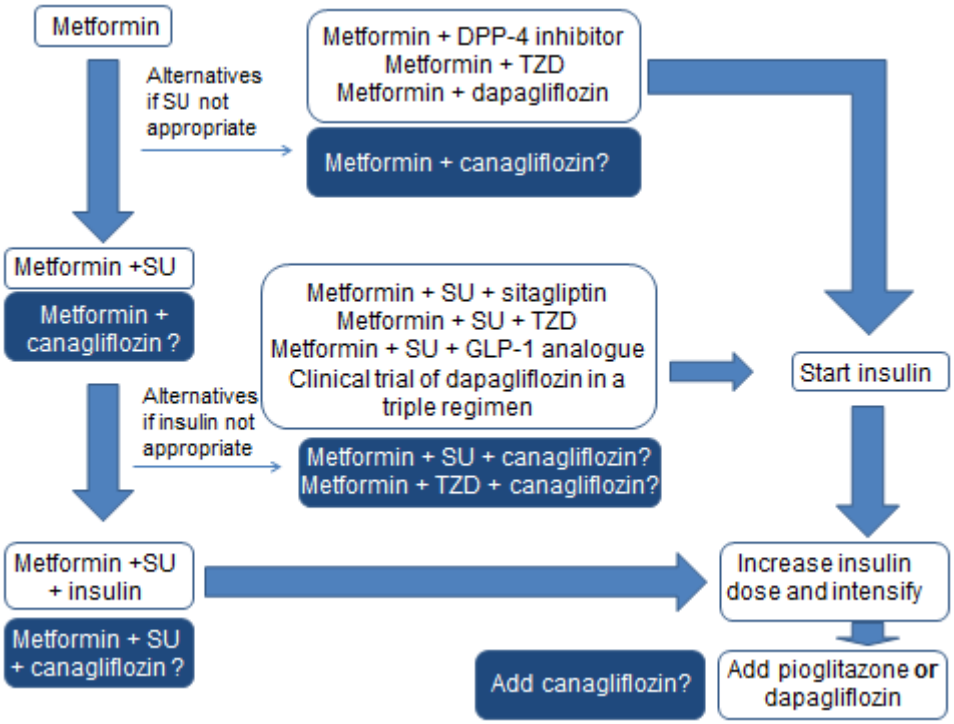
Economic evaluation	Cost effectiveness of treatments will be expressed in incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies. A time horizon of 40 years will be used in the manufacturer's base case. Costs will be considered from an NHS and Personal Social Services perspective.

3.2 The manufacturer's submission proposed the following places for canagliflozin in the diabetes treatment pathway:

- Dual therapy: adding canagliflozin to metformin, instead of adding a sulfonylurea or other agent where type 2 diabetes is not adequately controlled by metformin alone. Within its European marketing authorisation, canagliflozin may be used as part of a dual therapy in combination with metformin or a sulfonylurea but only the combination with metformin is covered in the manufacturer's submission.
- Triple therapy: adding canagliflozin to a combination of metformin and another antihyperglycaemic agent where type 2 diabetes is not adequately controlled by dual therapy. Within its European marketing authorisation, canagliflozin may be used as part of a triple therapy either in combination with metformin and a sulfonylurea or in combination with metformin and a thiazolidinedione. Both of these triple combinations are covered in the manufacturer's submission.
- Add-on therapy to insulin: adding canagliflozin to insulin. Within its European marketing authorisation, canagliflozin may be used as add-on therapy with other glucose-lowering medicinal products including insulin. The combination of canagliflozin and insulin with or without metformin is covered in the manufacturer's submission.

Figure 2 shows the manufacturer's approach to the decision problem in relation to existing NICE guidance.

Figure 2 Manufacturer's approach to the decision problem in a simplified treatment pathway showing NICE recommendations on pharmacological treatments for type 2 diabetes (clinical guideline 87 and technology appraisal guidance 203, 248 and 288)



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SU, sulfonylurea; TZD, thiazolidinedione

4 Clinical-effectiveness evidence

4.1 The manufacturer's literature search identified 85 citations for use in the systematic literature review. The manufacturer identified 11 phase III clinical trials that evaluated canagliflozin in combination therapy for treating type 2 diabetes. The manufacturer indicated that 5 of these trials would not provide useful information for approaching the decision problem (see pages 56–58 of the manufacturer's submission for details). No non-randomised clinical trials were included in the manufacturer's submission.

4.2 The manufacturer described 6 phase III randomised controlled trials in detail in its submission (table 1). Of these, 2 evaluated canagliflozin as part of dual therapy in combination with metformin (DIA3006 and DIA3009), 3 as part of triple therapy in combination with metformin and either a sulfonylurea or pioglitazone (DIA3012,

DIA3002, DIA3015) and 1 with insulin with or without other antidiabetic treatments (DIA3008 insulin sub-study). The trials enrolled 12–28% patients in Europe, of whom 27 patients were in the UK.

Table 1 Overview of clinical trials in the manufacturer's submission

Trial no.	Intervention	Comparator	Total treatment duration	Treatment groups
Dual therapy: patients on baseline metformin				
DIA3009	Canagliflozin + metformin	Glimepiride + metformin	104 weeks (52-week core double blind & 52-week extension double blind)	Canagliflozin 100 mg (n=483) Canagliflozin 300 mg (n=485) Glimepiride (n=484)
DIA3006	Canagliflozin + metformin	Sitagliptin + metformin	52 weeks (26-week core double blind & 26-week extension double blind)	Canagliflozin 100 mg (n=368) Canagliflozin 300 mg (n=367) Sitagliptin 100 mg (n=366) Placebo/sitagliptin (n=183)
Triple therapy: patients on baseline metformin plus SU				
DIA3015	Canagliflozin + metformin and SU	Sitagliptin + metformin and SU	52 weeks	Canagliflozin 300 mg (n=378) Sitagliptin 100 mg (n=378)
DIA3002	Canagliflozin + metformin and SU	Placebo + metformin and SU	52 weeks (26-week core double blind & 26-week extension double blind)	Canagliflozin 300 mg (n=156) Canagliflozin 100 mg (n=157) Placebo (n=156)
Triple therapy: patients on baseline metformin plus pioglitazone				
DIA3012	Canagliflozin + metformin and pioglitazone	Placebo + metformin and pioglitazone (crossover to sitagliptin + metformin and pioglitazone at 26 weeks)	52 weeks (26-week core double blind & 26-week extension double blind)	Canagliflozin 100 mg (n=115) Canagliflozin 300 mg (n=114) Placebo (n=115)
Add-on to insulin: patients on baseline insulin ± other anti-diabetics				
DIA3008 insulin sub-study	Canagliflozin + insulin with or without other anti-diabetics.	Placebo + insulin with or without other anti-diabetics.	18 weeks	Canagliflozin 100 mg (n=566) Canagliflozin 300 mg (n=587) Placebo (n=565)

SU, sulfonylurea
Source: Adapted from table 3 on page 25 and from table 6 in appendix 3 of the manufacturer's submission

4.3 Except for the DIA3008 insulin sub-study, all included trials had a broadly similar study design. After a 14-week pre-treatment period,

patients in DIA3009, DIA3006, DIA3015, DIA3002 and DIA3012 with uncontrolled type 2 diabetes (1 or 2 baseline therapies) were randomised to the addition of treatment with canagliflozin, active comparator, placebo or both. A double-blind treatment period of 26 or 52 weeks was followed by an extension period of the same duration (except in DIA3015, which did not have an extension period). DIA3008 insulin sub-study was part of the larger CANVAS study (an ongoing safety study in 4330 patients with high risk or history of cardiovascular disease that will report in 2017). The sub-study included a 2-week single-blind run-in period, 18-week double-blind treatment phase and 4-week follow-up. All studies except DIA3015 evaluated 2 doses of canagliflozin (100 mg and 300 mg; DIA3015 used the higher dose only). Further details about trial methodology are given in appendix 4 of the manufacturer's submission. The primary outcome for all studies was change in HbA_{1c} from baseline to the end of the double-blind treatment period. Secondary outcomes included change in body weight, change in systolic blood pressure, and incidence of hypoglycaemia. These secondary outcomes were incorporated into the manufacturer's economic model and results for the modified intention-to-treat populations are reported below. The modified intention-to-treat population was defined as randomised patients who received at least 1 dose of study drug using a last observation carried forward approach. Results for other secondary outcomes, including longer-term change in HbA_{1c} and change in blood lipids, and pre-planned and post-hoc analyses of achieving HbA1c targets, are reported in the manufacturer's submission (pages 82 and 86–89 for dual therapy regimens, pages 92–102 for triple-therapy regimens and pages 105–107 for add-on to insulin).

4.4 Eligible patients were adults with type 2 diabetes who had inadequate glycaemic control with existing treatment. In the studies included in the manufacturer's submission, inadequate glycaemic control was defined as an HbA_{1c} level of at least 7.0% up to 10.5%,

except for DIA3009 where the range was at least 7.0% up to 9.5%. All patients enrolled into CANVAS had a history of, or were at high risk of, cardiovascular disease; those enrolled in the DIA3008 insulin sub-study were on insulin alone or in combination with standard of care.

Manufacturer's results for dual therapy

4.5 A summary of efficacy results from DIA3009 and DIA3006 is given in table 2. In DIA3009, canagliflozin 100 mg plus metformin was non-inferior to glimepiride and metformin at week 52 in reducing HbA_{1c} (mean change in HbA_{1c} [minus glimepiride] −0.01%, 95% confidence interval [CI] −0.11 to 0.09). At week 52, canagliflozin 300 mg and metformin produced a statistically superior mean reduction in HbA_{1c} compared with glimepiride plus metformin, with a mean change (minus glimepiride) of −0.12% (95% CI −0.217 to −0.023, p<0.001). In DIA3006, mean change in HbA_{1c} (minus placebo) was −0.627% (95% CI −0.758 to −0.481) for canagliflozin 100 mg plus metformin and −0.77% for canagliflozin 300 mg plus metformin (95% CI −0.914 to −0.636), compared with −0.66% (95% CI −0.795 to −0.516) for sitagliptin plus metformin (p<0.001 versus placebo for canagliflozin arms).

4.6 In DIA3009, there was a greater improvement in systolic blood pressure at 52 weeks with both doses of canagliflozin compared with glimepiride (mean difference in systolic blood pressure reduction [minus glimepiride] −3.5 mmHg [95% CI −4.9 to −2.1] with canagliflozin 100 mg and −4.8 mmHg [95% CI −6.2 to −3.40 with canagliflozin 300 mg). In DIA3006, canagliflozin 100 mg and 300 mg decreased systolic blood pressure from baseline to 26 weeks with a difference in mean systolic blood pressure (minus placebo) of −5.36 mmHg (95% CI −7.280 to −3.439) and −6.58 mmHg (95% CI −8.504 to −4.653) respectively compared with −3.54 mmHg (95% CI −5.273 to −1.413) in the sitagliptin arm (p<0.001 for both canagliflozin doses compared with placebo).

