NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Canagliflozin for the Treatment of Type 2 Diabetes Mellitus

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List of abbreviations

ABCD	Association of British Clinical Diabetologists
ACE-i	Angiotensin Receptor Blocker inhibitor
ADA	American Diabetes Association
AE	Adverse Event
AHA	Anti-Hyperglycaemic Agent
ANCOVA	Analysis of covariance
AWMSG	All Wales Medicines Strategy Group
BDR	Background Diabetic Retinopathy
BID	Twice daily
BIM	Budget Impact Model
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CANA	Canagliflozin
CANTATA-D	CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator
CANTATA-D2	CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator
CANTATA-M	CANagliflozin Treatment and Trial Analysis - Monotherapy
CANTATA-MP	CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone
CANTATA-MSU	CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea
CANTATA-SU	CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride
CANVAS	Canagliflozin CardioVascular Assessment Study
CDC model	Centers for Disease Control model
CKD	Chronic Kidney Disease
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CoDHY	Consensus in Diabetes, Obesity, and Hypertension
COPD	Chronic Obstructive Pulmonary Disease
CrI	Credibility Interval
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular Disease
CT	Computed Tomography
DFI	Diabetic Foot Infection
DFU	Diabetic Foot Ulcer
DIA3001	Phase 2 dose ranging study
DIA3005	CANagliflozin Treatment and Trial Analysis – Monotherapy (CANTATA-M)
DIA3009	CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU)
DIA3006	CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator (CANTATA-D)
DIA3002	CANagliflozin Treatment And Trial Analysis - Metformin and Sulfonylurea (CANTATA-MSU)
DIA3015	CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator (CANTATA-D2)
DIA3012	CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP)
DIA3008	Canagliflozin CardioVascular Assessment Study (CANVAS)
DIA3010	Phase 3 older patient study

DIA3014	Phase 3 renal impairment study
DIC	Deviance Information Criterion
DMO	Diabetic Macular Oedema
DPP-4	Dipeptidyl peptidase-4
DPP-4-i	Dipeptidyl peptidase-4 inhibitor
DSA	Deterministic Sensitivity Analysis
DUK	Diabetes UK
DXA	Dual-energy X-ray absorptiometry
EASD	European Association for the Study of Diabetes
ECHO-T2DM	Economics and Health Outcomes Model of T2DM
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
FBG	Fasting Blood Glucose
FE model	Fixed Effects model
FPG	Fasting plasma glucose
FRG	Familial Renal Glucosuria
FR-MMTT	Frequently Sampled Mixed Meal Tolerance Test
GEE	General Estimating Equations
GI	Gastro-intestinal
GLP-1	Glucagon-like peptide-1
GLP-1-a	Glucagon-like peptide-1 agonist
GMI	Genital Mycotic Infection
GMM	Growth Mixture Model
H2H	Head-to-head
HbA1c	Haemoglobin A1c
HCP	Healthcare professional
HRG	Healthcare Resource Group
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
IR	Immediate Release
ISPOR	International Society for Pharmaco-economics and Outcomes Research
ITT	Intention-To-Treat
IVRS	Interactive Web Response System
LE	Life Expectancy
LEA	Lower Extremity Amputation
LOCF	Last Observation Carried Forward
LOS	Length of Stay
LPA	Latent Profile Analysis
LS	Least Square
MAA	Market Authorisation Application
MACE	Major Adverse Cardiovascular Events
MCMC	Markov Chain Monte Carlo
MDQ	Mood Disorder Questionnaire
MET	Metformin
MET+TZD	Metformin and a thiazolidinedione
MET+SU	Metformin and a sulphonylurea
MI	Myocardial Infarction
mITT	Modified Intention-To-Treat
MOA	Mechanism of action
MMRM	Mixed Model Repeated Measures
MR	Modified release
NDA	National Diabetes Audit
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NMA	Network Meta-Analysis

NPH	Neutral Protamine Hagedorn
NR	Not Reported
NYHA	New York Heart Association
OAD	Oral Anti-Diabetic
PCI	Percutaneous Coronary Intervention
PBO	Placebo
PbR	Payment by Results
PDMS	Prediabetes and the Metabolic Syndrome Congress
PDR	Proliferative diabetic retinopathy
PP	Per Protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta- Analyses
PRO	Patient Reported Outcomes
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral Vascular Disease
QALY	Quality Adjusted Life Year
QD	Once daily
QOF	Quality and Outcomes Framework
QW	Once weekly
RCT	Randomised controlled trial
RE model	Random Effects model
REP	Rochester Epidemiology Project
RTg	Renal Threshold for Glucose
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT	Sodium glucose co-transporter
SLR	Systematic Literature Review
SOC	Standard of Care
SMBG	Self Monitoring Blood Glucose
SMDM	Society for Medical Decision Making
SU	Sulphonylurea
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SUCRA	Surface Under the Cumulative Ranking
T2DM	Type 2 Diabetes Mellitus
TDS	Third daily
THIN	The Health Information Network
TTO	Time Trade Off
Tx	Treatment
TZD	Thiazolidinediones

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Type 2 diabetes mellitus (T2DM) is a common condition affecting nearly three million people living in the UK. It is caused by a combination of insulin resistance and insulin deficiency and is an incurable, progressive condition. T2DM is characterised by elevated blood sugar levels which are measured using the surrogate marker glycosolated haemoglobin A1c (HbA1c). Long term exposure to elevated blood sugar levels is known to cause damage to small blood vessels (microvasculature) in the body leading to blindness, kidney failure, peripheral neuropathy and vascular disease. T2DM is also a risk factor for cardiovascular disease (CVD). A compounding risk factor for T2DM is being overweight as this increases insulin resistance. Consequently, the management of T2DM is multifactorial and involves diet and lifestyle advice and intervention, the lowering the blood sugar levels by medication and the management of cardiovascular (CV) risk factors such as blood pressure and lipids. Despite the number of management programmes and agents available to manage T2DM many patients do not reach their HbA1c targets.

Canagliflozin (Invokana®) is a sodium glucose co-transporter 2 inhibitor (SGLT-2-i) available in 100mg and 300mg strengths that will be indicated for the treatment of adults aged 18 years and older with T2DM to improve glycaemic control (See Appendix 1) 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 anti-hyperglycaemic medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Canagliflozin has an insulin-independent mode of action (MoA) which complements those of other anti-hyperglycaemic agents (AHAs; see Section 1.2). Canagliflozin inhibits the activity of SGLT-2, blocking glucose re-absorption in the kidney and increasing the amount of glucose excreted in the urine. As a consequence, canagliflozin has a range of important metabolic effects on patients with diabetes. As well as lowering blood glucose as measured by HbA1c, it induces a loss of 60-80g of sugar in the urine every day, calorific loss of approximately 300 calories/day which manifests as weight reduction predominantly due to fat loss and has a mild osmotic diuresis which results in blood pressure [BP] reduction. (1-4)

As determined by the SmPC, patients receiving canagliflozin commence treatment at 100mg per day, and are permitted to increase onto a dose of canagliflozin 300mg per day if there is a need for tighter glycaemic control (i.e. HbA1c ≥7.5% [≥59mmol/mol]). This is expected to occur after 6 months on canagliflozin 100mg if the patient is tolerating the medication. (5) This provides clinicians with dose flexibility to achieve tighter glycaemic control without needing to switch to alternative treatments. This is

an advantage over other novel oral agents (such as the DPP-4 inhibitors [DPP-4-i] and dapagliflozin) which are only licensed as a single effective therapeutic dose.

It is expected that the majority of T2DM patients receiving canagliflozin 100mg as part of a dual therapy will not require a dose increase, however it is likely that a higher proportion of patients receiving canagliflozin 100mg as part of a triple therapy or as an add-on to insulin therapy would require tighter glycaemic control and would therefore be switched to canagliflozin 300mg. Canagliflozin is expected to be used in T2DM patients for glycaemic control if weight gain, and/or high BP and/or hypoglycaemia are of concern (see Section 2.5).

Canagliflozin is expected to be used:

- In combination with metformin (MET),
- In combination with MET+SU in triple therapy
- In combination with insulin plus SoC.

The expected annual cost of canagliflozin, £477.26 for canagliflozin 100mg, and £608.63 for canagliflozin 300mg.

Clinical evidence

Canagliflozin has been studied in the largest pre-licence Phase 3 programme for T2DM to date, involving 12 randomised clinical trials (RCTs) and over 10,000 subjects enrolled in multiple centres across the globe, including the UK (see Section 6.2.4). As well as a number of trials versus placebo, and in specific populations, the Phase 3 programme included three randomised active comparator studies that compared canagliflozin regimens with regimens that are standard of care in the UK in both dual and triple therapy:

- Dual therapy: DIA3009: CANA + Met vs. SU + Met.
  DIA3006: CANA + Met vs. DPP-4-i + Met.
- Triple therapy: DIA3015: CANA + Met + SU vs. DPP-4-i + Met + SU.

The primary end-point in all Phase 3 studies (except DIA3008) was change in HbA1c from baseline (see Section 6.3.5). In the head- to-head studies, canagliflozin 300mg demonstrated superiority in glycaemic control (lowering of HbA1c) to glimepiride titrated to maximal dose in dual therapy (in combination with metformin) up to 2 years and to sitagliptin 100mg in triple therapy up to approximately 1 year (see Table 1 and Section 6.5.3). Canagliflozin 100mg demonstrated similar reduction in HbA1c to sitagliptin in dual therapy (in combination with metformin). Both doses of canagliflozin demonstrated consistent and sustained reductions in HbA1c across all trials including placebo-controlled studies; the reduction inHbA1c was greater with canagliflozin 300mg than with canagliflozin 100mg (see Section 6.5.3). When added to insulin a consistent pattern was observed with significant HbA1c reductions, weight loss and SBP reduction vs. placebo + SoC at 18 weeks (see Section 6.5.3).

Both doses of canagliflozin demonstrated statistically significant reductions in weight and systolic blood pressure (SBP) vs. sitagliptin and glimepiride (see Section 6.5.3). Weight loss with canagliflozin is primarily related to fat loss rather than to fluid loss from a diuretic effect. Obesity and hypertension are known co-morbidities of T2DM and risk factors for CVD in their own right, and thus BP reduction and weight loss effects are treatment benefits from the perspective of patients and clinicians. Conversely, many other commonly used AHAs, such as SUs, are associated with weight gain, whilst others are weight neutral. Such treatments also fail to demonstrate positive effects on BP.

[redacted]

[redacted] As observed in studies of other AHAs, patients with higher baseline HbA1c achieve greater reductions in HbA1c with canagliflozin than those with lower baseline HbA1c. Pre-specified sub-group analyses revealed that baseline HbA1c was the only consistent factor affecting change in HbA1c over time. Other factors such as age, sex, race, ethnicity, BMI and β-cell function did not have a significant impact on the change in HbA1c across studies.