4.7 In DIA3009 at week 52, both doses of canagliflozin were associated with a statistically greater change in body weight compared with glimepiride. Weight loss was −4.2 kg (standard error [SE] 0.2) for canagliflozin 100 mg and −4.7 kg (SE 0.2) canagliflozin 300 mg compared with a slight increase in weight with glimepiride +1.0 kg (SE 0.2). In DIA3006 at week 26, a weight loss of −3.7 kg (SE 0.2) was observed with canagliflozin 100 mg and 4.2 kg (SE: 0.2) with canagliflozin 300 mg compared with −1.2 kg (SE 0.2) with sitagliptin. Both doses of canagliflozin demonstrated statistical superiority to sitagliptin up to week 52 with a difference in mean weight reduction (minus sitagliptin) of −2.1 kg for canagliflozin 100 mg and −2.5 kg for canagliflozin 300 mg respectively, $p<0.001$ for both doses.

Table 2 Overview of efficacy outcomes at primary time point with dual therapy

Trial no. (acronym)	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active comparator
Change in HbA_{1c}(%)				
DIA3009	**(n=483)**	**(n=485)**		**Glimepiride (n=482)**
Change from baseline LS mean (SE)	−0.82 (0.039)	−0.93 (0.039)		−0.81 (0.039)
Diff. of LS means (SE) (minus glimepiride at week 52) (95% CI)	−0.01 (0.050) (−0.109 to 0.085)	−0.12 (0.050) (−0.217 to −0.023)		
DIA3006	**(n=368)**	**(n=367)**	**(n=181)**	**Sitagliptin (n=366)**
Change from baseline LS mean (SE)	−0.79 (0.044)	−0.94 (0.044)	−0.17 (0.060)	−0.82 (0.044)
Diff. of LS means (SE) (minus placebo at week 26)	−0.62 (0.071)	−0.77 (0.071)		−0.66 (0.071)
p-value	<0.001	<0.001		N/A
95% CI	(−0.758 to −0.481)	(−0.914 to −0.636)		(−0.795 to −0.516)
Change in systolic blood pressure (mmHg)				
DIA3009	**(n=483)**	**(n=485)**		**Glimepiride (n=482)**
Change from baseline LS mean (SE)	−3.27 (0.6)	−4.56 (0.6)		0.20 (0.6)
Diff. of LS means (SE) (minus glimepiride at week 52) 95% CI	−3.48 (0.7) (−4.9 to −2.1)	−4.76 (0.7) (−6.2 to −3.4)		
DIA3006	**(n=368)**	**(n=367)**	**(n=183)**	**Sitagliptin (n=366)**
Change from baseline LS mean (SE)	−3.84 (0.602)	−5.06 (0.605)	1.52 (0.829)	−1.83 (0.611)
Diff. of LS means (SE) (minus placebo at week 26)	−5.36 (0.979)	−6.58 (0.981)		−3.34 (0.984)
p-value	<0.001	<0.001		N/A
95% CI	(−7.280 to −3.439)	(−8.504 to −4.653)		(−5.273 to −1.413)
Change in body weight (kg)				
DIA3009	**(n=483)**	**(n=485)**		**Glimepiride (n=482)**
Change from baseline LS mean (SE)	−4.2 (0.2)	−4.7 (0.2)		1.0 (0.2)
Diff. of LS means (SE) (minus glimepiride)	−5.2 (0.3)	−5.7 (0.3)		
p-value	<0.001	<0.001		
95% CI	(−5.7 to −4.7)	(−6.2 to −5.1)		
DIA3006	**(n=368)**	**(n=367)**	**(n=181)**	**Sitagliptin (n=355)**
Change from baseline LS mean (SE)	−3.7 (0.2)	−4.2 (0.2)	−1.2 (0.3)	−1.2 (0.2)
Diff. of LS means (SE) (minus placebo)	−2.5 (0.3)	−2.9 (0.3)		−0.0 (0.3)
p-value	<0.001	<0.001		
95% CI	(−3.1 to −1.9)	(−3.5 to −2.3)		(−0.6 to 0.6)

Key: CI, confidence interval; diff., difference; LS, least squares; SE, standard error
Source: adapted from table 17 on page 80 (HbA_{1c}), table 18 in appendix 6 (systolic blood pressure) and table 16 in appendix 6 of the manufacturer's submission

Manufacturer's results for triple therapy

4.8 Results for change in HbA_{1c} in DIA3015, DIA3002 and DIA3012 are given in table 3. In DIA3015 at week 52, canagliflozin 300 mg produced a superior reduction in HbA_{1c} compared with sitagliptin 100 mg, with a difference in mean change in HbA_{1c} for canagliflozin 300 mg (minus sitagliptin) of −0.37% (95% CI −0.25 to −0.50). DIA3002 and DIA3012 showed a statistically significant reduction in HbA_{1c} at the primary endpoint (at 26 weeks for both studies) for both doses of canagliflozin compared with placebo. Mean reduction in HbA_{1c} at week 26 with canagliflozin 100 mg (minus placebo) was −0.71% (95% CI −0.904 to −0.524, p<0.001) in DIA3002 and −0.62% (95% CI −0.811 to −0.437, p<0.001) in DIA3012. Mean reduction with canagliflozin 300 mg was −0.92% (95% CI −1.114 to −0.732, p<0.001) in DIA3012 and −0.76% (95% CI −0.951 to −0.575, p<0.001), in DIA3002.

Table 3 Change in HbA_{1c} (%) at the primary time point with triple therapy

Trial no. (acronym)	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active comparator
Triple therapy: treatment on a background of metformin and sulfonylurea				
DIA3015		**(n=377)**		**Sitagliptin (n=378)**
Change from baseline − LS mean (SE)		−1.03 (0.048)		−0.66 (0.049)
Diff. of LS means (SE) (minus sitagliptin) 95% CI		−0.37 (0.064) (−5.0 to −2.5)		
DIA3002	**(n=157)**	**(n=156)**	**(n=156)**	
Change from baseline - LS mean (SE)	−0.85 (0.075)	−1.06 (0.076)	−0.13 (0.075)	
Diff. of LS means (SE) (minus placebo) 95% CI, p-value	−0.71 (0.097) (−0.904 to −0.524), <0.001	−0.92 (0.097) (−1.114 to −0.732), <0.001		
Triple therapy: treatment on a background of metformin and thiazolidinedione				
DIA3012	**(n=113)**	**(n=114)**	**(n=115)**	
Change from baseline - LS mean (SE)	−0.89 (0.069)	−1.03 (0.070)	−0.26 (0.069)	
Diff. of LS means (SE) (minus placebo) 95% CI, p-value	−0.62 (0.095) (−0.811 to −0.437), <0.001	−0.76 (0.096) (−0.951 to −0.575), <0.001		

Key: CI, confidence interval; diff., difference; LS, least squares; SE, standard error
Source: adapted from table 18 on page 92 of the manufacturer's submission

4.9 Both doses of canagliflozin, when used as triple therapy, resulted in a statistically significant greater reduction in systolic blood pressure compared with sitagliptin or placebo in DIA3015 and DIA3012 but not DIA3002 (table 4). In DIA3015, canagliflozin 300 mg statistically significantly decreased systolic blood pressure compared with sitagliptin 100 mg (0.9 mmHg), with the difference in mean change (minus sitagliptin) in systolic blood pressure at week 52 of −5.9 mmHg (95% CI −7.642 to −4.175, p<0.001). Similarly, a statistically significant difference was seen in DIA3012, with a mean difference in systolic blood pressure (minus placebo) of −4.07 (95% CI −6.879 to −1.251, p=0.005) with canagliflozin 100 mg and −3.46 (95% CI −6.281 to −0.643, p=0.016) with canagliflozin 300 mg. No statistically significant difference in mean systolic blood pressure (minus placebo) was seen in DIA3002 with canagliflozin 100 mg (−2.24 [95% CI −4.719 to 0.241, p=0.077]) or canagliflozin 300 mg (−1.62 [95% CI −4.111 to 0.866, p=0.201]).

Table 4 Change in systolic blood pressure (mmHg) at the primary time point with triple therapy

Trial no. (acronym)	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active comparator
Triple therapy: treatment on a background of metformin and sulfonylurea				
DIA3015		**(n=377)**		**Sitagliptin (n=378)**
Change from baseline				
LS mean (SE)		−5.06 (0.656)		0.85 (0.666)
Diff. of LS means (SE) (minus sitagliptin)		−5.91 (0.883)		
p-value		<0.001		
95% CI		(−7.642 to −4.175)		
DIA3002	**(n=157)**	**(n=156)**	**(n=156)**	
Change from baseline				
LS mean (SE)	−4.89 (0.976)	−4.27 (0.980)	−2.65 (0.982)	
Diff. of LS means (SE) (minus placebo)	−2.24 (1.262)	−1.62 (1.266)		
p-value	0.077	0.201		
95% CI	(−4.719 to 0.241)	(−4.111 to 0.866)		
Triple therapy: treatment on a background of metformin and thiazolidinedione				
DIA3012	**(n=113)**	**(n=114)**	**(n=115)**	
Change from baseline				
LS mean (SE)	−5.30 (1.036)	−4.70 (1.044)	−1.24 (1.033)	
Diff. of LS means (SE) (minus placebo)	−4.07 (1.430)	−3.46 (1.433)		
p-value	0.005	0.016		
95% CI	(−6.879 to −1.251)	(−6.281 to −0.643)		

Key: CI, confidence interval; diff., difference; LS, least squares; SE, standard error
Source: adapted from table 23 in appendix 6 of the manufacturer's submission

4.10 Both doses of canagliflozin, when used in triple therapy, lowered body weight (table 5). In DIA3015 at week 52, canagliflozin 300 mg treatment resulted in statistically significant reductions in body weight relative to sitagliptin 100 mg (−2.8 kg [95% CI −3.3 to −2], p<0.001). In DIA3002 at week 26, canagliflozin 100 mg and 300 mg (in combination with metformin and a sulfonylurea) resulted in a reduction in weight of −2.1 kg (SE 0.3) and −2.6 kg (SE 0.3) respectively compared with a weight change of −0.7 kg (SE 0.3) in the placebo group. Changes in body weight were also evident at week 52 with a difference in mean weight change (minus placebo) of −1.0 kg (95% CI −1.8 to −1.2) for canagliflozin 100 mg and

−2.1 kg (95% CI −2.9 to −1.2) for canagliflozin 300 mg. In DIA3012 at week 26, a change in weight of −2.7 kg (SE 0.3) and −3.8 kg (SE 0.3) was observed for canagliflozin 100 mg and 300 mg (in combination with metformin and a thiazolidinedione).

Table 5 Change in body weight (kg) at the primary time point with triple therapy

Trial no. (acronym)	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active comparator
Triple therapy: treatment on a background of metformin and sulfonylurea				
DIA3015		**(n=377)**		**Sitagliptin (n=378)**
Change from baseline LS mean (SE)		−2.5 (0.2)		0.3 (0.2)
Diff. of LS means (SE) (minus sitagliptin) p-value 95% CI		−2.8 (0.3) <0.001 (−3.3 to −2.2)		
DIA3002	**(n=157)**	**(n=156)**	**(n=156)**	
% Change from baseline LS mean (SE)	−2.1 (0.3)	−2.6 (0.3)	−0.7 (0.3)	
Diff. of LS means (SE) (minus placebo) p-value 95% CI	−1.4 (0.4) <0.001 (−2.1 to −0.7)	−2.0 (0.4) <0.001 (−2.7 to −1.3)		
Triple therapy: treatment on a background of metformin and thiazolidinedione				
DIA3012	**(n=113)**	**(n=114)**	**(n=115)**	
Change from baseline N LS mean (SE)	113 −2.8 (0.3)	112 −3.8 (0.3)	114 −0.1 (0.3)	
Diff. of LS means (SE) (minus placebo) p-value 95% CI	−2.7 (0.4) <0.001 (−3.6 to −1.8)	−3.7 (0.4) <0.001 (−4.6 to −2.8)		

Source: adapted from table 25 in appendix 6 of the manufacturer's submission

Manufacturer's results for add-on treatment to insulin

4.11 Results for key efficacy outcomes in the DIA3008 insulin sub-study are given in table 6. At week 18, the difference in mean change in HbA_{1c} versus placebo was −0.65% (95% CI −0.73 to −0.56) in the canagliflozin 100 mg group and −0.73% (95% CI −0.82 to −0.65) in canagliflozin 300 mg arm (p<0.001 both comparisons). Both doses of canagliflozin resulted in a significant reduction in systolic blood

pressure (p<0.001) compared with placebo. The difference in mean systolic blood pressure change (minus placebo) was −2.58 mmHg (95% CI −4.060 to 1.091) with canagliflozin 100 mg and −4.38 mmHg (95% CI −5.850 to −2.903) with canagliflozin 300 mg. Change in body weight (minus placebo) at week 18 was −1.8 kg (95% CI −2.2 to −1.6) in the canagliflozin 100 mg group and −2.3 kg (95% CI −2.7 to −2.1) in the canagliflozin 300 mg group (p<0.001 for both comparisons).

Table 6 Overview of efficacy outcomes at the primary time point with insulin add-on therapy

Trial no. (acronym)	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo
DIA3008 insulin sub-study	**(n=566)**	**(n=587)**	**(n=565)**
Change in HbA_{1c} (%)			
Change from baseline LS mean (SE)	−0.63 (0.031)	−0.72 (0.030)	0.01 (0.032)
Diff. of LS means (SE) (minus placebo at week 18) p-value 95% CI	−0.65 (0.044) <0.001 (−0.731 to −0.559)	−0.73 (0.043) <0.001 (−0.815 to −0.645)	
Change in systolic blood pressure (mmHg)			
Change from baseline LS mean (SE)	−5.07 (0.538)	−6.87 (0.528)	−2.50 (0.542)
Diff. of LS means (SE) (minus placebo at week 18) p-value 95% CI	−2.58 (0.757) <0.001 (−4.060 to 1.091)	−4.38 (0.751) <0.001 (−5.850 to −2.903)	
Change in body weight (kg)			
Change from baseline LS Mean (SE)	−1.8 (0.1)	−2.3 (0.1)	0.1 (0.1)
Diff. of LS Means (SE) (minus placebo at week 18) p-value 95% CI	−1.9 (0.2) <0.001 (−2.2 to −1.6)	−2.4 (0.2) <0.001 (−2.7 to −2.1)	

Key: CI, confidence interval; diff., difference; LS, least square; SE, standard error
Source: adapted from table 19 on page 103 (HbA_{1c}), table 31 in appendix 6 of the manufacturer's submission (systolic blood pressure) and table 32 in appendix 6 (body weight)

Manufacturer's subgroup analyses

4.12 As requested in the decision problem, results for the subgroup analyses by baseline body mass index and baseline HbA_{1c} thresholds were presented in the manufacturer's submission. There was no difference in change in mean HbA_{1c} over time according to baseline BMI. Larger absolute reductions in HbA_{1c} were observed

in patients with baseline HbA_{1c} of 9% or higher compared with patients with a baseline HbA_{1c} of less than 8%. The manufacturer noted that these results were expected and are comparable to those reported for other antihyperglycaemic agents (see tables 35–37 in appendix 5 of the manufacturer's submission and the manufacturer's clarification response for details).

Manufacturer's meta-analysis

4.13 The manufacturer conducted a systematic literature review to identify randomised controlled trials that evaluated treatments relevant to the NICE scope for this appraisal in patients with type 2 diabetes (see pages 111–112 of the manufacturer's submission for details). A total of 38 studies were included in the manufacturer's base-case network meta-analysis (see table 7 for a summary of these studies)[a].

Table 7 Summary of studies included in the manufacturer's base-case network meta-analysis

Background treatment (n)	Treatment duration	Trial design	Comparators	Primary outcome
Metformin (n=38)	Maximum duration ~2 years (28 trials had results at 26±4 weeks and 17 trials at 52±4 weeks)	Double blinded (n=28); open-label (n=4)	DPP-4 (n=22). GLP-1 analogues and sulfonylureas were the next most frequently assessed, followed by pioglitazone and SGLT-2 inhibitors	Change in HbA_{1c} from baseline (all but 4 trials)
Metformin plus sulfonylurea (n=10)	Maximum study duration ~1 year (with results reported at 6 months)	Double blinded (n=7); open-label (n=3)	Insulin (n=5), GLP-1 analogues (n=4), DPP-4 inhibitors (n=3) and SGLT-2 inhibitors (n=2)	Change in HbA_{1c} from baseline (all 10 trials)
Metformin plus pioglitazone (n=2)	26 weeks (n=1); ~1 year (n=1; also had results at 6 months).	Double blinded (n=2)	SGLT-2 inhibitor (n=1) and DPP-4 inhibitor (n=1)	Change in HbA_{1c} from baseline (both trials)
Insulin (n=14)	~1 year (n=3; also had results at 6 months)	All trials bar 1 were double-blinded	Metformin plus pioglitazone was the most common add-on treatment, followed by DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 analogues	Change in HbA_{1c} from baseline (at least 9 trials)

Key: dipeptidyl peptidase-4, DPP-4; GLP-1, glucagon-like peptide 1; n, number of trials; SGLT-2, sodium glucose-cotransporter 2
Source: page113–114 of the manufacturer's submission

[a]Post-meeting clarification: the manufacturer's base-case network meta-analyses included 38 studies with a background of metformin, 10 studies with a background of metformin and a sulfonylurea, 2 studies with a background of metformin and pioglitazone and 14 studies with a background of insulin.

4.14 The manufacturer used a Bayesian hierarchical model for the network meta-analysis. After assessing relative goodness of fit of fixed effects and random effects models using the Deviance Information Criterion, the model associated with the lowest score was selected (with a difference of at least 3 points). All analyses were conducted by background therapy. The manufacturer conducted sensitivity analyses to determine the robustness of results (see appendix 7 of the manufacturer's submission).

4.15 The manufacturer's main submission reported outcomes that were relevant to its economic model (change in HbA_{1c}, weight/body mass index, systolic blood pressure and incidence of hypoglycaemia) for the comparators included in the model. Only results that are directly relevant to the manufacturer's economic model are reported in the tables below. Results are presented in ranked order, with the treatment with the greatest probability of ranking first listed at the top of each table. Full results, including SUCRA (Surface Under the Cumulative Ranking) scores and results for drugs that were excluded from the cost-effectiveness modelling, are described on pages 266–290 of the appendices to the manufacturer's submission.

Dual therapy with a metformin background

4.16 Table 8 shows the differences in HbA_{1c} change at 52 weeks for canagliflozin 100 mg and 300 mg compared with the different comparators as dual therapy with a metformin background. Canagliflozin 300 mg was associated with a greater reduction in HbA_{1c} than all comparators except liraglutide 1.2 mg, and was more effective than canagliflozin 100 mg for all comparators.

Table 8 Manufacturer's meta-analysis results for mean difference in HbA_{1c} (%) at 52 weeks for canagliflozin versus active comparators with metformin background (random effects model)

	Canagliflozin 100 mg Median [credible interval]	Canagliflozin 300 mg Median [credible interval]
Liraglutide 1.2 mg	0.40 [−0.33 to 1.11]	0.27 [−0.46 to 0.98]
Canagliflozin 300 mg	0.13 [−0.25 to 0.52]	–
Pioglitazone 30 mg	0.11 [−0.44 to 0.84]	−0.02 [−0.57 to 0.72]
Exenatide 10 µg	0.02 [−0.65 to 0.55]	−0.11 [−0.78 to 0.42]
Glimepiride	0.00 [−0.45 to 0.46]	−0.13 [−0.58 to 0.33]
Canagliflozin 100 mg	–	−0.13 [−0.52 to 0.25]
Sitagliptin 100 mg	−0.01 [−0.48 to 0.44]	−0.14 [−0.61 to 0.31]
Dapagliflozin 10 mg	−0.14 [−0.81 to 0.47]	−0.27 [−0.94 to 0.34]

Source: adapted from table 134, appendix 7 of the manufacturer's submission

4.17 As shown in table 9, canagliflozin 100 mg and 300 mg were associated with higher weight reductions at 52 weeks compared with a DPP-4 inhibitor (sitagliptin 100 mg; differences of −2.12 kg and −2.48 kg), a sulfonylurea (glimepiride; differences of −3.97 kg and −4.33 kg) and pioglitazone 30 mg (differences of −4.57 kg and −4.93 kg). The reduction in weight was at least similar for canagliflozin 100 mg and 300 mg compared with dapagliflozin 10 mg (differences of −0.11 kg and −0.48 kg). When comparing canagliflozin with the GLP-1 analogues, canagliflozin 100 mg and 300 mg gave a lesser weight reduction than exenatide 10 µg (differences of 1.47 kg and 1.11 kg) but a greater weight reduction than liraglutide 1.2 mg (−0.49 and −0.85 kg).

Table 9 Manufacturer's meta-analysis results for mean difference in weight (kg) at 52 weeks for canagliflozin versus active comparators with metformin background (fixed effects model)

	Canagliflozin 100 mg Median [credible interval]	Canagliflozin 300 mg Median [credible interval]
Exenatide 10 µg	1.47 [−1.48 to 4.41]	1.11 [−1.84 to 4.05]
Canagliflozin 300 mg	0.37 [−0.17 to 0.91]	–
Canagliflozin 100 mg	–	−0.37 [−0.91 to 0.17]
Dapagliflozin 10 mg	−0.11 [−1.10 to 0.89]	−0.48 [−1.47 to 0.53]
Liraglutide 1.2 mg	−0.49 [−1.37 to 0.38]	−0.85 [−1.73 to 0.02]
Sitagliptin 100 mg	−2.12 [−2.66 to −1.57]	−2.48 [−3.03 to −1.93]
Glimepiride	−3.97 [−5.54 to −2.48]	−4.33 [−5.89 to −2.85]
Pioglitazone 30 mg	−4.57 [−6.28 to −2.93]	−4.93 [−6.64 to −3.29]

Source: adapted from table 139 in appendix 7 of the manufacturer's submission

4.18 The manufacturer reported that canagliflozin 100 mg and 300 mg were associated with higher reductions in systolic blood pressure compared with glimepiride (difference of −3.52 mmHg and −4.73 mmHg), liraglutide 1.2 mg (difference of −3.50 mmHg and −4.71 mmHg) and sitagliptin 100 mg (difference of −2.84 mmHg and −4.04 mmHg), and smaller reductions in systolic blood pressure than pioglitazone 30 mg (difference of 2.05 mmHg and 0.83 mmHg) (table 10).