Table 1. Primary endpoint results in active comparator RCTs presented in this submission (2;6;7)

Trial no. (acronym)	Canagliflozin 100mg	Canagliflozin 300mg	Placebo	Active comparator
Dual therapy: treatment on a background of metformin				
DIA3009	**(n = 483)**	**(n = 485)**		**Glimepiride (n = 482)**
N	478	474		473
HbA1c at baseline (%), mean (SD)	7.78 (0.787)	7.79 (0.779)		7.83 (0.795)
LS Mean change at week 52 (SE)	-0.82 (0.039)	-0.93 (0.039)		-0.81 (0.039)
Diff. of LS Means (SE) (- Glimepiride)	-0.01 (0.050)	-0.12 (0.050)		
(95% CI)	(-0.109;0.085)	(-0.217;-0.023)		
DIA3006	**(n = 368)**	**(n = 367)**	**(n = 181)**	**Sitagliptin (n = 366)**
N	365	360	181	354
HbA1c at baseline (%), mean (SD)	7.94 (0.879)	7.95 (0.931)	7.96 (0.896)	7.92 (0.875)
LS Mean change at week 26 (SE)	-0.79 (0.044)	-0.94 (0.044)	-0.17 (0.060)	-0.82 (0.044)
Diff. of LS Means (SE) (- placebo))	-0.62 (0.071)	-0.77 (0.071)		-0.66 (0.071)
P-Value	<0.001	<0.001		N/A
95%CI	(-0.758;-0.481)	(-0.914;-0.636)		(-0.795;-0.516)
Triple therapy: treatment on a background of MET+SU				
DIA3015		**(n = 377)**		**Sitagliptin (n = 378)**
N		377		378
HbA1c at baseline (%), mean (SD)		8.1% (0.9)		8.1% (0.9)
LS Mean change at week 52 (SE)		-3.04 (0.407)		-0.30 (0.413)
Diff. of LS Means (SE) (- sitagliptin)		-0.37 (0.064)		N/A
95%CI		(-5.5 to -2.7)		N/A

DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride trial (CANTATA-SU); DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2);

During the course of the Phase 3 trials, a modest dose-related increase in lipid values was observed. Increases across the lipid profile including LDL, HDL and triglycerides, however the HDL/LDL ratio relatively unchanged. The mean change in LDL-C vs. placebo was 0.11 mmol/L and 0.21mmol/L for the 100mg and 300mg doses, respectively (see Section 6.5.3). (8) A meta-analysis of Phase 2 and 3 studies (n=9,632) revealed a hazard ratio (HR) for CV disease (MACE) of 0.91 (95% CI: 0.68, 1.22) in favour of canagliflozin, indicating that no CV risk has emerged from the clinical trial programme.(9)

The complementary metabolic outcomes observed with canagliflozin (i.e. improvement in HbA1c, BP and weight) are all important for patients as they are risk factors for the development of micro- and macro-vascular complications of the disease. As a result, controlling these parameters are important objectives in the effort to prevent long term complications of the disease.

The adverse event (AE) profile of canagliflozin is predictable due to its MoA (see Section 6.9.2). The most common AEs were genital mycotic infections (GMIs) in women (approximately 12% during the first year), which were generally easy to treat with topical antifungal therapy. Recurrence rates were low and rarely led to discontinuation of treatment. The rate of urinary tract infections (UTIs) was slightly elevated vs. placebo (the majority being lower UTIs), and were mild and treatable with standard therapy. AEs related to osmotic diuresis, such as hypovolaemia were identified, although this risk can be managed by correcting for hypovolaemia prior to commencing therapy, keeping the dose to 100mg in those patients at risk, and not using canagliflozin in patients whose estimated glomerular filtration rate (eGFR) <45mL/min/1.73m^2.

Studies in combination with metformin have demonstrated that canagliflozin has a low inherent risk of hypoglycaemia, with similar rates to placebo (see Section 6.9.2). This is due to the MoA as the renal threshold for glucose (RTg) re-absorption (see Section 1.2) is not decreased below approximately 4mmol/L. However, like other AHAs, when combined with medications known to cause hypoglycaemia, such as SUs and insulin, hypoglycaemia rates are naturally higher.

Overall, canagliflozin demonstrated lower use of rescue therapy up to 52/104 weeks than active comparators (sitagliptin and glimepiride) or placebo, demonstrating that patients are more likely to remain on canagliflozin than switch to another AHA or add another therapy.

Comparators

The main comparators in dual therapy (in combination with MET) are SU and DPP-4-i. In triple therapy (in combination with MET+SU or MET+TZD), the main comparator is DPP-4-i, as it is for add-on therapy to insulin plus SoC. All other comparators listed in the decision problem (see Section 5) were included for completeness as part of the clinical systematic literature review (SLR) and the NMA, and economic evaluation results are available in Section 7.7.

Economic evaluation

The Economics and Health Outcomes Model of T2DM (ECHO-T2DM), a validated stochastic (first and second order) micro-simulation model of the long-term costs and health outcomes in T2DM, was used to extrapolate the results from the clinical trials into long-term health economic outcomes in a large number of possible scenarios for the use of canagliflozin in the three lines of therapy investigated (see Section 7.2).

Economic modelling was intentionally conservative, with many assumptions being unfavourable to canagliflozin, including:

- Low disutility associated with weight gain, immediate weight regain upon discontinuation of canagliflozin;
- High disutilities associated with SGLT2-i-specific AEs;
- Exclusion of dose adjustment from 100mg to 300mgdose adjustment from the base case (due to lack of clinical data for this dose adjustment posology recommended by the CHMP).

As with all other economic models developed in diabetes, ECHO-T2DM assesses the clinical impact of canagliflozin on intermediate bio-markers (HbA1c, SBP, and weight), which are known to reduce the relative risks of long-term micro- and macro-vascular complications. The ECHO-T2DM model uses baseline patient and disease characteristics from the clinical trials that are generalisable to the patient population

and therapeutic management of T2DM in England and Wales. For methodological consistency, a NMA was used to estimate treatment effects for available parameters across each line of therapy versus all relevant comparators defined in the decision problem.

Overall, the results of the economic evaluation show a consistent picture across a range of comparisons, demonstrating that canagliflozin as an add-on therapy to other AHAs is a cost-effective treatment option. Analyses versus the main comparators of interest (SU and DPP-4-i in dual therapy and DDP-4-i in triple therapy) at both the 100mg and 300mg dose demonstrate incremental cost-effectiveness ratios (ICERs) that are all within the range considered cost-effective by NICE (see Table 2).

For patients inadequately controlled with MET alone, use of canagliflozin in dual therapy is cost-effective when compared to SU and DPP-4-i (see section 7.7.1). The base-case ICERs for canagliflozin 100mg are all below £1,600, and for canagliflozin 300mg plus MET are £4,899/QALY versus SU plus MET, and £18,349/QALY versus DPP-4-i plus MET. In triple therapy (combination with MET+SU), canagliflozin 100mg is both more effective and cost-saving vs. DPP-4-i; canagliflozin 300mg vs. DPP-4-i has an ICER of £13,287/QALY. In combination with MET+TZD, the ICERS vs. DPP-4-i are £1,095 and £21,430/QALY for canagliflozin 100mg and 300mg, respectively.

Clinical data for dose modification of canagliflozin 100mg to 300mg are not available, and so the clinical criteria and modelling of this step was discussed with UK clinicians. (5) Dose modification allows patients to increase the dose from 100mg to 300mg if patients tolerate 100mg and there is a need for improved glycaemic control. Modelling dose modification, consistent with the anticipated label, suggests that this tends to increase the cost-effectiveness of canagliflozin by increasing the number of QALYs generated (see section 7.7.9) across different treatment lines.

Scenario analyses showed that the structural assumptions around the ECHO-T2DM modelling are robust and that there are few assumptions that impact the costs and/or QALYs (see Sections 7.7.7 to 7.7.9). Furthermore, scenario results using RCT data (where head-to-head data were available) are directionally consistent with the modelling results using the NMA.

Two-way deterministic sensitivity analyses (DSAs) performed on the key comparisons confirm that canagliflozin is cost-effective in most analyses. The key driver from a DSA perspective was HbA1c drift.

Table 2. Summary of cost-effectiveness results

ICER vs. canagliflozin	SU	DPP-4-i
Dual therapy (Met)		
Cana 100mg	1,537	97
Cana 300mg	4,899	18,349
Triple therapy (Met+SU)		
Cana 100mg	N/R	Dominates
Cana 300mg	N/R	13,287
Triple therapy (Met+TZD)		
Cana 100mg	N/R	1,095
Cana 300mg	N/R	21,430
Add-On to insulin + Met		
Cana 100mg	N/R	Dominated
Cana 300mg	N/R	8,925

Legend: N/A: not applicable (indirect comparison through NMA not possible); N/R: not relevant to the decision problem; ***cana:*** *canagliflozin*
 # Canagliflozin is cost-saving but less effective vs. GLP-1-a, therefore these ICERs are the cost/QALY for GLP-1-a therapy to replace canagliflozin

In conclusion, the economic evidence presented in this submission are a consistent set of results demonstrating that canagliflozin is a cost-effective treatment option for T2DM patients when combined with metformin in dual therapy and when combined with metformin plus SU or TZD in triple therapy. These conclusions are robust to changes in assumptions across a range of deterministic sensitivity analyses and scenario analyses.

These cost-effectiveness results are consistent with the results observed in the head-to-head RCTs which showed that canagliflozin 300mg was more effective than SU and DPP-4-i in terms of reduction of HbA1c, weight and BP, whilst the 100mg dose demonstrated non-inferiority in HbA1c improvement and superiority in weight and BP reduction. Canagliflozin is therefore a useful treatment option for these patient groups. AEs were generally manageable and there is no evidence from a large clinical trial programme of any evidence of increased risk of CVD.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Invokana®.

Approved name: canagliflozin.

Therapeutic class: canagliflozin is a SGLT-2-i.

Pharmaco-therapeutic group: Drugs used in diabetes; other blood glucose lowering drugs, excluding insulins.

ATC code: A10BX11.

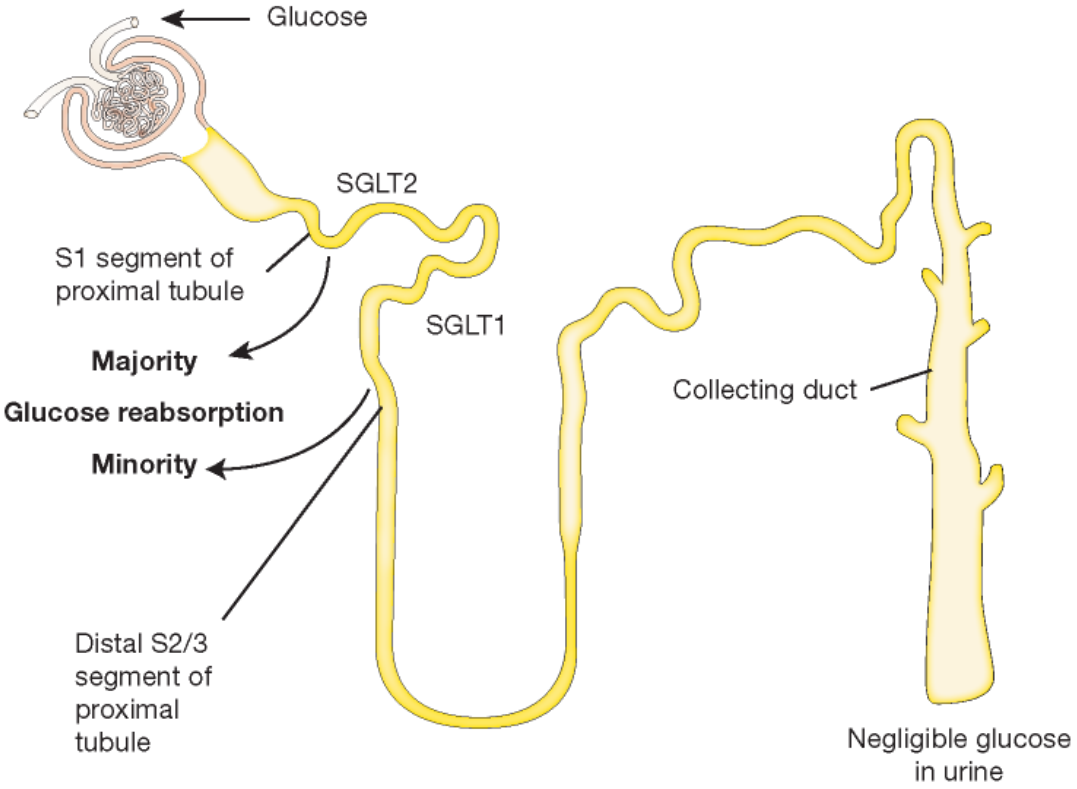
1.2 What is the principal mechanism of action of the technology?

Most currently available medications to treat hyperglycaemia in T2DM increase sensitisation to, or secretion of insulin. Canagliflozin is an SGLT-2-i, and has an insulin-independent mechanism of action, complementary to the majority of medications used in T2DM.

Glucose re-absorption and SGLT-2 inhibition

Patients with diabetes have elevated threshold for renal glucose re-absorption which may contribute to persistent high blood glucose. (10;11) SGLT2- is responsible for approximately 90% of glucose re-absorption from urinary filtrate in the proximal tubule of the nephron (Figure 1). (12) The remaining 10% of the filtered glucose is reabsorbed by SGLT-1 in the distal segment of the proximal tubule.

Figure 1. Renal glucose re-absorption regulated by SGLT2 and SGLT1 (13)



Legend: SGLT: sodium glucose co-transporter.