Table 10 Manufacturer's meta-analysis results for mean difference in systolic blood pressure (mmHg) at 52 weeks for canagliflozin versus active comparators with metformin background (fixed effects model)

	Canagliflozin 100 mg Median [credible interval]	Canagliflozin 300 mg Median [credible interval]
Canagliflozin 300 mg	1.22 [0.05 to 2.36]	–
Pioglitazone 30 mg	2.05 [−3.22 to 7.37]	0.83 [−4.44 to 6.15]
Canagliflozin 100 mg	–	−1.22 [−2.36 to −0.05]
Sitagliptin 100 mg	−2.84 [−4.44 to −1.22]	−4.04 [−5.64 to −2.44]
Liraglutide 1.2 mg	−3.50 [−6.55 to −0.43]	−4.71 [−7.73 to −1.66]
Glimepiride	−3.52 [−5.02 to −2.05]	−4.73 [−6.22 to −3.26]

Source: adapted from table 142 in appendix 7 of the manufacturer's submission

4.19 As shown in table 11, canagliflozin 100 mg and 300 mg were associated with a lower risk of hypoglycaemia compared with a sulfonylurea and higher risk of hypoglycaemia compared with

dapagliflozin 10 mg and a DPP-4 inhibitor. The manufacturer advised that the difference in risk of hypoglycaemia compared with dapagliflozin in this network meta-analysis was likely to be because of differences in how hypoglycaemic events were reported in the clinical trials but did not provide any further explanation for this.

Table 11 Manufacturer's meta-analysis results for odds ratio in all hypoglycaemic events at 52 weeks for canagliflozin versus active comparators with metformin background (fixed effects model)

	Canagliflozin 100 mg Median [credible interval]	Canagliflozin 300 mg Median [credible interval]
Dapagliflozin 10 mg	3.65 [1.44 to 9.93]	3.43 [1.34 to 9.23]
Sitagliptin 100 mg	1.77 [0.97 to 3.44]	1.66 [0.90 to 3.23]
Canagliflozin 300 mg	1.07 [0.71 to 1.61]	–
Canagliflozin 100 mg	–	0.94 [0.62 to 1.40]
Glimepiride	0.11 [0.07 to 0.16]	0.10 [0.07 to 0.15]

Source: adapted from table 144 on page 278 of the appendices to the manufacturer's submission

Triple therapy with a metformin plus sulfonylurea background

4.20 Comparisons for canagliflozin and comparators with a metformin and sulfonylurea background as shown in table 12. Compared with a DPP-4 inhibitor (sitagliptin 100 mg), canagliflozin 100 mg produced a similar reduction in HbA_{1c} (0.07%), while canagliflozin 300 mg was associated with a slightly greater HbA_{1c} reduction (−0.17%). Canagliflozin 100 mg gave a similar HbA_{1c} reduction (difference of 0.03%) compared with a GLP-1 analogue (exenatide 10 µg), and canagliflozin 300 mg with a higher HbA_{1c} reduction (difference of −0.21%). Canagliflozin 100 mg and 300 mg were associated with greater weight reduction than a DPP-4 inhibitor (difference of −2.03 kg and −2.64 kg respectively) and similar weight reduction to a GLP-1 analogue (difference of –0.14 kg and 0.47 kg respectively). Canagliflozin 100 mg and 300 mg were associated with a higher reduction in systolic blood pressure than sitagliptin 100 mg (difference of −5.76 mmHg and −5.16 mmHg respectively). Canagliflozin 100 mg and 300 mg were associated

with a similar risk of hypoglycaemia as sitagliptin 100 mg and exenatide 10 µg.

Table 12 Manufacturer's meta-analysis results at 26 weeks for canagliflozin versus active comparators with metformin plus sulfonylurea background (random effects model)

	Canagliflozin 100 mg	**Canagliflozin 300 mg**
Mean difference in HbA_{1c} (%)		
	Median [credible interval]	Median [credible interval]
Long-acting insulin	0.35 [−1.43 to 2.16]	0.11 [−1.52 to 1.77]
Canagliflozin 300 mg	0.24 [−1.09 to 1.58]	–
Sitagliptin 100 mg	0.07 [−1.48 to 1.64]	−0.17 [−1.30 to 0.97]
Exenatide 10 µg	0.03 [−1.78 to 1.79]	−0.21 [−1.87 to 1.42]
Canagliflozin 100 mg	–	−0.24 [−1.58 to 1.09]
Mean difference in weight (kg)		
Canagliflozin 300 mg	0.62 [−4.34 to 5.57]	–
Exenatide 10 µg	0.47 [−6.09 to 7.24]	−0.14 [−6.15 to 6.08]
Canagliflozin 100 mg	–	−0.62 [−5.57 to 4.34]
Sitagliptin 100 mg	−2.03 [−7.78 to 3.76]	−2.64 [−6.83 to 1.56]
Long-acting insulin	−3.97 [−10.62 to 2.70]	−4.59 [−10.70 to 1.57]
Mean difference in systolic blood pressure (mmHg)		
Canagliflozin 100 mg	–	0.61 [−2.07 to 3.34]
Canagliflozin 300 mg	−0.61 [−3.34 to 2.07]	–
Long-acting insulin	−4.17 [−9.06 to 0.69]	−3.56 [−8.43 to 1.25]
Sitagliptin 100 mg	−5.76 [−9.02 to −2.53]	−5.16 [−6.94 to −3.38]
Odds ratio of all hypoglycaemic events		
Canagliflozin 100 mg	–	1.29 [0.80 to 2.08]
Exenatide 10 µg	0.96 [0.46 to 2.00]	1.23 [0.62 to 2.48]
Canagliflozin 300 mg	0.78 [0.48 to 1.25]	–
Sitagliptin 100mg	0.75 [0.43 to 1.29]	0.96 [0.72 to 1.29]
Long-acting insulin	0.32 [0.12 to 0.82]	0.41 [0.16 to 1.04]

Source: adapted from tables 146, 152, 156 and 158 on pages 279 and 281–283 of the manufacturer' submission in appendix 7 of the manufacturer's submission

Triple therapy with a metformin plus thiazolidinedione background

4.21 Comparisons for canagliflozin and comparators with a metformin and thiazolidinedione background as shown in table 13. Compared with sitagliptin 100 mg, canagliflozin 100 mg was associated with a smaller reduction in HbA_{1c} at 26 weeks (difference of 0.07%) and

canagliflozin 300 mg a greater reduction (difference of −0.07%). Canagliflozin 100 mg and 300 mg were associated with weight reductions compared with sitagliptin 100 mg (differences of −2.70 kg and −3.65 kg respectively). No statistical analysis was conducted for changes in systolic blood pressure because of limitations in the evidence base. Canagliflozin 100 mg was associated with a similar risk of hypoglycaemic events as sitagliptin 100 mg, whereas canagliflozin 300 mg was associated with a higher risk.

Table 13 Manufacturer's meta-analysis results for at 26 weeks for canagliflozin versus active comparators with metformin plus pioglitazone background (fixed effects model)

	Canagliflozin 100 mg Median [credible interval]	**Canagliflozin 300 mg** Median [credible interval]
Mean difference in HbA_{1c} (%)		
Canagliflozin 300 mg	0.14 [−0.05 to 0.33]	–
Sitagliptin 100 mg	0.07 [−0.19 to 0.33]	−0.07 [−0.33 to 0.19]
Canagliflozin 100 mg	–	−0.14 [−0.33 to 0.05]
Mean difference in weight (kg)		
Canagliflozin 300 mg	0.95 [0.18 to 1.72]	–
Canagliflozin 100 mg	–	−0.95 [−1.72 to −0.18]
Sitagliptin 100 mg	−2.70 [−10.10 to 4.62]	−3.65 [−11.07 to 3.67]
Odds ratio of all hypoglycaemic events		
Canagliflozin 100 mg	–	2.15 [0.54 to 11.25]
Sitagliptin 100 mg	0.86 [0.10 to 7.09]	1.89 [0.30 to 13.72]
Canagliflozin 300 mg	0.46 [0.09 to 1.87]	1.00

Source: adapted from tables 160, 166 and 168 on pages 284, 285 and 268 in appendix 7 of the manufacturer' submission

Add-on to insulin ± antihyperglycaemic background

4.22 As described in table 14, the reduction in HbA_{1c} at 26 weeks with canagliflozin 100 mg and 300 mg was greater than with sitagliptin 100 mg (difference of −0.01% and −0.15% respectively) and dapagliflozin 10 mg (difference of −0.01% and −0.15%). The higher dose of canagliflozin gave greater HbA_{1c} reduction than exenatide 10 µg (difference of −0.05%) but the lower dose did not (difference of 0.09%). A similar pattern was observed for the comparison of

canagliflozin and pioglitazone 30 mg (difference of −0.10% for canagliflozin 300 mg and 0.04% for canagliflozin 100 mg). Pioglitazone 45 mg produced greater HbA_{1c} reduction than either canagliflozin 100 mg or 300 mg.

4.23 Canagliflozin 100 mg and 300 mg were associated with greater weight reduction than a DPP-4 inhibitor (difference of −2.10 kg and −2.67 kg respectively), pioglitazone 30 mg (difference of −3.28 kg and −3.85 kg respectively) and dapagliflozin 10 mg (difference of −0.41 kg and −0.98 kg respectively) but not exenatide 10 µg (0.64 kg and 0.07 kg). Canagliflozin 100 mg and 300 mg were associated with higher reductions in systolic blood pressure compared with dapagliflozin 10 mg (difference of −0.92 mmHg and −2.62 mmHg respectively). When comparing canagliflozin and exenatide 10 µg, canagliflozin 300 mg was associated with lower reduction in systolic blood pressure (difference of −1.33 mmHg) but canagliflozin 100 mg was not (0.38 mmHg). No analysis of body mass index results or all hypoglycaemic events was conducted because of lack of data at 26 weeks for the canagliflozin trial.

Table 14 Manufacturer's meta-analysis results for at 26 weeks for canagliflozin versus active comparators with insulin background (fixed effects model)

	Canagliflozin 100 mg Median [credible interval]	Canagliflozin 300 mg Median [credible interval]
Mean difference in HbA_{1c} (%)		
Canagliflozin 300 mg	0.14 [0.06 to 0.22]	–
Exenatide 10 µg	0.09 [−0.17 to 0.35]	−0.05 [−0.31 to 0.21]
Pioglitazone 30 mg	0.04 [−0.23 to 0.30]	−0.10 [−0.37 to 0.17]
Canagliflozin 100 mg	–	−0.14 [−0.22 to −0.06]
Sitagliptin 100 mg	−0.01 [−0.17 to 0.16]	−0.15 [−0.31 to 0.02]
Dapagliflozin 10 mg	−0.01 [−0.17 to 0.15]	−0.15 [−0.31 to 0.01]
Metformin	−0.02 [−0.38 to 0.33]	−0.16 [−0.52 to 0.19]
Mean difference in weight (kg)		
Canagliflozin 300 mg	0.57 [0.24 to 0.90]	–
Exenatide 10 µg	0.64 [−0.44 to 1.71]	0.07 [−1.01 to 1.14]
Metformin	0.34 [−2.69 to 3.39]	−0.23 [−3.26 to 2.83]
Canagliflozin 100 mg	–	−0.57 [−0.90 to −0.24]
Dapagliflozin 10 mg	−0.41 [−1.01 to 0.20]	−0.98 [−1.59 to −0.38]
Sitagliptin 100 mg	−2.10 [−2.67 to −1.53]	−2.67 [−3.24 to −2.11]
Pioglitazone 30 mg	−3.28 [−11.72 to 5.14]	−3.85 [−12.31 to 4.57]
Mean difference in systolic blood pressure (mmHg)		
Canagliflozin 300 mg	1.71 [0.31 to 3.12]	–
Exenatide 10 µg	0.38 [−3.46 to 4.23]	−1.33 [−5.19 to 2.52]
Canagliflozin 100 mg	–	−1.71 [−3.12 to −0.31]
Dapagliflozin 10 mg	−0.92 [−3.93 to 2.08]	−2.62 [−5.64 to 0.40]

Source: tables 170, 176 and 178 from the appendices to manufacturer's submission

Adverse events

4.24 The phase III clinical trial programme evaluated the safety of canagliflozin in 10,285 people with type 2 diabetes. The manufacturer provided data from 3 pre-specified pooled safety datasets, focusing on the broad dataset that included data for canagliflozin 100 mg (n=3092), canagliflozin 300 mg (n=3085) and all non-canagliflozin arms (placebo, glimepiride and sitagliptin [n=3262]).

4.25 In the broad dataset, the incidence of patients who experienced any adverse event was similar across groups (76.6% for canagliflozin 100 mg, 77.0% for canagliflozin 300 mg and 76.8% in the non-canagliflozin group). The incidence of adverse events leading to discontinuation in the broad dataset was higher in the canagliflozin 300 mg group (7.3%) than the canagliflozin 100 mg (5.6%) and non-canagliflozin (5.0%) groups. Adverse events that led to discontinuation of more than 0.2% of subjects in the canagliflozin 300 mg group were decreased glomerular filtration rate, renal impairment and increased blood creatinine. The incidence of AEs considered related to study drug by the investigator was slightly higher in the canagliflozin 100 mg and 300 mg groups (33.6% and 29.4%) than the non-canagliflozin group (21.8%). The incidence of serious AEs and deaths was similar in the canagliflozin and non-canagliflozin groups. Adverse events occurring in at least 5% of subjects in a canagliflozin group were naso-pharyngitis, hypoglycaemia, upper respiratory tract infection, urinary tract infection, diarrhoea, arthralgia, back pain, and headache (see tables 22 and 23 on pages 142–5 of the manufacturer's submission for further details).

4.26 The manufacturer noted that SGLT-2 inhibitors are associated with an elevated incidence of genital mycotic infections because of urinary glucose excretion. In the broad dataset, the incidence of genital mycotic infections adverse events in women was higher in those receiving canagliflozin 100 mg (14.7%) and canagliflozin 300 mg (13.9%) than in those taking placebo (3.1%). In men, the incidence was 7.3% in the canagliflozin 100 mg group and 9.3% in the canagliflozin 300 mg groups, compared with 1.6% of men in the non-canagliflozin group.

ERG's comments on the manufacturer's clinical-effectiveness evidence

4.27 The ERG considered that only the trials with active comparator arms were relevant to the NICE scope, which were DIA3009 and

DIA3006 (dual therapy) and DIA3015 (triple therapy trial) and judged all 3 to be of generally good methodological quality. The ERG considered the manufacturer's submission to provide a generally unbiased estimate of canagliflozin's treatment effect within the stated scope of the decision problem, and that the manufacturer's interpretation of the evidence was largely appropriate and justified.

4.28 However, the ERG identified some exceptions and uncertainties:

- A lack of direct evidence for comparisons with treatments other than sitagliptin and glimepiride.
- No discussion of the implications of differences in results between the modified intention-to-treat analyses (reported in the manufacturer's submission) and per protocol analyses (reported in the trial journal publications and clinical study reports). The ERG advised that the per protocol analyses for the 2 dual therapy trials showed that canagliflozin 300 mg was only non-inferior to sitagliptin and glimepiride, and not superior as it was in the modified intention-to-treat analyses analyses.
- Low volume of direct evidence for some of the loops in the networks meta-analyses, which led the ERG to conclude that the results should be interpreted with caution.
- Uncertainty in the manufacturer's justification for network meta-analysis for triple therapy assessing effects at 26 weeks, rather than the 52 weeks.
- The exclusion of background treatments that did not include metformin (because including this would better reflect all the potential uses of canagliflozin within its European marketing authorisation).
- Lack of evidence for the longer-term efficacy and safety of canagliflozin (because most outcomes were measured up to 52 weeks in the clinical trials).

- Uncertainty in the manufacturer's favourable interpretation of adverse events related to canagliflozin compared with other treatments, and the discontinuation rates compared with sitagliptin and glimepiride.

5 Comments from other consultees

5.1 A professional group highlighted that SGLT-2 inhibitors, including canagliflozin, have a different mechanism of action compared with other oral agents and insulin, and that this made canagliflozin a useful add-on treatment. It perceived the weight loss with canagliflozin to be valuable because type 2 diabetes and some of its treatments (insulin, thiazolidinedione and sulfonylureas) are associated with weight gain. A professional group and a clinical specialist further noted that canagliflozin's side effects focus on osmotic symptoms and risk of bladder and mycotic infection, which may severely impact on quality of life, but that ongoing clinical experience is required to assess adverse effects. A professional organisation also indicated that cardiovascular outcomes will need to be closely monitored in longer-term studies, and a clinical specialist noted the relevance of the ongoing CANVAS study.

5.2 The professional organisation described how the clinical trials have largely focused on people with type 2 diabetes who have levels of glycaemic control that are only slightly over target, and considered it highly likely that people with type 2 diabetes treated in routine clinical practice will have higher glycaemic indices. It stated that because the treatment is orally effective in a common condition, this is likely to lead to widespread use and considered that it would ultimately be used in primary care (although early clinical experience is likely to be through specialist recommendation). Other than prescribing costs, there should be no associated increase in budgetary requirement.

6 Cost-effectiveness evidence

6.1 The manufacturer's submission included de novo economic analyses of canagliflozin combination treatment for type 2 diabetes using the following regimens:

- Dual therapy in combination with metformin
- Triple therapy in combination with metformin and a sulfonylurea
- Triple therapy in combination with metformin and a thiazolidinedione
- Add-on treatment to insulin (with or without other antihyperglycaemic agents).

The manufacturer advised that these populations reflected the licensed indications for canagliflozin and patients in the phase III clinical trials, and it considered these patients to be representative of the population most likely to receive canagliflozin in clinical practice in England. The 100 mg and 300 mg doses of canagliflozin were considered separately in the base case (increasing the dose from 100 mg to 300 mg according to the summary of product characteristics [see section 2.2] was explored in a scenario analysis). Comparator treatments used at the different points in the treatment pathway were sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogues, dapagliflozin and insulin (see table 15 and section 6.4).

Table 15 Comparisons made with canagliflozin in the manufacturer's cost-effectiveness analyses

Comparator	Dual therapy with metformin	Triple therapy		Add-on to insulin
		Metformin and sulfonylurea	Metformin and thizolidinedione	
Sulfonylurea	Yes	*Not applicable*	–	–
Thiazolidinedione	Yes	–	*Not applicable*	–
DPP-4 inhibitor	Yes	Yes	Yes	Yes
GLP-1 analogue	Yes	Yes	–	Yes
Dapagliflozin	Yes	–	–	Yes
Insulin	–	Yes	–	*Not applicable*

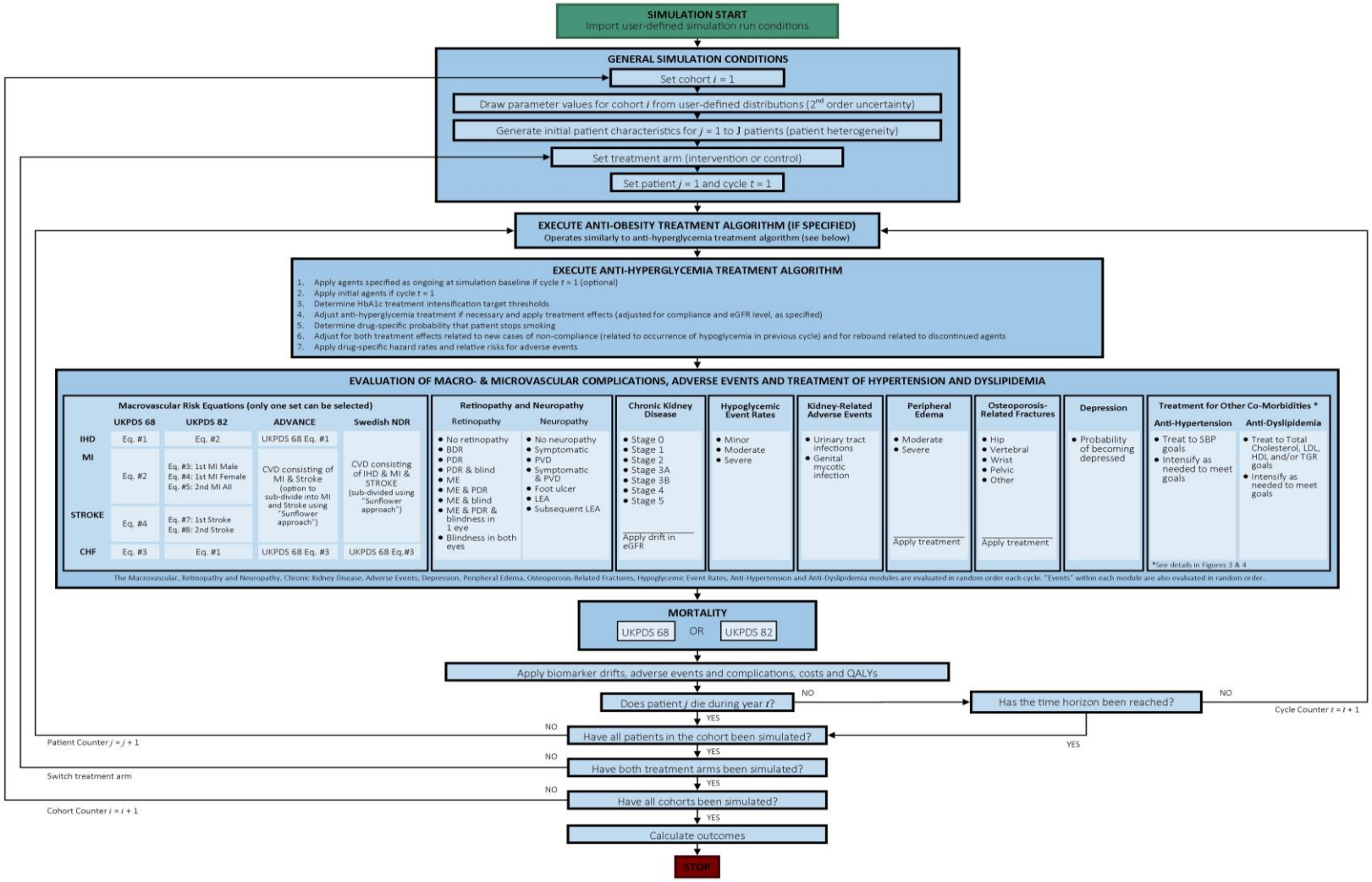
Source: adapted from table 32 on page 175 of the manufacturer's submission