When the capacity of SGLT-2 is exceeded, glucose spills into the urine and is excreted. At this point, the RTg has been reached. In people without T2DM the RTg is reached at a blood sugar level of approximately 10mmol/L. When blood sugar levels rise above this, glucosuria can occur. However, in people with T2DM the RTg can be as high 13-14mmol/L, due to up-regulation of the SGLT-2 receptors. (14)

SGLT-2-i block the activity of SGLT-2, leading to inhibition of glucose reabsorption and urinary glucose excretion (UGE). Typically, treatment with SGLT-2-i results in excretion of approximately 70-80g of glucose in the urine during a 24 hour period. (1;3)

The physiological consequences of treatment with SGLT-2-i are a lowering of blood glucose as measured by HbA1c, loss of approximately 300 calories/day, which manifests as weight reduction predominantly due to fat loss, and a mild osmotic diuresis causing BP reduction. (2) The RTg is reduced to approximately 4.4-5.0mmol/L, and therefore SGLT-2-i exhibit a low inherent risk for hypoglycaemia when used as monotherapy of add-on to metformin. However, an increased frequency of GMIs and urinary tract infections (UTI) are expected, as a consequence of glucose in the urine.

A model for SGLT2 inhibition exists in individuals with the genetic condition, familial renal glucosuria (FRG). In FRG, SGLT2 mutations can cause high levels of glucose (up to 100g/day) to be excreted in the urine, although plasma volume, renal function, and electrolyte balance have not been reported to be abnormal in these individuals, nor has hypoglycaemia been reported. Further, individuals with FRG are not known to have clinical sequelae as a result of this condition. (10;15-17)

Canagliflozin mode of action

Canagliflozin confirms the MoA of SGLT-2, with the monotherapy study (DIA3005), which demonstrates that HbA1c was reduced by approximately 1% over 26 weeks, with additional benefit of weight loss and BP reduction, and hypoglycaemia rates comparable to placebo (3.6%, 3.0% and 2.6% for canagliflozin 100mg and 300mg and placebo, respectively). (18)

In Phase 3 studies, canagliflozin 300mg provided a greater reduction in postprandial glucose excursion than observed with the 100mg dose. This additional effect may be attributed partially to local inhibition of intestinal SGLT1 (an important intestinal glucose transporter) related to transient high concentrations of canagliflozin in the intestinal lumen prior to medicinal product absorption (canagliflozin is a low potency inhibitor of SGLT1). (19) Studies have shown no glucose or galactose malabsorption with canagliflozin, and clinical studies have shown no excess incidence of gastro-intestinal (GI) side-effects associated with the use of canagliflozin.

By promoting glucosuria through inhibition of SGLT2, canagliflozin treatment reduces hyperglycaemia through an insulin-independent mechanism. Therefore, canagliflozin is expected to be effective in a wide range of patients irrespective of β-cell function. Clinically meaningful glycaemic improvements can be expected for patients with new-onset T2DM with only moderate impairment of β-cell function, in addition to improvements in patients with greater β-cell functional loss, such as those with long-standing T2DM who require insulin. This has been demonstrated in the phase III clinical trial programme. (20-22)

An improvement in the homeostasis model assessment for beta-cell function (HOMA β-cell) and in β-cell insulin secretion response to a mixed-meal challenge has been observed in clinical studies with canagliflozin. These results support the hypothesis that this pathway may also contribute to the glucose lowering observed in the clinical program. (20;23)

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Central marketing authorisation is still pending. The marketing authorisation application (MAA) was submitted to the European Medicines Agency (EMA) on 26th June 2012. Positive Committee for Medicinal Products for Human Use Committee for Medicinal Products for Human Use (CHMP) opinion for INVOKANA (canagliflozin) was obtained on 19th September 2013, and a final European decision was received on 25th November 2013. (24)

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The EPAR and final version of the summary of product characteristics (SmPC) will not be available until regulatory approval. A draft version of the SmPC is provided in Appendix 1. (25)

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Canagliflozin is expected to receive the following indication (see Appendix 1):

Canagliflozin is indicated in adults aged 18 years and older with T2DM to improve glycaemic control as:

- Monotherapy
  When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- Add-on Therapy
  Add-on therapy with other anti-hyperglycaemic medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The efficacy and safety of canagliflozin has been studied in the biggest pre-licence Phase 3 programme for T2DM to date, including 12 Phase 3 clinical trials (which include 2 sub-studies of DIA3008) in over 10,000 patients enrolled in multiple centres across the globe, including the UK. These studies spanned a range of clinical uses to treat T2DM:

- As monotherapy (trial DA3005);
- As dual therapy, in combination with metformin (trials DIA3006 and DIA3009), or a SU (trial DIA3008 SU sub-study),
- As triple therapy, in combination with MET+SU (Trials DIA3002 and DIA3015) or MET+TZD (trial DIA3012);
- And as add-on to insulin therapy, in combination with insulin (with or without other AHAs (trial DIA3008 insulin sub-study).

Three of these studies were head-to-head RCTs investigating the efficacy of canagliflozin compared to the “gold standard” active comparators: the DPP-4-i sitagliptin and the SU glimepiride.

Canagliflozin was also evaluated in four more trials, covering its use across all line of therapy in specific patient populations:

- DIA3010 was conducted in older patients,
- DIA3004 was conducted in patients with moderate renal impairment,
- DIA3014 was conducted in T2DM Asian patients,
- DIA3008 is on-going in patients at high risk for CV diseases.

Table 3 below details the completed studies of canagliflozin in T2DM, from which evidence is available. There are currently no ongoing other studies investigating canagliflozin for the treatment of T2DM.

Table 3. Completed and ongoing Phase II and III studies of canagliflozin for the treatment of T2DM

Positioning and combinations		Trial no. (acronym)	Design/duration	Study population	Treatment group (n=)
Phase II study					
Dual therapy	Met+	DIA 2001 - Dose-ranging study NCT00642278 (26)	Phase 2b double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging study Total duration of 12 weeks.	Patients with a diagnosis of T2DM: - who must have been on stable dose of metformin for at least 3 months - with HbA1c level ≥7% and ≤10.5% - and who met all other enrolment criteria.	Canagliflozin 50, 100, 200, or 300mg once daily (QD) or 300mg twice daily (BID), versus sitagliptin 100mg QD or placebo: Canagliflozin 50mg (n=64) Canagliflozin 100mg (n=64) Canagliflozin 200mg (n=65) Canagliflozin 300mg QD (n=64) Canagliflozin 300mg BID (n=64) Sitagliptin 100mg (n=65) Placebo (n=65)
Phase 3 Studies					
Mono-therapy		DIA3005 NCT01081834 (18)	Phase 3 randomised, double-blind, 3-arm, parallel-group, active-controlled, multicentre study. Total duration of 52 weeks split into 26-week core double blind & 26-week extension double blind periods.	Patients with a diagnosis of T2DM: - who met one of the two following criteria: (i) not on an AHA at screening or (ii) on AHA monotherapy or MET+SU combination therapy - with HbA1c ≥7.0 and ≤10.0% - and who met all other enrolment criteria.	Canagliflozin 100mg and 300mg QD versus placebo QD: Canagliflozin 300mg (n= 197) Canagliflozin 100mg (n= 195) Placebo (n= 192)

Positioning and combinations		Trial no. (acronym)	Design/duration	Study population	Treatment group (n=)
Dual therapy	Met+	DIA3009 NCT00968812 (2)	Phase 3 randomised, double-blind, 3-arm, parallel-group, active-controlled, multicentre study. Total duration of 104 weeks split into 52-week core double blind & 52-week extension double blind periods	Patients with a diagnosis of T2DM: - who must have been taking a stable dosage of metformin as monotherapy at screening. - with HbA1c between ≥7% and ≤9.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD in combination with metformin versus Glimepiride 1, 2 or 4mg per day (titrated to maximal effect up to 6-8mg per day) in combination with metformin: Canagliflozin 100mg (n=483) Canagliflozin 300mg (n=485) Glimepiride (n=484)
		DIA3006 NCT01106677 (6)	Phase 3 randomised, double-blind, 4-arm, parallel-group, placebo and active-controlled, multicentre study. Total duration of 52 weeks split into 26-week core double blind & 26-week extension double blind periods	Patients with a diagnosis of T2DM: - who must have been treated with metformin IR. - With HbA1c between ≥7% and ≤10.5% at Week -2 - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD in combination with protocol-specified dose of metformin Immediate release (IR) versus Sitagliptin 100mg QD with metformin IR, and versus placebo QD/sitagliptin with metformin IR: Canagliflozin 100mg (n=368) Canagliflozin 300mg (n=367) Sitagliptin 100mg (n=366) Placebo/sitagliptin (n=183)
	SU+	DIA3008 SU sub-study NCT01032629 (27)	Sub-study of CANVAS, phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre study to evaluate the safety, tolerability, and CV risk with canagliflozin plus SoC compared with placebo plus SoC. Total duration of this sub-study was18 weeks. All analyses conducted for endpoints after this time point were not pre-defined in the clinical study protocol.	Patients with a diagnosis of T2DM: - who had an elevated risk of CV disease - who were on SU monotherapy at study entry - with HbA1c ≥7.0 and ≤10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD versus placebo QD as an add-on to SU therapy with or without other AHAs: Canagliflozin 100mg (n=74) Canagliflozin 300mg (n=72) Placebo (n=69)

Positioning and combinations		Trial no. (acronym)	Design/duration	Study population	Treatment group (n=)
Triple therapy	Met+SU+	DIA3015 NCT01137812 (7)	Phase 3 randomised, double-blind, 2-arm, parallel-group, active-controlled, multicentre study. Total duration of 52 weeks.	Patients with a diagnosis of T2DM: - who have received stable MET+SU therapy at maximally or near-maximally doses - with HbA1c between ≥7% and 10.5% - and who met all other enrolment criteria.	Canagliflozin 300mg QD in combination with MET+SU versus Sitagliptin 100mg QD in combination with MET+SU: Canagliflozin 300mg (n=378) Sitagliptin 100mg (n=378)
		DIA3002 NCT01106625 (28)	Phase 3 randomised, double-blind, 3-arm, parallel-group, placebo-controlled, multicentre study. Total duration of 52 weeks split into 26-week core double blind & 26-week extension double blind periods	Patients with a diagnosis of T2DM: - who must had previously been received stable MET+SU therapy at maximally or near-maximally doses - HbA1c between ≥7% and 10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg and 300mg QD in combination with MET+SU vs. placebo QD in combination with MET+SU: Canagliflozin 300mg (n= 156) Canagliflozin 100mg (n= 157) Placebo (n= 156)
	Met+TZD+	DIA3012 NCT01106690 (29)	Phase 3 randomised, double-blind, 3-arm, parallel-group, placebo-controlled, multicentre study. Total duration of 52 weeks split into 26-week core double blind & 26-week extension double blind periods.	Patients with a diagnosis of T2DM: - who must have previously received AHAs and metformin - with HbA1c between ≥7% and 10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD in combination with MET+TZD vs. placebo QD (cross-over to sitagliptin at 26 weeks) in combination with MET+TZD: Canagliflozin 100mg (n=115) Canagliflozin 300mg (n=114) Placebo (n=115)

Positioning and combinations		Trial no. (acronym)	Design/duration	Study population	Treatment group (n=)
Add-on to insulin	Ins±AHA+	DIA3008 insulin sub-study NCT01032629 (30)	Sub-study of CANVAS, phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre study to evaluate the safety, tolerability and CV risk with canagliflozin plus SoC compared with placebo plus SoC in subjects with T2DM. Total duration of this sub-study was18 weeks. All analyses conducted after this time point were not pre-defined in the clinical study protocol.	Patients with a diagnosis of T2DM: - who were at an elevated risk of CV disease - who were not on AHA therapy or on AHA monotherapy or combination therapy with any approved agents - with HbA1c ≥7% and 10.5% - and who met all other enrolment criteria. A subpopulation in this trial was deemed the most relevant for the UK: Population 2 (subjects taking insulin ≥30 units per day at study entry).	Canagliflozin 100mg & 300mg QD versus placebo QD as an add-on to insulin therapy with or without other AHAs: Canagliflozin 100mg (n=566) Canagliflozin 300mg (n=587) Placebo (n=565)
Special population Studies	Older patients (all line of therapies)	DIA3010 Older patient study NCT01106651 (31;32)	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre study. Total duration of this trial was 104 weeks split into a 26-week core treatment period followed by a 78-week extension period.	Older patients (≥55 to ≤80 years of age) with diagnosis of T2DM: - who were either not on AHA therapy or were on a stable AHA regimen - with HbA1c ≥7.0% and ≤10.0% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD versus placebo QD with or without other AHAs: Canagliflozin 100mg (n=241) Canagliflozin 300mg (n=236) Placebo (n=237)
Special population Studies	Renal impaired patients (all line of therapies)	DIA3004 Renal Impairment study NCT01064414 (33;34)	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre study. Total duration of 52 weeks split into 26-week core double blind & 26-week extension double blind periods.	Patients with a diagnosis of T2DM: - who had moderate renal impairment [eGFR ≥30 and <50 mL/min/1.73 m^2] - with HbA1c ≥7.0% and ≤10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD versus placebo QD with or without other AHAs: Canagliflozin 100mg (n=90) Canagliflozin 300mg (n=89) Placebo (n=90)