6.2 The manufacturer's systematic literature review of relevant published cost-effectiveness analyses identified 52 studies and a similar a systematic literature review found 21 economic evaluation models of type 2 diabetes. The manufacturer chose the ECHO-T2DM model, which was a stochastic micro-simulation model in which cohorts of individual hypothetical patients were created and simulated over time using Monte Carlo (first order uncertainty) techniques (see figure 3 for summary of model structure). Second order (parameter) uncertainty was captured by hypothetical cohorts of 1000 patients defined by baseline characteristics sourced from the canagliflozin clinical trials including demographics (for example, age and gender), biomarker values (for example, HbA_{1c}, systolic blood pressure and body mass index) and disease indicators (for example, disease duration and history of complications). Individual patient outcomes were simulated over time through health states capturing micro- and macrovascular complications and death. There were 1000 patient cohorts for each model run for the base-case comparisons and patient cohorts were simulated until death or the end of the designated follow-up period. Results of key parameter values (including treatment effects, risk equation coefficients, and quality-adjusted life year [QALY] disutility weights) were then aggregated. The model used a lifetime time horizon (40 years), the cycle length was 1 year, health benefits and costs were each discounted at 3.5% and the analysis was from an NHS perspective.

6.3 The manufacturer's model included 3 parallel sets of microvascular complications (to reflect increasing severity of retinopathy, chronic kidney disease and neuropathy) and 4 types of macrovascular complications (ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure – because of interdependence with neuropathic outcomes, peripheral vascular disease was located in the microvascular neuropathy submodule). These were represented by Markov health states and were associated with

costs, utility values and, in some cases, a possible treatment contraindication (for example, end-stage renal disease for pioglitazone) or excess risk of death (for example, myocardial infarction or stroke). Annual probabilities of experiencing worsening microvascular complications were derived primarily from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the Rochester Epidemiology Project, and the Centers for Disease Control model of chronic kidney disease. Risk equations from the original UKPDS Outcomes Model were used to simulate macrovascular complications in the base case.

Figure 3 Structure of the manufacturer's economic model



6.4 The manufacturer selected a comparator to represent each treatment class in its economic model:

- Pioglitazone – because it is the only thiazolidinedione available for prescribing in clinical practice in England.
- Sitagliptin – because it is the DPP-4 inhibitor most used in the UK and was a comparator in 2 canagliflozin trials.
- Liraglutide – this was the GLP-1 analogue of choice where data allowed because it has wider use in UK clinical practice (but twice-daily exenatide was the only GLP-1 analogue in the network meta-analyses for triple therapy [with metformin and sulfonylurea] and add-on to insulin).
- Insulin aspart –because it is the most widely used short-acting insulin in UK clinical practice.
- For the sulfonylurea class, the manufacturer used glimepiride for efficacy (because it was used in the clinical trial programme) and gliclazide for cost (because it has the highest level of prescribing in the UK).

6.5 The manufacturer's model simulated the treatment pathway using a treatment algorithm defined by:

- treatment sequence (including rescue medication)
- decision rules for treatment intensification (for example, HbA_{1c} exceeding a threshold value or a contraindication developing)
- 2 types of treatment-specific profiles (insulin and non-insulin), which related to treatment effects, durability and biomarker evolution, discontinuation rules, adverse-event rates, non-compliance and contraindication.

6.6 The estimates of the biomarker effects for each drug (HbA_{1c} decrease and impact on systolic blood pressure, lipids and body weight) were derived from the meta-analyses and applied to the first cycle of the economic model. The manufacturer used 52-week data for dual therapy, and 26-week data for triple therapy and add-

on to insulin. After applying initial treatment effects, patients were individually evaluated for HbA_{1c} failure, reaching maximum treatment duration, and for contraindications or adverse events that would cause treatment discontinuation. The following treatment pathways were taken if HbA_{1c} exceeded 7.5%:

- In dual and triple therapy, except when long-acting insulin was the comparator, canagliflozin or the comparator was discontinued and patients switched to long-acting insulin (insulin glargine) and received post-prandial insulin if necessary.
- If insulin was the comparator in triple therapy, patients in the insulin arm additionally received prandial insulin. For the canagliflozin arm, patients switched from canagliflozin to long-acting insulin, then prandial insulin as needed.

6.7 Biomarker values after the first cycle were estimated using annual drift values (see page 185 of the manufacturer's submission). The manufacturer's model allowed patients to take anti-dyslipidaemia and anti-hypertension medications, and applied rescue treatments when patients exceeded biomarker thresholds for dyslipidaemia and hypertension (see page 188 of the manufacturer's submission).

6.8 The manufacturer's model incorporated adverse events associated with pharmacological treatment (including weight change, hypoglycaemic events, upper and lower urinary tract infections, genital mycotic infections and gastrointestinal upset, including nausea), which were defined by event rates, costs and QALY disutility weights. Because canagliflozin's mode of action is primarily through inhibition of SGLT-2 in the kidney, eGFR was taken into account in estimating efficacy and discontinuation (eGFR less than 60 mL/min/1.73m^2) and kidney-related adverse events were included.

6.9 The manufacturer explained that although its clinical trials included some patient-reported outcomes, these were exploratory endpoints

and the trials were too short to assess potential changes in health-related quality of life associated with disease complications in its economic model. Instead, the manufacturer mainly used published utility values that had been elicited from the non-interventional, observational CODE-2 study. Utility decrements were applied to the baseline quality of life value (1.027) for patient characteristics, microvascular and macrovascular complications, hypoglycaemic events, obesity and adverse events (see pages 198–199 of the manufacturer's submission for further details of utility values).

6.10 The manufacturer's systematic literature review identified 3 studies that provided costs used in the economic model. Drug acquisition costs were sourced from the British national formulary 65 (July 2013). Annual costs per patient were £477.26 for canagliflozin 100 mg, £608.63 for canagliglozin 300 mg, £30.44 for glimepiride, £19.60 for gliclazide, £36.13 for pioglitazone, £433.86 for sitagliptin, £955.49 for liraglutide, £830.82 for twice-daily exenatide and £477.30 for dapagliflozin. Because the cost of insulin changes with body weight, insulin costs were applied in the model as a cost per kg per day. The annual costs per IU were £4.26 for NPH insulin, £10.11 for insulin glargine and £6.89 for insulin aspart. No costs were assigned to background therapies (because they were assumed to be equal between comparisons) or to administration costs (because oral antihyperglycaemic drugs do not require supervised administration and GLP-1 analogues and insulin are self-injected). The manufacturer advised that renal monitoring had not been included as an additional cost for a canagliflozin-containing regimen because this generally forms part of routine monitoring of patients with diabetes. Health state costs were derived from NICE clinical guideline 87 for managing type 2 diabetes and the NICE clinical guideline 73 for managing chronic kidney disease, or retrieved from scientific literature and inflated to 2011/12 values (see appendix 11 of the manufacturer's

submission). Available NHS reference costs and PbR tariffs were used where appropriate.

6.11 The annual costs of treating complications and comorbidities, and the derivation of health state costs are detailed in appendix 11 of the manufacturer's submission. The manufacturer calculated costs associated with urinary tract infections and genital mycotic infections using clinical guidelines, the Hospital & Community Health Services index and the British national formulary, and validated these with clinical specialists. Only costs for treating severe hypoglycaemia were included in the manufacturer's economic model because it was assumed that treating minor and moderate hypoglycaemic events would not use NHS resources.

Manufacturer's cost-effectiveness results

6.12 The manufacturer presented pairwise comparisons, using cohorts of simulated patients from the probability distribution of patient characteristics for canagliflozin 100 mg and canagliflozin 300 mg in dual therapy, triple therapy and as an add-on to insulin (see tables 16–21 below). At the clarification stage, the manufacturer provided some updated cost-effectiveness results after identifying that, where body mass index was not available in the network meta-analysis, the change in actual body mass index had been used instead of being calculated using a weighted average of height in the UK general population. The updated ICERs were generally more favourable for canagliflozin than the ones they replaced.

Manufacturer's base case – dual therapy

6.13 As described in table 16, canagliflozin 100 mg as part of a dual-therapy regimen showed QALY gains and increased costs compared with a sulfonylurea (incremental cost-effectiveness ratio [ICER] of £1537 per QALY gained), a DPP-4 inhibitor (ICER of £97 per QALY gained) and dapagliflozin (£2993 per QALY gained). Compared with a GLP-1 analogue, canagliflozin 100 mg was less

effective and less costly (incremental costs −£2424; incremental QALYs −0.048). Canagliflozin 100 mg was dominated by pioglitazone (that is, canagliflozin was more costly and less effective).

Table 16 Manufacturer's base-case cost-effectiveness results for canagliflozin 100 mg in dual therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Thiazolidinedione	£23,236	13.667	9.119	–	–	–	–
Canagliflozin 100 mg	£26,069	13.669	8.960	£2833	0.001	-0.159	Dominated
Sulfonylurea	£25,894	13.664	8.751				
Canagliflozin 100 mg	£26,182	13.666	8.938	£288	0.003	0.188	£1537
Dapagliflozin	£26,086	13.673	8.923				
Canagliflozin 100 mg	£26,149	13.678	8.930	£63	0.005	0.007	£2993†
DPP-4 inhibitor	£26,100	13.688	8.928				
Canagliflozin 100 mg	£26,102	13.692	8.941	1	0.003	0.013	£97
GLP-1 analogue	£28,390	13.650	8.970				
Canagliflozin 100 mg	£25,966	13.644	8.921	-£2424	-0.006	-0.048	£71,769a†

[a]Canagliflozin 100 mg is less costly and less effective than a GLP-1 analogue so the ICER is for a GLP-1 analogue to replace canagliflozin 100 mg; †Corrected ICER provided at clarification

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: table 62 on page 234 of the manufacturer's submission

6.14 In a dual-therapy regimen, the manufacturer's results (table 17) showed that canagliflozin 300 mg produced higher costs and greater QALY gains than a sulfonylurea (ICER of £4899 per QALY gained), a DPP-4 inhibitor (ICER of £18,349 per QALY gained) and dapagliflozin (ICER of £21,626 per QALY gained). Similar to the 100 mg dose, canagliflozin 300 mg was less costly and less effective than a GLP-1 analogue (incremental costs −£1892; incremental QALYs −0.025). Like the 100 mg dose, canagliflozin 300 mg was also dominated by pioglitazone (that is, it was more costly and less effective).