Positioning and combinations		Trial no. (acronym)	Design/duration	Study population	Treatment group (n=)
	Asian population study (all line of therapies)	DIA3014 South-Asian study NCT01381900 (35)	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre, 18-week study to evaluate the efficacy, safety and tolerability of canagliflozin in T2DM Asian patients inadequately controlled on metformin alone or in combination with a SU. Total duration of 18-weeks double-blind period.	Patients with a diagnosis of T2DM: - who were on metformin monotherapy or metformin + SU therapy - with HbA1c ≥7.0% and ≤10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD versus placebo QD with or without other AHAs: Canagliflozin 100mg (n=225) Canagliflozin 300mg (n=227) Placebo (n=226)
CV risk assessment Study		DIA3008 NCT01032629 (9)	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre study to evaluate the safety, tolerability and CV risk with canagliflozin plus SoC compared with placebo plus SoC in subjects with T2DM. Total duration of this trial is expected to be approximately 4 years, depending on the occurrence of sufficient events to evaluate the study hypothesis and objectives (i.e. assess the effect of canagliflozin on CV risk in subjects with T2DM, with inadequate glycaemic control, who have a history or high risk of CV disease). The current cohort of patients (4,330) will continue to be followed and the study will report in 2017.	Patients with a diagnosis of T2DM: - who had elevated CV risk - with HbA1c ≥7.0 and ≤10.5% - and who met all other enrolment criteria.	Canagliflozin 100mg & 300mg QD versus placebo QD with or without other AHAs: Canagliflozin 100mg (n=1,445) Canagliflozin 300mg (n=1,441) Placebo (n=1,441)

AHA: Anti-hyperglycaemic agent; DIA3006Trial: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial; DIA3015 Trial: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial; DIA3012 Trial: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone; DIA3002 Trial: CANagliflozin Treatment And Trial Analysis - Metformin and SUlphonylurea; DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT-2 Add-on to Metformin Versus Glimepiride; DIA3008 Trial: CANagliflozin cardioVascular Assessment Study; CV: Cardiovascular; Met+: in combination with metformin; SU+: in combination with sulfonylurea: Met+SU+: in combination with metformin and sulfonylurea; Met+TZD+: in combination with metformin and a thiazolidinedione; CV: cardiovascular; BID: twice daily; HbA1c: Haemoglobin A1c; QD: once daily; T2DM: type 2 diabetes.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

[redacted]

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Canagliflozin was launched in the USA in April 2013 (following FDA approval in March 2013), as well as in Australia on 6th September 2013 (TGA approval).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

[redacted]

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4. Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet
Acquisition cost (excluding VAT)	Expected prices: Canagliflozin 100mg (30 tablets): £39.20 Canagliflozin 300mg (30 tablets): £49.99
Method of administration	Oral
Doses	The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥ 60mL/min/1.73 m^2 or CrCl ≥ 60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily. (25)
Dosing frequency	Once daily
Average length of a course of treatment	T2DM is a chronic disease with subsequent treatments often being additive to the existing therapy, thus moving from monotherapy to dual and then triple therapy. Treatment duration depends upon the reduction in HbA1c experienced after the start of each newly added therapy experienced by patients. Patients remain on treatment whilst their disease is controlled, as determined by HbA1c monitoring. Current clinical guidelines recommend an add-on therapy when HbA1c rises back above 7.5% (58.5mmol/mol). (38;39) Canagliflozin, treatment should be discontinued when eGFR is persistently below 45mL/min/1.73 m^2 or CrCl persistently below 45mL/min as it is not expected to be sufficiently effective in these patients. (25)
Average cost of a course of treatment	The expected annual costs for canagliflozin is: Canagliflozin 100mg: £477.26 Canagliflozin 300mg: £608.63
Anticipated average interval between courses of treatments	*Not applicable*
Anticipated number of repeat courses of treatments	*Not applicable*
Dose adjustments (25)	*Patients requiring tighter glycaemic control* In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥ 60mL/min/1.73 m^2 or CrCl ≥ 60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily. Care should be taken when increasing the dose in patients ≥75 years of age, patients with known CVD, or other patients for whom the initial canagliflozin-induced diuresis poses a risk. In patients with evidence of volume depletion, correcting this condition prior to initiation of canagliflozin is recommended.

	Use as add-on therapy to insulin When canagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g., SU), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia. *Patients with renal impairment* For patients with an eGFR 60mL/min/1.73 m^2 to < 90mL/min/1.73 m^2 or CrCl 60mL/min to < 90mL/min and who have a low risk of adverse reactions associated with reduced intravascular volume, no dose adjustment is needed. Canagliflozin should not be initiated in patients with an eGFR < 60mL/min/1.73 m^2 or CrCl < 60mL/min. In patients tolerating canagliflozin whose eGFR falls below 60mL/min/1.73 m^2 or CrCl 60mL/min, the dose of canagliflozin should be adjusted to or maintained at 100mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45mL/min/1.73 m^2 or CrCl persistently below 45mL/min as it is not expected to be sufficiently effective in these patients. Canagliflozin should also not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in such populations. It should be noted that this expected wording in section of 4.4 (special warnings and precaution for use) defers form the renal precautions from the currently licenses SGLT-2-i (dapagliflozin). *Patients with hepatic impairment* For patients with mild or moderate hepatic impairment, no dose adjustment is required. Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients. *Older patients* Renal function and risk of volume depletion should be taken into account.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are required to select patients for treatment with canagliflozin. Canagliflozin is taken orally with or without food, preferably before the first meal of the day. Tablets should be swallowed whole.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Monitoring of renal function is recommended as follows:

- Prior to initiation of canagliflozin and at least annually, thereafter
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically, thereafter
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year.

The monitoring of change in eGFR is, aligned with the NICE recommended monitoring of diabetes patients with chronic kidney disease (CKD). (38)

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

For patients not receiving adequate glycaemic control on their current pharmaco-therapies together with diet and exercise, (25) canagliflozin is expected to be used in combination with metformin as dual therapy, and is also expected to be used in combination with MET+SU or MET+TZD, as well as in combination with insulin + SoC,

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Diabetes mellitus is a metabolic disease associated with two major defects: 1) decreased insulin secretion by the pancreas (insulin deficiency), and 2) resistance to the action of insulin in various tissues, such as the liver and muscles (insulin resistance). (39) Failure to produce insulin, or of insulin to act properly, or both, leads to raised glucose (sugar) levels in the blood (hyperglycaemia).

The two most common types of diabetes are (39):

- Type 1 diabetes mellitus (T1DM);
- Type 2 diabetes mellitus (T2DM).

Only T2DM is being considered for this technology appraisal.

Diabetes mellitus is one of the most common non-communicable diseases, with a prevalence of 4.57% which equates to 2.8 million people living with a diagnosis of diabetes in the UK, based on figures collected in 2011. (40) The majority of these (almost 90%) have adult-onset T2DM. (40) The prevalence of diabetes is projected to increase by about 20,000 people in the UK every year over the next 20 years. (41) A recent UK focused study estimated that the cost of treating T2DM in 2035/2036 would be £15.1bn in direct costs and £20.5bn in indirect costs, in real terms. Diabetes currently accounts for around 10% of the total health spend but is projected that it will account for around 17% in 2035/2036. (42)

The cause of T2DM has been linked to genetic and lifestyle factors, such as being overweight or obese with physical inactivity. (39) Although T2DM symptoms are similar to those of T1DM, they are often less marked (e.g. frequent urination, increased thirst, hunger, weight loss, blurred vision, and/or extreme fatigue and irritability) and most patients are asymptomatic. T2DM can remain undetected for many years, and its diagnosis is often made from associated complications or incidentally through an abnormal blood or urine glucose test. It is thought that as many as 850,000 people may have undiagnosed T2DM in the UK. (43)

Diabetes-related complications

Uncontrolled hyperglycaemia associated with T2DM increases the risk of micro-vascular (such as retinopathy, nephropathy or neuropathy) and macro-vascular (such as stroke, Myocardial infarction [MI], Congestive Heart Failure [CHF], or ischaemic Heart Disease [IHD]) complications over the long term. (39;44-46) For example, patients with diabetes are at a significantly increased risk of retinopathy compared to

the general population. (47) Other complications, such as CKD, UTIs and GMIs are also higher in this group than the general population. (48;49)

A range of other complications that are also more common in diabetes compared to the general population and are summarised in Table 5.

Table 5. Additional risk of complication among people with diabetes (50)

Complication	Country	Additional risk of complications among people with diabetes
Angina	England and Wales	+71.3%
MI	England and Wales	+48.0%
CHF	England and Wales	+64.9%
Stroke	England and Wales	+24.9%
Renal Replacement therapy (ESKD)	England and Wales	+144%
Minor amputation (below the ankle)	England and Wales	+331%
Major amputation (above the ankle)	England and Wales	+210%
Adapted from Table 2 of the National Diabetic Audit 2010-11– Report 2: Complications and Mortality. *Note: Retinopathy has not been included as it only affects people with diabetes*		

Diabetes complications generally arise after many years of exposure to high blood glucose, high BP and high cholesterol and are compounded by factors such as increasing age, inactivity, obesity and smoking. (50)

The Global Burden of Disease Study 2010 estimated that the number of deaths attributable to diabetes in 2010 has doubled over the last 20 years. (51) T2DM is now ranked thirteenth in the list of leading causes of years of life lost (YLL) in Western Europe, with a global rank of 19. It should be noted that the UK has dramatically improved their ranking in diabetes-associated YLL over the past 20 years to become the country with the lowest rates of age-standardised YLLs for diabetes in Europe. (51)

Management of T2DM

The overall goal of T2DM management is prevention of long-term complications while avoiding hypoglycaemic events. Each 1% reduction in mean HbA1c has been shown to be associated with reductions in risk for any end point related to diabetes. This includes a 21% reduction in for deaths, a 14% reduction for myocardial infarction and a 37% reduction for micro-vascular complications. (52) One of the most utilised agents for lowering HbA1c are the SUs. Whilst they are effective lowering HbA1c, particularly rapidly, they are associated with both weight gain and hypoglycaemia; two side effects clinicians are actively trying to manage against. Hypoglycaemia is often unacceptable to the patient and costly to the health service. Insulin therapy presents a similar issue, as well as being administered by injection.

The management of T2DM is multi-factorial and involves the use of AHAs, alongside treatment of co-morbidities such as hypertension and dyslipidaemia with a focus on weight control, dietary and exercise advice and lifestyle management. (53)

The primary aim of AHAs is to achieve long-term control of blood glucose levels, as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines. (45) The benefit of glycaemic control in T2DM patients has been demonstrated in various studies including the United Kingdom Prospective Diabetes Study (UKPDS) which showed a

three-fold increase in diabetes-related complications in subjects with mean HbA1c levels >10% (median 10.6%) compared to those with HbA1c <6% (median 5.6%). (52) Meta-analyses have confirmed the role of intensive glucose lowering on CV death (i.e. fatal MI or stroke), all-cause mortality and micro-vascular complications such as micro-albuminuria in T2DM patients. (54)

Current clinical guidelines recommend setting individualised treatment goals for patients, and NICE guidelines recommend a HbA1c target level of less than 7.5% (59mmol/mol) in T2DM patients on two or more oral glucose-lowering drugs or patients requiring insulin. (37)

Weight loss after T2DM diagnosis improves insulin sensitivity and can contribute to the achievement of glycaemic and BP goals, improve CV risk factors, and may have a positive impact on the health-related quality of life (HRQL) of T2DM patients. Weight control is an important component of T2DM management, although no specific treatment targets are recommended in the clinical guidelines.