Table 17 Manufacturer's base-case cost-effectiveness results for canagliflozin 300 mg in dual therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Thiazolidinedione	£23,204	13.665	9.092	–	–	–	–
Canagliflozin 300 mg	£26,556	13.663	8.951	£3,353	-0.003	-0.141	Dominated
Sulfonylurea	£25,753	13.671	8.761	–	–	–	–
Canagliflozin 300 mg	£26,729	13.690	8.961	£976	0.019	0.199	£4899
DPP-4 inhibitor	£25,926	13.644	8.902	–	–	–	–
Canagliflozin 300 mg	£26,501	13.655	8.933	£576	0.011	0.031	£18,349
Dapagliflozin	£26,044	13.670	8.910	–	–	–	–
Canagliflozin 300 mg	£26,668	13.679	8.932	£625	0.009	0.023	£21,626[†]
GLP-1 analogue	£28,515	13.652	8.972	–	–	–	–
Canagliflozin 300 mg	£26,624	13.657	8.947	-£1,892	0.005	-0.025	£107,181[a†]

[a]Canagliflozin 300mg is less costly and less effective so the ICER is for a GLP-1 analogue to replace canagliflozin 300 mg
[†]Corrected ICER provided at clarification

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: table 63 on page 234 of the manufacturer's submission

Manufacturer's base case – triple therapy

6.15 The manufacturer also presented cost-effectiveness results for triple-therapy regimens containing canagliflozin 100 mg (table 18) and canagliflozin 300 mg (table 19). In a triple-therapy combination with metformin and a sulfonylurea, canagliflozin 100 mg dominated a DPP-4 inhibitor (that is, it was less costly and more effective), and was less costly and less effective than a GLP analogue (ICER of £265,928 per QALY gained for a GLP-1 analogue to replace canagliflozin 100 mg). Canagliflozin 100 mg was associated with greater costs and QALY gains than long-acting insulin, with an ICER of £183 per QALY gained. In a triple-therapy combination with metformin and a thiazolidinedione, canagliflozin 100 mg had higher costs and QALY gains than a DPP-4 inhibitor, producing an ICER of £1095 per QALY gained.

Table 18 Manufacturer's base-case cost-effectiveness results for canagliflozin 100 mg in triple therapy

Comparator	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Background of metformin and a sulfonylurea							
DPP-4 inhibitor	£25,776	12.964	7.060	–	–	–	–
Canagliflozin 100 mg	£25,734	12.967	7.076	£−42	0.004	0.016	Dominates
Long-acting insulin	£25,577	12.972	5.193	–	–	–	–
Canagliflozin 100 mg	£25,712	12.982	5.707	£135	0.010	0.514	£183[†]
GLP-1 analogue	£27,119	12.978	7.101	–	–	–	–
Canagliflozin 100 mg	£25,822	12.980	7.102	−£1297	0.002	0.001	£265,928[a†]
Background of metformin and a thiazolidinedione							
DPP-4 inhibitor	£22,557	8.294	8.287	–	–	–	–
Canagliflozin 100 mg	£22,565	12.597	12.595	£7	0.002	0.007	£1095

[a]Canagliflozin 100 mg is less costly and less effective so the ICER is for a GLP-1 analogue to replace canagliflozin 100 mg
[†]Corrected ICER provided at clarification

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Source: tables 64 and 66 on page 235 of the manufacturer's submission

6.16 In combination with metformin and a sulfonylurea, canagliflozin 300 mg compared with a DPP-4 inhibitor had an ICER of £13,287 per QALY gained and dominated a GLP-1 analogue (that is, was less costly and more effective). In combination with metformin and a thiazolidinedione, the ICER for canagliflozin 300 mg compared with a DPP-4 inhibitor was £21,430 per QALY gained. Canagliflozin 300 mg compared with long-acting insulin gave an ICER of £607 per QALY gained.

Table 19 Manufacturer's base-case cost-effectiveness results for canagliflozin 300 mg in triple therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Background of metformin and a sulfonylurea							
DPP-4 inhibitor	£26,196	12.967	7.047	–	–	–	–
Canagliflozin 300 mg	£26,657	12.976	7.082	£461	0.009	0.035	£13,287
Long-acting insulin	£26,326	12.992	5.139	–	–	–	–
Canagliflozin 300 mg	£26,705	12.993	5.763	£379	0.002	0.624	£671[†]
GLP-1 analogue	£27,153	12.936	7.068	–	–	–	–
Canagliflozin 300 mg	£26,468	12.944	7.072	−£685	0.008	0.004	Dominates
Background of metformin and a thiazolidinedione							
DPP-4 inhibitor	£22,586	12.606	8.274	–	–	–	–
Canagliflozin 300 mg	£23,277	12.623	8.306	£691	0.017	0.032	£21,430

[†]Corrected ICER provided at clarification

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: tables 65 and 67 on page 235 of the manufacturer's submission

Manufacturer's base case – add-on to insulin

6.17 As shown in table 20, canagliflozin 100 mg as an add-on treatment to insulin dominated dapagliflozin (that is, it was less costly and more effective). When compared with a DPP-4 inhibitor and a GLP-1 analogue, canagliflozin 100 mg was associated with lower costs and lower QALY gains (£1340 saved per QALY lost and £12,915 saved per QALY lost, respectively).

Table 20 Manufacturer's base-case cost-effectiveness results for canagliflozin 100 mg as add-on to insulin

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4 inhibitor	£29,423	10.858	5.612	–	–	–	–
Canagliflozin 100 mg	£29,410	10.855	5.602	-£13	-0.003	-0.010	£1,340[a]
Dapagliflozin	£29,580	10.852	5.550	–	–	–	–
Canagliflozin 100 mg	£29,508	10.846	5.553	-£72	-0.007	0.003	Dominates
GLP-1 analogue	£30,229	10.834	5.653	–	–	–	–
Canagliflozin 100 mg	£29,393	10.836	5.588	-£836	0.002	-0.065	£12,915[a]

[a]Canagliflozin 100 mg is less costly and less effective so the ICER is for a GLP-1analogue to replace canagliflozin 100 mg

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: table 68 on page 236 of the manufacturer's submission

6.18 As shown in table 21, canagliflozin 300 mg as an add-on treatment to insulin produced greater costs and QALY gains than a DPP-4 inhibitor (ICER of £7975 per QALY gained) and dapagliflozin (ICER of £5992 per QALY gained). Compared with a GLP-1 analogue, canagliflozin 300 mg was associated with lower costs and lower QALY gains (£35,575 saved per QALY lost).

Table 21 Manufacturer's base-case cost-effectiveness results for canagliflozin 300 mg as add-on to insulin

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4 inhibitor	£29,328	10.829	5.585	–	–	–	–
Canagliflozin 300 mg	£29,650	10.838	5.625	£322	0.009	0.040	£7975
Dapagliflozin	£29,618	10.853	5.572	–	–	–	–
Canagliflozin 300 mg	£29,946	10.863	5.627	£327	0.009	0.055	£5992
GLP-1 analogue	£30,333	10.851	5.636	–	–		–
Canagliflozin 300 mg	£29,807	10.859	5.621	-£526	0.007	-0.015	£35,575[a]

[a] Canagliflozin 300 mg is less costly and less effective so the ICER is for a GLP-1 analogue to replace canagliflozin 300 mg

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: table 69 on page 236 of the manufacturer's submission

Manufacturer's sensitivity analyses

6.19 The manufacturer conducted deterministic and probabilistic sensitivity analyses for canagliflozin compared with a DPP-4 inhibitor (in dual therapy, triple therapy and as an add-on to insulin therapy) and with a sulfonylurea in dual therapy, because it perceived these to be the key comparators for canagliflozin. The manufacturer did not report results for other comparators used in its base case, including dapagliflozin.

6.20 The manufacturer's deterministic sensitivity analyses showed that metabolic drift of HbA_{1c} associated with canagliflozin and its comparators was a key driver of the model. The manufacturer commented that, except for HbA_{1c} drift, the ICERs for the comparisons of both doses of canagliflozin with a sulfonylurea in dual therapy were largely insensitive to parameter changes. However, the manufacturer noted the ICERs for canagliflozin

compared with a DPP-4 inhibitor were generally less stable. For full details, see pages 324–341 of appendix 13 of the manufacturer's submission.

6.21 The manufacturer presented results of probabilistic sensitivity analyses for canagliflozin compared with some of the comparators used in its base case (see table 22). It noted that that there was greater uncertainty where the incremental changes in costs and QALYs were small and commented that, at a maximum acceptable ICER of £20,000 per QALY gained, the probability of canagliflozin 100 mg being cost effective compared with a DPP-4 inhibitor was 45–56% for the different comparisons. The manufacturer stated that there was less uncertainty in the dual therapy comparisons of canagliflozin (100 mg and 300 mg) with sulfonylurea, with the probability of cost effectiveness being around 90% for both doses. For further details of the manufacturer's sensitivity analyses (including scatter plots and cost-effectiveness acceptability curves), see pages 245–254 of the manufacturer's submission.

Table 22 Manufacturer's probabilistic sensitivity analyses showing probability of canagliflozin being cost effective

Comparison	Probability of canagliflozin being cost-effective at a maximum acceptable ICER of £20,000/QALY	Probability of canagliflozin being cost effective at a maximum acceptable ICER of £30,000/QALY
Dual therapy with metformin background		
Canagliflozin 100 mg and sulfonylurea	92.9%	93.6%
Canagliflozin 300 mg and sulfonylurea	89.5%	92.1%
Canagliflozin 100 mg and DPP-4 inhibitor	54.5%	54.9%
Canagliflozin 300 mg and DPP-4 inhibitor	51.6%	54.9%
Triple therapy with metformin and sulfonylurea background		
Canagliflozin 100 mg and DPP-4 inhibitor	55.7%	55.6%
Canagliflozin 300 mg and DPP-4 inhibitor	55.1%	58.2%
Add-on to insulin		
Canagliflozin 100 mg and DPP-4 inhibitor	44.7%	45.2%
Canagliflozin 300 mg and DPP-4 inhibitor	60.7%	63.7%

Key: ICER, incremental cost-effectiveness ratio
Source: pages 245–254 of the manufacturer's submission

6.22 The manufacturer undertook scenario analyses that included exploration of dose modification from the recommended starting dose of 100 mg to 300 mg (see section 2.1 for details of the summary of product characteristics). Modelling techniques were used because this had not been studied in clinical trials. If patients in the simulated cohort had tolerated the 100 mg dose of canagliflozin but did not have HbA_{1c} less than 7.5% at 6 months, then the canagliflozin dose was increased to 300 mg in cycle 2. The manufacturer based this assumption on clinical specialist opinion. Switching to the higher dose was only permitted at the end of the first cycle: patients who tolerated treatment and had satisfactory glycaemic control continued the 100 mg dose and switched to standard rescue therapy when needed. It was assumed that patients who switched to the higher dose experienced the same treatment effects as patients treated with 300 mg for the full 12 months. The manufacturer stated that the dose intensification scenario improved the cost effectiveness of canagliflozin for 11 out of 12 comparisons made. Only the ICER comparing canagliflozin with a sulfonylurea in dual therapy increased (from £1537 per QALY gained to £1721 per QALY gained) and canagliflozin dominated in 7 of the scenarios (that is, it was less costly and more effective). For the results of the scenario analyses, see pages 256–271 of the manufacturer's submission.