The importance of controlling glycaemia, BP and weight in patients with T2DM has been confirmed by several long-term studies such as UKPDS study. (52;55) Based on these results, clinical guidelines currently recommend that physicians monitor BP closely and set a target of <130/80mmHg for people with kidney, eye or CV damage and <140/80mmHg for other T2DM patients. (37)

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The following patient number estimates are derived from data within the National Diabetic Audit report. The marketing authorisation would cover all of these groups:

- There are 2,323,150 individuals diagnosed with diabetes in England and Wales (2,177,450 and 145,700 respectively), based on a prevalence of 4.57% in England and 4.70% in Wales) (40) and mid-2012 population estimate (56).
- A total of 2,090,835 people have T2DM in England and Wales, assuming 90% of people with diabetes have T2DM (43).,
- 1,672,668 of which are receiving a pharmacological therapy (i.e. patients who have failed on diet and exercise and are treated with pharmacological intervention).
- An estimated 1,166,650 people with T2DM receive a monotherapy of which 84% receive metformin and 14% receive a SU. (55)
- An estimated 384,714 receive dual therapy after failure on metformin monotherapy (23%). (57)
    - Of which 357,784 (93%) receive an add-on to metformin therapy. (57)
- An estimated 150,534 receive a triple therapy after failure on a dual therapy (9%). (57)
    - Of which 135,486 (90%) receive an add-on to MET+SU therapy, and 9,484 (7%) an add-on to MET+TZD therapy. (57)

- An estimated 334,534 receive an add-on to insulin therapy after failure on either a dual or a triple therapy (20%). (57)

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Although YLLs due to diabetes reduced significantly in the UK between 1990 and 2010 (51), the life expectancy of someone with T2DM still remains 10 years lower than the general population (43). The additional risk of death among people with diabetes was +36.4% in England in 2011. (50) The number of diabetes-associated deaths may be under-estimated as causes of death may be classified as CV disease, renal failure or stroke, even when diabetes may have been an underlying cause. (58)

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific sub-groups were addressed.

NICE has completed four previous appraisals in diabetes, three of which were single technology appraisals of AHAs, and one technology appraisal of insulin pumps:

- Technology Appraisal No. 288, June 2013. 'Dapagliflozin in combination therapy for treating T2DM'. Proposed review date: December 2014. (59)
- Technology Appraisal No. 248, February 2012. 'Diabetes (type 2) – exenatide (prolonged release)'. Guidance on static list. (60)
- Technology Appraisal No. 203, October 2010, 'Liraglutide for the treatment of T2DM. Under consideration for review. (61)
- Technology Appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review)'. Guidance on static list. (62)

Relevant clinical guidelines are:

- Clinical Guideline No. 87 (partial update of Clinical Guideline No. 66), May 2009 'T2DM- newer agents' Review in preparation. Publication date May 2009. (36)
- Clinical Guideline No. 66 (partially updated by Clinical Guideline No. 87), May 2008 'T2DM: full guideline' Review in preparation. Publication date 2008. (37)

These documents were used to develop the clinical pathways presented in Figure 2 and Figure 3 presented below.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Robust clinical treatment pathways have recently been developed by NICE. Figure 2 and Figure 3, adapted from NICE Pathways in Diabetes, present the current clinical pathways for T2DM patients considered for dual, triple and add-on to insulin therapy. First-line therapy currently involves monotherapy with either metformin or SU. (63)

Figure 2. Current clinical pathway for the management of blood-glucose-lowering therapy (except insulin) for T2DM (63)

1st LINE OPTIONS in addition to lifestyle measures: **START ONE OF**

Metformin (MF)	**Sulfonylurea*** (SU) - If intolerant to metformin or - if weight loss/osmotic symptoms

Review if not reaching target move to 2nd

Glycaemic Target: HbA1c < 6.5% (48 mmol/mol)

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; **ADD ONE OR SUBTITUTE WITH ONE OF**

ORAL (continue MF if tolerated)				**INJECTABLES** (if willing to self inject;)
Sulfonylurea* (SU)	**SGLT-2 inhibitors*** - if intolerant to SU, and - If hypoglycaemia is a concern (e.g. Driving, occupational hazards, at risk of falls) and - If weight gain is a concern	**DPP-IV inhibitors*** - if intolerant to SU, and - If hypoglycaemia is a concern (e.g. Driving, occupational hazards, at risk of falls) and - If weight gain is a concern	**Thiazolidinedione*** (TZD) - if intolerant to SU, and - If hypoglycaemia is a concern (e.g. Driving, occupational hazards, at risk of falls), and - If no congestive heart failure or is at higher risk of fracture	**GLP-1 agonists**** - If intolerant to MF or SU, and - If intolerant to TZD or DPP-IV, and - If desire to lose weight **Usually initiated after consultation with specialists**

Review if not reaching target move to 3rd line

Glycaemic Target: HbA1c < 7.5% (59 mmol/mol)

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; **ADD OR SUBSTITUTE WITH ONE OF**

ORAL (continue MF/SU if tolerated)		**INJECTABLES** (if willing to self inject; continue MF/SU if tolerated)	
DPP-IV inhibitors* - If insulin is unacceptable, and - If weight gain is a concern	**Thiazolidinedione*** - If insulin is unacceptable, and - If no congestive heart failure	**GLP-1 agonists**** - If insulin is unacceptable, and - BMI > 35kg/m^2 - If desire to lose weight	**Insulin*** (inject before bed) - Especially if marked hyperglycaemia - If osmotic symptoms or rising HbA1c; NPH insulin initially - If hypoglycaemia is a concern; use basal analogue insulin as an alternative - Add prandial insulin with time if/when required

Usually initiated after consultation with specialists

	Usual recommended approach
	Alternative approach - special considerations recommended in Guidelines
*	Continue medication if either individualised target is achieved OR HbA1c falls ≥ 0.5% / 5.5 mmol/mol in 6 months
**	Continue medication if either individualised target is achieved OR HbA1c falls ≥ 1% / 11 mmol/mol AND weight reduces by ≥ 3% in the first 6 months

.

Dual therapy

The recommended treatment option in adults with T2DM who are inadequately controlled on monotherapy with metformin (see Figure 2), is to start a combined therapy with metformin and a SU. However, for patients intolerant to SU alternative options are recommended:

- Combined therapy of metformin and a SGLT-2-i or a DPP-4-i when hypoglycaemia and weight gain is a concern,
- Combined therapy of metformin and a TZD when hypoglycaemia is a concern and the patient does not suffer from CHF,
- Combined therapy of metformin and a GLP-1 agonist (GLP-1-a) when weight is a concern and patients have a body mass index (BMI) > 35kg/m^2.

As part of its licensed indication, canagliflozin can be used as part of a dual therapy either in a combination with metformin or a SU (note that only its indication as dual therapy in combination with metformin is covered by this submission). The proposed place in the treatment pathway for canagliflozin as dual therapy in combination with metformin, is as an alternative to a SU or other add-on agents.

Triple therapy

The recommended treatment option in adults with T2DM, who are inadequately controlled on dual therapy with a combination of metformin and another AHA (see Figure 2), is to start a combined triple therapy of metformin, a SU and insulin.

However, this recommendation is not favoured in clinical practice as many patients prefer not to start an injectable medication. In addition, insulin is known to cause weight gain and hypoglycaemia and is therefore often unacceptable (because of employment, social, recreational personal issues, or obesity) (64), alternative AHA options are recommended (oral therapies are often preferred):

- A triple therapy of metformin, a SU and a DPP-4-i when hypoglycaemia and weight gain is a concern,
- A triple therapy of metformin, a SU and a TZD when hypoglycaemia is a concern and the patient has heart failure or is at higher risk of fracture,
- A triple therapy of metformin, a SU and a GLP-1-a when weight is a concern and patients have a BMI > 35 kg/m^2, or weight loss would benefit other comorbidities.

The licensed indication of canagliflozin covers its use as triple therapy either in combination with MET+SU or in combination with MET+TZD; both triple combinations are covered by the current submission. The proposed place in therapy for canagliflozin as triple therapy is in T2DM patients inadequately controlled on dual therapy with a combination of metformin and another AHA.

Figure 3. Current clinical pathway for the management of insulin-based therapy for T2DM (61)

ADD-ON TO INSULIN OPTIONS (in addition to lifestyle measures, adherence to medication and dose optimisation)

Insulin* (inject before bed)

- Especially if marked hyperglycaemia
- If osmotic symptoms or rising HbA1c; NPH insulin initially
- If hypoglycaemia is a concern; use basal analogue insulin as an alternative
- Begin with human NPH insulin taken at bedtime or twice daily according to need
- Alternatively, consider a once-daily long-acting insulin analogue (insulin detemir, insulin glargine)
- Consider twice-daily biphasic human insulin (pre-mixed) (particularly if HbA1c ≥ 9.0%)
- Consider pre-mixed preparations of insulin analogues (including short-acting insulin analogues) rather than pre-mixed human

Review if not reaching target

Glycaemic Target: HbA1c < 7.5% (59 mmol/mol)

INTENSIFYINSULIN REGIMEN OR CONSIDER ADDING OTHER DRUGS:

INSULIN INTENSIFICATION (continue MF/SU if tolerated)	**ORAL** (continue MF/SU if tolerated)	
	Thiazolidinedione* (TZD)	**SGLT-2 inhibitors**
- Increase insulin dose and intensify regimen over time. - Monitor those using basal insulin regimens (NPH or a long-acting analogue [insulin detemir, insulin glargine]) for need for short-acting insulin before meals or pre-mixed insulin. - Monitor those using pre-mixed insulin once or twice daily for need for further injection of short-acting insulin before meals or change to mealtime plus basal regimen.	- If a thiazolidenedione has previously had a marked glucose-lowering effect, or - blood glucose control is inadequate with high-dose insulin - Do not start or continue a thiazolidinedione if the person has heart failure or is at higher risk of fracture	- Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes

	Usual recommended approach
	Alternative approach - special considerations recommended in Guidelines
*	Continue medication if either individualised target is achieved OR HbA1c falls ≥ 0.5% / 5.5 mmol/mol in 6 months

Add-on to insulin therapy

The recommended treatment option in adults with T2DM (see Figure 3), when hyperglycaemia remains particularly marked, and when an insulin-based regimen does not maintain HbA1c <7.5% (or other agreed individualised target), is to intensify the insulin regimen with or without another AHA. Two options are available:

- Increase the insulin dose,
- Add another OAD to the insulin-based combination already used:
    - Pioglitazone can be added when a TZD has previously had a marked glucose-lowering effect.
    - Dapagliflozin can be added.

Canagliflozin's licensed indication covers its use as part of an insulin-based therapy with or without OAD. The proposed place in therapy is for canagliflozin to be used as an adjunct to an insulin-based regimen that has failed to maintain blood glucose below the target level.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Maintaining appropriate levels of blood glucose, BP, weight and cholesterol for the longest duration possible, whilst avoiding side effects such as hypoglycaemia are key objectives for most physicians. While the main efficacy of AHAs is to control glycaemia, most agents, through insulin-dependent mechanisms, can lose their effectiveness as pancreatic β-cell function declines. (13) In addition, SUs, the most commonly prescribed AHA as add-on to metformin are known to induce weight gain and hypoglycaemia. Insulin has similar side effects associated with it. New classes of drugs such as the SGLT-2-i, which work via insulin-independent mechanisms, provide a complementary mode of action and may help maintain glycaemic control, delaying disease progression, delaying the use of injectable AHA therapies such as insulins or GLP-1-a, and providing added benefits in terms of weight loss and reduction in BP.

It should also be noted that AHAs vary in their side-effect profiles which also impact patient experience and HRQL.

New therapies for T2DM continue to be needed, given that a key finding from the National Diabetic Audit was that more than 80% of patients are still not managed adequately, with HbA1c, cholesterol and BP outside of their target ranges. (40)

2.7 Please identify the main comparator(s) and justify their selection.

The comparators for canagliflozin that are presented in this submission are detailed in the decision problem. They are the SoC therapies that have been recommended by either UK clinical guidelines or NICE guidance. (36;37;59-61;63)

All comparators covered by the Final Scope have been considered and Table 6 below details for which of these comparators, adequate data is available to allow indirect comparison as part of the economic section. (65)

Table 6. List of comparators

Line of therapy	Final scope	Comparator covered in this submission	Justification	Source
Dual therapy	For the combination of canagliflozin and metformin, the comparators are: • SU (with metformin) • TZD (with metformin) • DPP-4-i (with metformin) • GLP-1-a (with metformin) • Dapagliflozin (with metformin).	All comparators will be covered as part of this submission.	Consistent with NICE Guidelines and the final scope. Efficacy data available through either head-to-head (H2H) trials, literature review allowing a network meta-analysis (NMA) to be conducted when no H2H data were available.	(36;37;60;61)
	For the combination of canagliflozin and SU, the comparators are: • TZD (with a SU) • DPP-4-i (with a SU) • GLP-1-a (with a SU).	Dual therapy in combination with a SU will not be covered as part of this submission.	DIA3008 SU sub-study was designed to examine the efficacy of canagliflozin plus SU over 18 weeks in patients with high CV risk. This combination demonstrated the primary endpoint of HbA1c reduction; however, rate of hypoglycaemia was high. This is expected when subjects are treated with therapies known to be associated with hypoglycaemia such as SUs, as the hypoglycaemia rate would reflect the action of these agents. Furthermore, many patients would be on SU monotherapy due to restriction on the use of metformin patients with Cr/Cl <45 ml/min) and would therefore a proportion would not be eligible for initiation on dual therapy with canagliflozin plus SU. (66)	
Triple therapy	For the combination of canagliflozin, metformin and a SU, the comparators are: • TZD (with MET+SU) • DPP-4-i (with MET+SU U) • GLP-1-a (with MET+SU) • Insulin (with MET+SU)	The comparators considered in this submission for canagliflozin in combination with MET+SU are: • DPP-4-i (with MET+SU) • GLP-1-a (with MET+SU)	A comparison of canagliflozin with TZD or insulin (with MET+SU) will not be conducted as insufficient clinical data were found to populate the NMA, and therefore no indirect estimate of the comparative efficacy of these combinations can be provided.	(36;37;60;61) Section 6.6. relative to NMA

Line of therapy	Final scope	Comparator covered in this submission	Justification	Source
Triple therapy (Con't)	For the combination of canagliflozin, metformin and TZD, the comparators are: • DPP-4-i (with MET+TZD) • GLP-1-a (with MET+TZD) • Insulin (with MET+TZD).	DPP-4-i (with MET+TZD) are the only comparator considered in this submission for canagliflozin in combination with MET+TZD..	A comparison of canagliflozin with GLP-1-a and insulins (with MET+TZD) will not be conducted as insufficient clinical data were found to populate the NMA, and therefore no indirect estimate of the comparative efficacy of these combinations can be provided.	
	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 (OAD) agents).	All comparators were considered as part of the SRL and the NMA. However, it was not possible to conduct any comparative economic evaluation.	[redacted]	(67)
Add-on to insulin	One or more OAD agents (in combination with insulin).	Canagliflozin in combination with insulin with or without metformin, will be compared to: • DPP-4-i (with insulin with or without metformin) • GLP-1-a (with insulin with or without metformin) • Dapagliflozin (with insulin with or without metformin)	Although the use of DPP-4-i and GLP-1-a in combination with insulin are not recommended by NICE or the clinical guidelines, these comparators are used in UK clinical practice. There are no efficacy data currently available to allow an indirect comparison with TZD which are recommended as part of the clinical guidelines. This comparison will therefore not be covered by this submission.	(36;37;67) Section 6.6. relative to NMA

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

As highlighted in section 1.2, UTIs and GMIs are considered to be the most clinically important AEs associated with canagliflozin. The management of these AEs is covered by existing clinical guidelines:

- GMIs: The NHS recommends that in case of balanitis due to a fungal infection, an antifungal cream or an antifungal medication such as fluconazole should be prescribed. In women experiencing acute vulvo-vaginal candidiasis, topical treatment with an oral antifungal such as clotrimazole is recommended. (68;69)

- UTIs: A lower UTI and a mild-to-moderate upper UTI infection can usually be treated at home using antibiotics. If an upper UTI is more serious, hospital treatment might be required. Antibiotics such as co-amoxiclav or ciprofloxacin are usually prescribed for 7 to 14 days (depending on the risk of developing complications). (70)

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As canagliflozin is an oral therapy, there are no anticipated costs due to location of care, staff and administration. Patient monitoring is expected to follow largely the same schedule and in the same setting as for patients treated with other AHAs, including the monitoring of change in eGFR in T2DM patients. (38)

However a clinician advisory board indicated that there may be a small amount of additional resource use required to assess and manage patients with UTIs or GMIs:

- For GMIs, this amounts to one General Practice (GP) visit for male patients, but none for female patients who can obtain topical and oral azole therapies over the counter.

- For UTIs, this amounts to two GP appointments for male patients and one for female patient.

2.10 Does the technology require additional infrastructure to be put in place?

Not applicable

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 **Please let us know if you think that this appraisal:**

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Canagliflozin is expected to be used across the broad population of T2DM patients, and therefore no equality issues are expected.

3.1.2 **How has the analysis addressed these issues?**

Not applicable

4 Innovation

4.1.1 **Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.**

Canagliflozin is an innovative product due to its insulin-independent mode of action which shows some evidence of β-cell protection.

In addition, SGLT-2-i such as canagliflozin possess limited inherent risk of hypoglycaemia due to their capacity to reduce the RTg to approximately 5mmol/L, but typically not lower. (14) Hypoglycaemia is generally a concern when glucose levels fall below 4mmol/L. (71)

BP and weight management present challenges when treating T2DM. The additional efficacy benefits (i.e. of glycaemic control plus weight loss, and BP reduction) associated with canagliflozin makes it suitable when considering an holistic view for managing T2DM patients with multiple co-morbidities.

Furthermore, canagliflozin 300mg has demonstrated some degree of local inhibition of intestinal SGLT1 as a result of transient high concentrations in the intestinal lumen prior to medicinal product absorption. This helps limit the postprandial excursion of glucose from the meal digestion at which canagliflozin is taken, without evidence of GI side effects. This SGLT1 effect is new for this class of agent and is currently under further investigation. (19)

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Not applicable

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Table 7. Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	**Dual therapy** Adults with T2DM that are inadequately controlled on monotherapy with either metformin or a SU.	**Dual therapy** Adults with T2DM that are inadequately controlled with metformin.	**Dual therapy** Adults with T2DM that are inadequately controlled with a SU will not be considered. Although the results from the DIA3008 SU sub-study trial are positive the rate of hypoglycaemia events using a combination of canagliflozin + SU are relatively high, and are seen as limiting when due to the need to control hypoglycaemia in T2DM. This is expected when subjects receive therapies known to be associated with hypoglycaemia such as SUs or insulin, as the hypoglycaemia rate would reflect the action of these agents. Furthermore, due to restriction of use of metformin in T2DM patients with impaired renal function, a high proportion of patients on a SU-based dual therapy would not be eligible for treatment initiation with canagliflozin.
	Triple therapy Adults with T2DM that are inadequately controlled on dual therapy with either of the following: • MET+SU. • Metformin **or** a SU in combination with a TZD, a DPP-4-i, or a GLP-1-a.	**Triple therapy** Adults with T2DM that are inadequately controlled on dual therapy with either: • MET+ SU. • MET+TZD.	**Triple therapy** Combination of canagliflozin with metformin and a DPP-4i or a GLP-1-a will not be considered. [redacted]
	Add-on therapy to insulin Adults with T2DM that are inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.	**Add-on therapy to insulin** Adults with T2DM that are inadequately controlled on monotherapy with insulin + SoC.	No change
Intervention	Canagliflozin (in combination with OADs and/or insulin)	Canagliflozin 100mg or 300mg once daily (in combination with OAD agents and/or insulin)	No change

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Comparator(s)	**Dual therapy** For the combination of canagliflozin and metformin, the comparators are: • SU (with metformin) • TZD (with metformin) • DPP-4-i (with metformin) • GLP-1-a (with metformin) • Dapagliflozin (with metformin). For the combination of canagliflozin and SU, the comparators are: • TZD (with a SU) • DPP-4-i (with a SU) • GLP-1-a (with a SU).	**Dual therapy** For the combination of canagliflozin and metformin, the comparators are: • SU (with metformin) • TZD (with metformin) • DPP-4-i (with metformin) • GLP-1-a (with metformin) • Dapagliflozin (with metformin).	**Dual therapy** A comparison of the combination of canagliflozin and SU with TZD and SU, DPP-4-i and SU, and GLP-1-a and SU will not be presented due to the reasons stated above in *Population*.
	Triple therapy For the combination of canagliflozin, metformin and a SU, the comparators are: • TZD (with MET+SU) • DPP-4-i (with MET+SU) • GLP-1-a (with MET+SU) • Insulin (with MET+SU) For the combination of canagliflozin, MET+TZD, the comparators are: • DPP-4-i (with MET+TZD) • GLP-1-a (with MET+TZD) • insulin (with MET+TZD). For the use of canagliflozin in any other triple therapy regimen, the comparator is: • Insulin (alone or in combination with one or more OAD agents).	**Triple therapy** For the combination of canagliflozin, metformin and a SU, the comparators are: • DPP-4-i (with MET+SU) • GLP-1-a (with MET+SU) • Insulin (with MET+SU) For the combination of canagliflozin, MET+TZD, the comparator is: • DPP-4-i (with MET+TZD)	**Triple therapy** A comparison of the combination of canagliflozin, metformin and a SU with pioglitazone or insulin (with MET+SU) will not be conducted as insufficient clinical data were found to populate the NMA, and therefore no indirect estimate of the comparative efficacy of these combinations can be provided. For the comparison of canagliflozin, MET+TZD, GLP-1-a and insulins will not be used as comparator, due to insufficient clinical data to populate the NMA, and therefore no indirect estimate of the comparative efficacy of these combinations can be provided The use of canagliflozin in any other triple therapy regimen will not be assessed, for reasons stated above in *Population*.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Comparator(s)	**Add-on therapy to insulin** • One or more OAD agents (in combination with insulin).	**Add-on therapy to insulin** Canagliflozin in combination with insulin with or without metformin, will be compared to: • DPP-4-i (with insulin with or without metformin) • GLP-1-a (with insulin with or without metformin) • Dapagliflozin (with insulin with or without metformin)	**Add-on therapy to insulin** Although use of DPP-4-i and GLP-1-a in combination with insulin are not recommended by NICE or the clinical guidelines, these comparators are used in clinical practice. There are no efficacy data currently available to allow an indirect comparison with TZD which are recommended as part of the clinical guidelines. This comparison will therefore not be covered by this submission.
Outcomes	The outcome measures that have been considered include: • HbA1c control • Frequency and severity of episodes of hypoglycaemia • Change in CV risk factors (including BP and serum lipids) • Weight change • Complications of diabetes (for example, CV, renal and eye) • Mortality • Adverse effects of treatment (including GMI and UTI) • HRQL.	The outcome measures that have been considered include: • HbA1c control • frequency and severity of episodes of hypoglycaemia • Change in CV risk factors (including BP and serum lipids) • Weight change • Complications of diabetes (for example, CV, renal and eye) • Mortality • Adverse effects of treatment (including GMI and UTI) • HRQL.	No change
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. A time horizon of 40 years will be used to estimate clinical and cost-effectiveness in the base case. A shorter time horizon will	No change

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	also be assessed in sensitivity analyses. Costs will be considered from an NHS and Personal Social Services perspective.	
Sub-groups to be considered	If evidence allows, sub-groups based on the following criteria will be considered: • BMI • baseline HbA1c	Sensitivity analyses will be conducted for patient with baseline HbA1c≥9% as pre-defined in some of the trials.	Sub-group analyses for BMI will not be conducted as the efficacy of canagliflozin in terms of change in HbA1c and secondary endpoints was not impacted by baseline BMI levels. It should also be noted that the economic model used in this submission (ECHO-T2DM) while being sensitive to change in BMI over time, does not differentiate between patients based on their baseline BMI level.
Special considerations, including issues related to equity or equality	(None stated)	None	No change

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Please note that a considerable amount of data has been extracted to the appendices from this section to ensure that the section is easily readable and contains the most pertinent information. All tables requested by NICE in Section 6 have been included, although many will be found in Appendix 2 (Search strategy for section 6.1.), Appendix 3 (complete list of studies for section 6.2.5), Appendix 4 (description of RCT methodology for section 6.3.), Appendix 5 (Quality assessment of RCT(s) –section 6.4), Appendix 6 (tables relative to results of the relevant trials for section 6.5.), Appendix 7(Meta-analysis for Section 6.6.), and Appendix 8 (Adverse events -Section 6.9.).