ERG's comments on the manufacturer's cost-effectiveness analyses

6.23 The ERG concluded that the methods and inputs in the manufacturer's economic evaluation were generally in line with the NICE reference case, but noted:

- Not all comparators in the NICE scope had been included in the manufacturer's decision problem.
- Comparators used were not always the most widely prescribed.
- The NICE reference case states that data from head-to-head trials should be presented in the reference-case analysis where

possible, but that the manufacturer had instead sometimes used results from the meta-analyses. The ERG indicated that although the manufacturer cited reasons of consistency for this approach, this not properly justify it because the manufacturer had not provided a fully incremental cost-effectiveness analysis (that is, only pairwise comparisons had been generated).

- It was not clear if the preference data for utility values wholly represented the population of England because they were derived from a European study (CODE-2).

The ERG considered the model to be internally consistent and very well validated.

6.24 Overall, the ERG considered the clinical-effectiveness data in the model to be appropriate (although sometimes network meta-analysis estimates were used instead of head-to-head trial data). It found the equations used for the extrapolation of biomarker outcomes to be well-established and appropriate for the patient population in England, and the drift assumptions for the biomarkers to be reasonable. However, the ERG was concerned that using only 1000 patients in the base case might not robustly capture the ICERs.

6.25 The ERG commented that health benefits had been measured and evaluated in line with the NICE reference case and that utility values had been appropriately incorporated into the manufacturer's model. The ERG generally agreed with the costs used by the manufacturer for drugs, adverse events and health states (complications and comorbidities), although there was some uncertainty in the costs used for insulin.

6.26 Although the ERG agreed with the manufacturer's conclusions from the results of the deterministic analyses as presented, the ERG considered that the uncertainty in the decision problem had not been fully explored, and that manufacturer did not present the

results in the most informative way. The ERG was unclear why second order uncertainty was not switched off in the deterministic sensitivity analyses (that is, by specifying only 1 patient cohort). Consequently, the ERG believed that the manufacturer's results were partly confounded by stochasticity in other parameters (that is, they included uncertainty from more than 1 source and do not truly reflect the uncertainty associated with varying 1 parameter).

6.27 The ERG reviewed the manufacturer's scenario analyses, focusing on the dose modification scenario. It noted that, like the deterministic sensitivity analyses, second-order uncertainty was not switched off in scenario analysis, meaning that the results are again partly confounded by parameter stochasticity. The ERG noted that the manufacturer's submission concludes from the dose-modification scenario analysis that the dose intensification schedule from 100 mg to 300 mg is cost effective, but the ERG did not consider that this conclusion applied to all treatment comparisons, noting that:

- Canagliflozin 100 mg compared with thiazolidinedione in dual therapy remained dominated in the scenario analyses as well as in the base case.
- Canagliflozin 100 mg as an add-on to insulin was cheaper and less effective than a DPP-4 inhibitor in the base case, but associated with an ICER of £503 per QALY gained in the scenario analysis.
- Canagliflozin 100 mg as an add-on to insulin was cheaper and less effective than a GLP-1 analogue in the base case and remained so in the scenario analysis.

6.28 The ERG concluded that although all relevant variables appeared to have been included in the manufacturer's probabilistic sensitivity analyses, it was unclear if uncertainty in the decision problem had been sufficiently explored because the distributional assumptions were not well described in the manufacturer's submission and were

not transparent in the model. The ERG also commented that standard errors used for the HbA_{1c} treatment effect parameters were too small and that cost-effectiveness acceptability data had not been presented for all base-case comparisons.

ERG's exploratory analyses

6.29 The ERG did exploratory work to:

- examine the variation in base-case ICERs by re-running some of the manufacturer's analyses
- examine the variation in final ICERs with no parameter uncertainty and 100,000 patients
- produce incremental analyses for dual therapy
- identify the probability that canagliflozin is cost effective compared with dapagliflozin
- determine the effect of modifying the clinical efficacy of glimepiride and exenatide.

6.30 The ERG found there was minimal variation in the ICERs when it re-ran the manufacturer's base-case analyses (see tables 67 and 68 on page 131 of the ERG report).

6.31 The ERG was unsure if the manufacturer's use of 1000 patients was sufficiently large to robustly estimate the ICERs, and about how the base-case results might change if parameter uncertainty was removed. Its exploratory analyses with a single cohort of 100,000 patients and no parameter uncertainty had a small impact on the different cost and QALY outcomes compared with manufacturer's base case analyses (typically hundreds of pounds or less, and thousandths of a QALY). The ERG noted, however, that the small differences in incremental QALYs could in some cases drive an apparently large variation in the ICER (see tables 69 and 70 on pages 132–133 of the ERG report).

6.32 The ERG did a fully incremental exploratory analysis for canagliflozin 100 mg in dual therapy in combination with metformin

(table 23). The exploratory analysis excluded thiazolidinediones because of safety concerns that have led to declining use in clinical practice in England. In the ERG's exploratory analysis using the manufacturer's base case, canagliflozin 100 mg had an ICER of £507 per QALY gained compared with the next best option (dapagliflozin). When using the ERG's preferred inputs (excluding parameter uncertainty and with 100,000 patients), canagliflozin 100 mg had an ICER of £84,800 per QALY gained compared with the next best option, a DPP-4 inhibitor. The ERG noted that dapagliflozin, canagliflozin 100 mg and a DPP-4 inhibitor were associated with a similar total cost and similar overall total QALYs.

Table 23 ERG's exploratory fully incremental analysis for canagliflozin 100 mg in dual therapy

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER compared to next cheapest option (excluding dominated)
Manufacturer's base case					
Sulfonylurea	£25,894	8.751			
Dapagliflozin	£26,086	8.923	£192	0.172	£1,116
Canagliflozin 100 mg[a]	£26,094	8.938	£8	0.015	£507
DPP-4 inhibitor	£26,100	8.928	£6	-0.01	Dominated
GLP-1 analogue	£28,390	8.97	£2,296	0.032	£71,763
ERG base case (100,000 patients and no parameter uncertainty)					
Sulfonylurea	£25,941	8.79			
DPP-4 inhibitor	£25,988	8.974	£47	0.180	£261
Dapagliflozin	£26,100	8.956	£112	-0.018	Dominated
Canagliflozin 100 mg[a]	£26,234	8.977	£245	0.003	£84,800
GLP-1 analogue	£28,576	9.016	£2,343	0.040	£59,214

[a] Data for canagliflozin 100 mg averaged across the 4 pairwise comparisons

6.33 The ERG did a fully incremental exploratory analysis (excluding thiazolidinediones) for canagliflozin 300 mg in dual therapy in combination with metformin (table 24). The ICER for canagliflozin 300 mg compared with the next best option (dapagliflozin) was £17,639 per QALY gained using data from the manufacturer's base case, and £17,903 per QALY gained compared with the next best

option (a DPP-4 inhibitor) using data from the ERG preferred inputs (more patients and no parameter uncertainty).

Table 24 ERG's exploratory fully incremental analysis for canagliflozin 300 mg in dual therapy

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER compared to next cheapest option (excluding dominated)
Manufacturer's base case					
Sulfonylurea	£25,753	8.761			
DPP-4 inhibitor	£25,926	8.902	£173	0.141	£1,227
Dapagliflozin	£26,044	8.910	£118	0.008	£14,750
Canagliflozin 300 mg[a]	£26,631	8.943	£587	0.033	£17,639
GLP-1 analogue	£28,515	8.972	£1,885	0.029	£65,548
ERG base case (100,000 patients and no parameter uncertainty)					
Sulfonylurea	£25,773	8.797			
Dapagliflozin	£26,121	8.965	£348	0.168	£2,078
DPP-4 inhibitor	£26,225	8.972	£104	0.007	£15,024
Canagliflozin 300 mg[a]	£26,809	9.004	£585	0.033	£17,903
GLP-1 analogue	£28,702	9.008	£1,893	0.004	£492,690

[a]Data for Canagliflozin 300 mg averaged across the 4 pairwise comparisons

6.34 The ERG noted that the manufacturer's submission did not report the probability of canagliflozin being cost effective compared with dapagliflozin. The ERG's exploratory analyses for dual therapy with metformin and an SGLT-2 inhibitor showed that the probability of canagliflozin 100 mg being cost effective compared with dapagliflozin was 52.5% at a maximum acceptable ICER of £20,000 per QALY gained and £30,000 per QALY gained. For canagliflozin 300 mg, the probability of cost effectiveness was 46.7% at a maximum acceptable ICER of £20,000 per QALY gained and 50% at £30,000 per QALY gained.

6.35 The ERG was aware that gliclazide was associated with approximately half of the hypoglycaemia episodes of glimepiride (the drug used to inform the clinical efficacy of sulfonylureas in the manufacturer's economic model). The ERG examined variation of −50% in glimepiride's hypoglycaemia event rate (instead of ± 20% used by the manufacturer in its sensitivity analyses) and agreed

with the manufacturer that this parameter was not unduly influential.

6.36 The ERG noted that the manufacturer had used efficacy data for exenatide 10 µg where efficacy data for liraglutide were not available. In its exploratory analyses, the ERG found that using cost and efficacy data for liraglutide reduced the ICER for a GLP-1 analogue compared with canagliflozin (as add-on to insulin), but canagliflozin still remained cheaper and less effective. The ERG concluded that this efficacy parameter did not seem to be especially influential and that its results were consistent with the manufacturer's deterministic sensitivity analyses.

7 Equality issues

7.1 No equality issues that needed to be considered by the Appraisal Committee were identified during the scoping process or in any of the submissions.

8 Innovation

8.1 The manufacturer stated that canagliflozin is an innovative product because its insulin-independent mode of action shows some evidence of β-cell protection, which limits the risk of hypoglycaemia. Moreover, it reduces blood pressure and promotes weight loss, which is beneficial when treating multiple comorbidities in people with type 2 diabetes. Canagliflozin 300 mg has demonstrated some degree of local inhibition of intestinal SGLT-1, which helps to limit increased glucose levels after a meal, without evidence of gastrointestinal side effects. This SGLT-1 effect is currently under investigation. The manufacturer indicated that it was unlikely that any potential significant and substantial health-related benefits had been excluded from the quality-adjusted life year (QALY) calculation.

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