6.1 Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.**

A systematic literature review has been carried out to identify all RCTs comparing canagliflozin as part of an add-on to metformin, MET+SU, MET+TZD or Insulin + OAD regimen vs. relevant comparators in adult patients with T2DM. Exact details of the search strategies are provided in Appendix 2.

A comprehensive literature search of the following electronic databases has been conducted:

- MEDLINE® (including MEDLINE® In-Process)
- Excerpta Medica Database (EMBASE®)
- Cochrane Central Register of Controlled Trials (CENTRAL)

MEDLINE and EMBASE were searched using the Embase.com interface. MEDLINE® In-process was searched using the Pubmed.com interface. CENTRAL was searched using the Cochrane library interface.

Databases were searched on the following dates (See Table 8).

Table 8. Search of electronic databases

Database	Service provider	Date of the search	Time span of the search
MEDLINE	Ovid	February 20, 2013, updated August 5, 2013	1949 - August 5, 2013
MEDLINE-IN-PROCESS	Ovid	February 20, 2013, updated August 5, 2013	Until August 5, 2013
EMBASE	Ovid	February 20, 2013, updated August 5, 2013	1947- August 5, 2013
The Cochrane CENTRAL Register	The Cochrane library	February 20, 2013, updated August 7, 2013	Until August 7, 2013

The following conference proceedings/publications and HTA sites were searched from 1st January 2010 onwards (as studies were assumed to be published within three years of a presentation at a congress):

- ADA (American Diabetes Association) scientific sessions
- IDF (International Diabetes Federation) - World diabetes congress
- CoDHY (Consensus in Diabetes, Obesity, and Hypertension)
- DUK (Diabetes UK)
- PDMS (Prediabetes and the Metabolic Syndrome Congress)
- PCDS (Primary Care Diabetes Society)
- ABCD (Association of British Clinical Diabetologists)
- EASD (European Association for the Study of Diabetes) annual meetings
- ClinicalTrial.gov
- National Institute for Health and Clinical Excellence (NICE), England
- Scottish Medicines Consortium (SMC), Scotland
- All Wales Medicines Strategy Group (AWMSG), Wales

Search terms were combined to capture three components of the study question: the disease of interest (T2DM), the interventions of interest and the study type of interest. Included in the review, were RCTs that had to meet pre-defined eligibility criteria related to the population characteristics, interventions, outcomes measures, relevant comparators, publication type (full-text publication/poster to be included), and the language of publication (English). In addition studies shorter than 12 weeks were excluded based on clinical expert opinion, as this is the minimum time thought to observe valid changes for the primary endpoint HbA1c (essentially a measure of average glucose of the past 2.5-3 months). The full inclusion criteria are listed in Section 6.2.

Implementation and reporting of the systematic review followed the recommendations and standards required by NICE and the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement.

Citations were first screened based on the title and abstract by a first reviewer according to the pre-specified inclusion/exclusion. A second reviewer quality checked the assessment and any discrepancies were resolved by discussion or by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this stage. Duplicates of citations (due to overlap in the coverage of the

databases) were also excluded and full-text copies of all references that could potentially meet the eligibility criteria were ordered at this stage.

Following this the eligibility criteria were applied to full-text citations. Data presented in the studies included at this stage were extracted in parallel by one reviewer, a second reviewer then performed the quality check on 20% of the publications. In addition, all data included in the meta-analysis were checked by a second analyst. Where more than one publication describing a single trial was identified, the data was compiled into a single entry in the data extraction table to avoid double counting of patients.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table 9. Eligibility criteria used in search strategy

	Clinical effectiveness	Rationale
Inclusion criteria	1. RCTs;	The review includes RCTs, as these are the gold standard of clinical evidence, minimising the risk of confounding factors besides allowing a comparison of the efficacy of the interventions
	2. In the treatment of inadequately controlled T2DM;	The population has been restricted to match the stated decision problem for the treatment of T2DM.
	3. At least one treatment of interest;	The interventions have been restricted to provide an indirect comparison between the canagliflozin and the comparators listed in the NICE scope.
	4. Study duration of 12 weeks or more.	The studies identified should at least be of 12 weeks duration to allow potential indirect comparison with canagliflozin.
	5. Outcomes: • HbA1c • FPG • BP • Body weight / BMI • Incidence of hypoglycaemia	These outcomes were chosen as these are frequently measured and reported in the trials involving T2DM patients; and are relevant to the interventions considered in this SLR and the scope.
Exclusion criteria	1. Studies in: • children, • animals or in vitro studies, • Dose ranging and Phase 1 studies	These studies were excluded as they are not relevant to the decision problem.
	2. Other type of studies: • Comparative observational • Editorial, letter, or comment • Case control studies • Cohort studies • Registries	These studies were not included as they are generally smaller, non-comparative studies. Other comparative studies which were not RCTs were also excluded due to the risk of confounding factors.
	3. Studies on other OAD which were not listed in NICE Scope	The interventions have been restricted to provide an indirect comparison between canagliflozin and the comparators listed in the NICE scope.
	4. Studies not in English	The restriction would not limit results substantially due to data availability in English language.

6.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.**

The search of literature databases and conference abstracts yielded 19,176 separate reference citations. Due to the overlap of coverage between the databases, 7,477 citations were found to be duplicates, leaving a total of 11,699 citations. Following screening of these citations, 648 potentially relevant references were identified and 11,051 were disregarded for various reasons (see Appendix 2). Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the 648 references, 440 references were disregarded as they did not meet the inclusion criteria, leaving 208 citations for data extraction and use in the SRL (also called narrative review. (72)

6.2.3 **When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

Table 10. List of relevant included RCTs related to Canagliflozin

Study	Primary study	Linked publications from |Janssen internal database	Linked publications from conference proceedings
DIA3009	Cefalu et al. The Lancet 2013 (2)	Clinical Study report (CSR) - JNJ-28431754 DIA3009 - 52-Week Core Double-Blind Period (2012) (73) CSR - JNJ-28431754 DIA3009 - 104-Week extension Double-Blind phase (2013) (74)	Niskanen et al. EASD 2012 (75) Toubro et al. EASD 2012 (76) Niskanen et al. CODhy 2012 (77) Toubro et al. CODhy 2012 (78) Cefalu et al. ADA 2012 (79) Cefalu et al. ADA 2013 (80)
DIA3006	Lavalle-Gonzalez et al. Diabetologia 2013 (6)	CSR - JNJ-28431754 DIA3006 - 26-Week Core Double-Blind Period (2012) (81) - 52-Week extension Double-Blind Period (2012) (82)	Lavalle-Gonzalez et al. ADA 2013 (83)
DIA3008 SU sub-study	N/P	CSR - JNJ-28431754 DIA3008 SU sub-study - 18-Week Core Double-Blind Period (2012) (84)	Fulcher et al. ADA 2013 (27)
DIA3015	Schernthaner et al. Diabetes Care 2013 (7)	CSR - JNJ-28431754 DIA3015 - 52-Week Core Double-Blind Period (2012) (85)	Schernthaner et al. CODhy 2012 (86) Gross et al. ADA 2012 (87) Schernthaner et al. EASD 2013 (88)
DIA3002	N/P	CSR - JNJ-28431754 DIA3002 - 26-Week Core Double-Blind Period (2012) (89) - 52-Week Extension Double-Blind Period (2013) (90)	Wilding et al. CODhy 2012 (91) Wilding et al. EASD 2012 (28) Wilding et al. ADA 2012 (28) Vercruysse et al. EASD 2013 (92)
DIA3012	N/P	CSR - JNJ-28431754 DIA3012 - 26-Week Core Double-Blind Period (2012) (93) - 52-Week Extension Double-Blind Period (2013) (94)	Forst et al. CODhy 2012 (95) Forst et al. ADA 2013 (29)
DIA3008 Insulin sub-study	N/P	CSR - JNJ-28431754 DIA3008 insulin sub-study - 18-Week Core Double-Blind Period (2012) (84)	Matthews et al. EASD 2012 (30) Rosenstock et al. ADA 2013 (96)
DIA3010 - Older patient study	Bode et al. Hospital Practice 2013 (32)	N/R	Bode et al. EASD 2012 (31) Toubro et al. EASD 2012 (76) Toubro et al. CODhy 2012 (78)
DIA3004 - Renal Impairment study	Yale et al. Diabetes Obes Metab 2013 (34)	N/R	Yale et al. EASD 2012 (33) Woo et al. CODhy 2012 (97) Yale et al. ADA 2012 (98) Yale et al. ADA 2013 (99) Woo et al. ADA 2013 (100) Nieto et al. EASD 2013 (101)
DIA3014 – Asian study	N/P	CSR - JNJ-28431754 DIA3014 - 18-Week Core Double-Blind Period (2018) (35)	N/P
DIA3008	Neal et al. Am Heart J 2013 (9)	N/R	Wysham et al. Poster presented at ADA 2013 (102)

Legend: N/P: not published; N/R: not relevant to the decision problem

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Canagliflozin has been studied in the largest pre-licence Phase 3 programme for T2DM to date, with over 10,000 subjects enrolled in multiple centres across the globe (including the UK) and over 8,000 subject/years of exposure on canagliflozin. There are 12 potentially relevant Phase 3 RCTs (including two sub-studies of trial DIA3008).

Monotherapy

One of these twelve studies evaluated canagliflozin as a monotherapy (DIA3005).(18) It should be noted that the SRL did not cover studies related to use of OAD as monotherapy as they are considered as not relevant to the decision problem.

Dual therapy

Three studies are in dual therapy, two of which are on a background of metformin and one of which is on a background of SU.

- DIA3009 (NCT00968812): canagliflozin 300mg and 100mg versus SU (glimepiride) on a background of metformin. (2)
- DIA3006 (NCT01106677): canagliflozin 300mg and 100mg versus placebo or sitagliptin on a background of metformin. (6)
- DIA3008 SU sub-study (NCT01032629): canagliflozin 300mg and 100mg versus placebo. (27)

Triple therapy

Three studies are in triple therapy, two of which are on a background of metformin plus SU and one of which is on a background of MET+TZD.

- DIA3015 (NCT01137812): canagliflozin 300 mg versus sitagliptin 100 mg on a background of MET+SU. (7)
- DIA3002 (NCT01106625): canagliflozin 300 mg and 100 mg versus placebo on a background of MET+SU. (28;91)
- DIA3012 (NCT01106690): canagliflozin 300mg and 100mg versus placebo/sitagliptin on a background of MET+TZD. (29;95)

Add-on to insulin therapy

One study is as add-on to insulin (with or without OAD).

- DIA3008 insulin sub-study (NCT01032629): canagliflozin 300mg and 100mg versus placebo on a background of Insulin + SoC. (30;96)

Four more studies have evaluated canagliflozin in various patient populations: DIA3010 was conducted in older T2DM patients (32), DIA3004 was conducted in T2DM patients with moderate renal impairment (34), DIA3014 was conducted in T2DM Asian patients (35) and DIA3008 was conducted in T2DM patients at high risk for CVD(9).

A table detailing the list of relevant RCTs can be found in Table 1 of Appendix 4. Note that this table does not include any information regarding study DIA3005 (use of canagliflozin as monotherapy), leaving a total of 11 studies to evaluate.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

As presented in table 6 of Appendix 3, 11 studies (including two sub-studies of trial DIA3008) comparing canagliflozin with a relevant comparator were identified. Within these 11 studies, canagliflozin was compared to sitagliptin, SU and placebo as illustrated below.

<u>Comparison with sitagliptin</u>
- Dual therapy as add-on to metformin: DIA3006
- Triple therapy as add-on to MET+SU: DIA3015

<u>Comparison with SU</u>
- Dual therapy as add-on to metformin: DIA3009

<u>Comparison with placebo</u>
- Dual therapy as add-on to metformin: DIA3006
- Dual therapy as add-on to SU: DIA3008 SU sub-study
- Triple therapy as add-on to MET+SU: DIA3002
- Triple therapy as add-on to MET+TZD: DIA3012
- Add-on to insulin: DIA3008 insulin sub-study
- Older patients: DIA3010 (all lines of therapy)
- Renal impaired patients: DIA3004 (all line of therapy)
- Asian T2DM patients: DIA3014
- All T2DM patients with an elevated risk of CV disease: DIA3008

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

A number of the phase 3 studies are not considered in detail in this submission for the reasons given below:

<u>DIA3008 SU sub-study - Dual therapy with canagliflozin+SU vs. placebo+SU (27)</u>

NICE guideline 87 (The management of T2DM) recommends metformin as the preferred first-line treatment. (37) However, a proportion of patients receive SU first-line because metformin is contra-indicated in patients with renal impairment (CrCL < 60 ml/min). The canagliflozin SmPC does not recommend starting patients whose CrCL < 60mls/min on canagliflozin therefore this population of patients on SU monotherapy would not be eligible for canagliflozin treatment. (Appendix 1).

DIA3010 Study in older subjects – all lines of therapies (31;32)

Data from this study is excluded as the background therapy could include any approved oral or injectable treatment. Patients were randomised to the addition of placebo or canagliflozin (100mg or 300mg) to their existing treatment and the results were not provided by line of therapy.

DIA3004 Study in patients with renal impairment (33;34)

Data from this study is excluded as the background therapy could include any approved oral or injectable treatment. Patients were randomised to the addition of placebo or canagliflozin (100mg or 300mg) to their existing treatment and the results were not provided by line of therapy. Furthermore, these patients had a stage 3 chronic kidney disease (CKD, eGFR ≥30 and <50 ml/min/1.73 m^2), outside of the expected license for canagliflozin. (25)

DIA3014 Asian study (35)

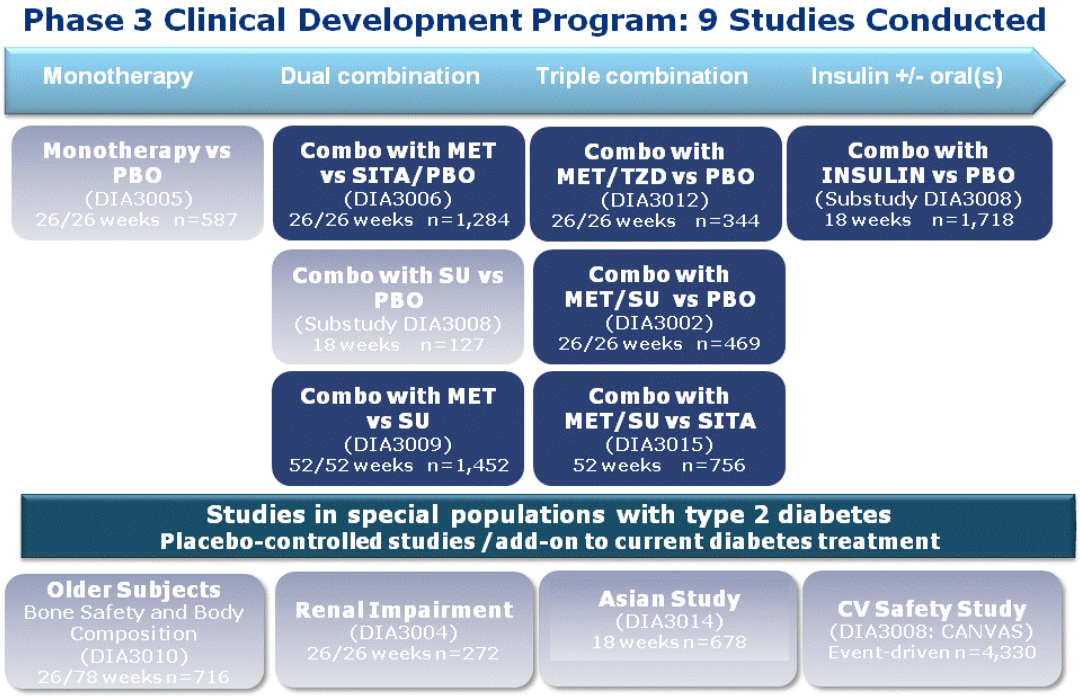
This study included T2DM patients with all lines of therapy and no sub-analyses by background regimen was conducted. Furthermore, the duration of the double-blind period was relatively short in duration at only 18 weeks.

DIA3008 CV safety study - CANVAS (9)

CANVAS is a safety study carried out in 4,330 patients which will report in 2017. DIA3008 will not report on efficacy with the exception of two 18-week sub-studies. One sub-study considered dual therapy with SU plus canagliflozin versus placebo and has been excluded from this submission (see above rationale in Table 7 of Section 5). The other DIA3008 sub-study considered insulin therapy plus canagliflozin versus insulin therapy plus placebo. The add-on to insulin sub-study was carried out over 18 weeks and efficacy data is available in poster format. This sub-study was included in the submission. (30;96)

The list of trials that will be detailed as part of this submission is presented in Figure 4 (see studies indicated as darker boxes).

Figure 4. Phase 3 clinical development programme for canagliflozin, studies included in this NICE submission (indicated as navy boxes).



Legend: PBO: Placebo, MET: Metformin, SITA: Sitagliptin, SU: Sulphonylurea, TZD: Thiazolidinedione, CANVAS: *Canagliflozin Cardiovascular Assessment Study.*

6.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

There are no relevant non-RCTs.

6.3 Summary of methodology of relevant RCTs

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

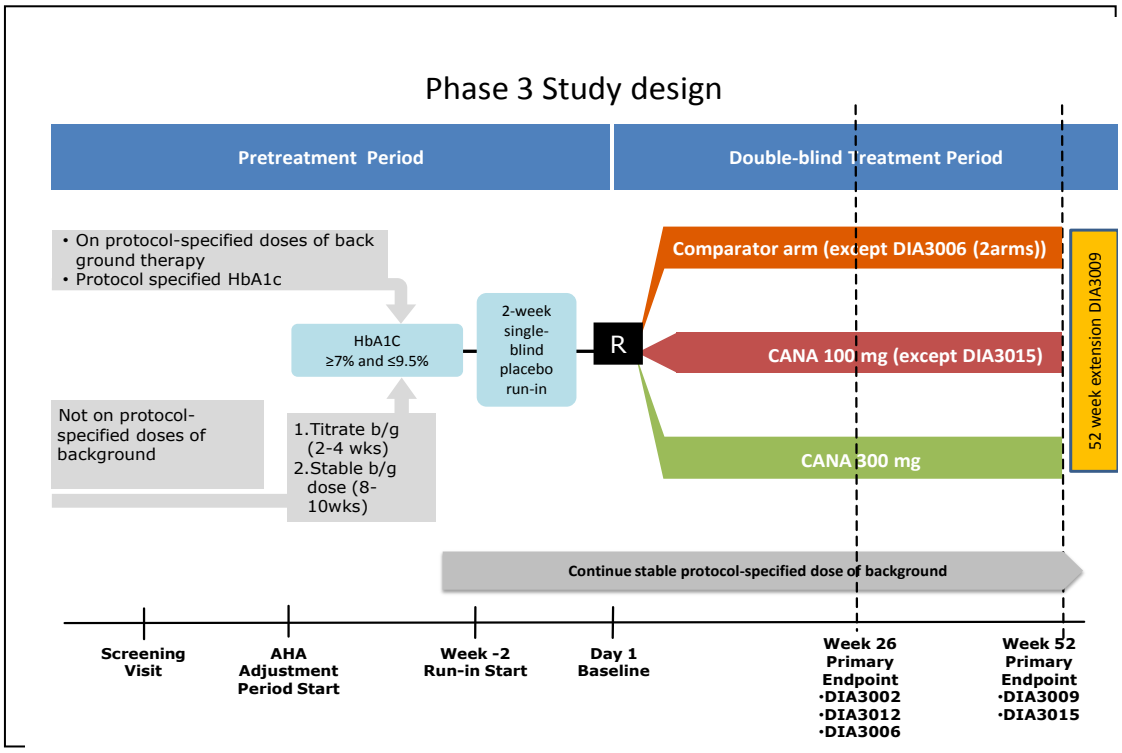
All studies included in this submission, except for DIA3008 insulin sub-study, follow the same broad study design and the same primary end-point. Therefore, study designs for DIA3006, DIA3009, DIA3012, DIA3002 and DIA3015 will be presented together (see Figure 5).

Table 2 of Appendix 4 illustrates the study methodology for the dual therapy studies (DIA3006 and DIA3009), Table 3 illustrates the study methodology for the triple therapy studies (DIA3012, DIA3002 and DIA3015) and Table 4 for the insulin sub-study (DIA3008 insulin sub-study).

Dual therapy and triple therapy studies

Studies DIA3009, DIA3006, DIA3015, DIA3002 and DIA3012 randomised patients uncontrolled on baseline therapy (one or two baseline therapies) to the addition of treatment with canagliflozin, active comparator, placebo or both. The studies all consisted of a pre-treatment period, a core double-blind treatment period and in all cases, except DIA3015, an extension period.

Figure 5. Schematic of study design for canagliflozin Phase 3 studies in dual and triple therapy



D

treatment was titrated and stabilised to the dose specified in the protocol. This was followed by a 2-week single-blind placebo run-in period. At randomisation patients

entered the canagliflozin arm (100mg or 300mg) and the control arm (placebo and/or active treatment) for the double-blind treatment period. At the end of this period the primary efficacy end-point (change in HbA1c from baseline to end of the double-blind treatment period) was determined. Patients continued in the study for an extension period of varying duration.

Diagrams of the design for each study are shown in Figures 1 to 6 in Section 10.4.2 (Appendix 4).

The main differences in the studies are in terms of the comparator and length of the study period and their background therapy:

- Comparator:
    - DIA3006 has both placebo and active (sitagliptin) control arms. Placebo comparison was made after the first 26-week core period of the study, patients in the placebo arm then crossed-over to sitagliptin to maintain the blind on the control for 52 weeks. However no further analyses were conducted on this arm after week 26. The active control arm of sitagliptin 100mg was assessed only at 52 weeks for non-inferiority.
    - DIA3009 and DIA3015 trials are active (SU and sitagliptin respectively) controlled.
    - DIA3012 and DIA3002 trials are placebo-controlled.
    - DIA3012 trial is placebo-controlled during the first 26-week core period of the study and assessment was done at this point. Patients in the placebo arm then cross-over to sitagliptin after 26 weeks to maintain a control arm for 52 weeks. However, no further assessment vs. the comparator is conducted.
- Length of the study period: DIA3006, DIA3012 and DIA3002 trials have a 26-week double-blind period followed up by a 26-week extension period (26/26), DIA3009 has a 52-week double-blind period followed up by a 52-week extension period (52/52) and DIA3015 has a 52-week double-blind period without an extension period (see Figure 5).
- There are slight differences in the secondary end-points, although all studies share the same primary end-point.

<u>DIA3008 (CANVAS) insulin sub-study- Add-on to insulin study</u>

The study comparing the addition of canagliflozin to placebo added to INS+SoC had a different study design to the studies outlined above. DIA3008 insulin sub-study is a prospective sub-study of the much larger CANVAS study. All patients enrolled into CANVAS had a history of CVD or were at high risk of CV disease. (30;96)

Patients enrolled into CANVAS were either not on anti-diabetic treatment or on monotherapy or combination with any approved treatment, including insulin. The patients included in the insulin sub-study were on insulin alone or INS+SoC. The dose of insulin was 30 IU/day or higher in patients included in the sub-study.(30;96) The DIA3008 insulin sub-study was 18 weeks in duration, although patients continue to be followed as per the specification of the overall CANVAS study.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

We have presented the dual therapy, triple therapy and add-on to insulin studies as three separate tables due to differences in study population by treatment line (see Table 11 and Table 12). In the tables relevant to dual therapy as add-on to metformin, and triple therapy as add-on to metformin and SU, common eligibility criteria between studies are listed first, followed by the criteria which differ between trials.

Table 11. Eligibility criteria in the RCTs – dual therapy

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Dual therapy: patients on baseline metformin		
Common criteria	• Man or woman ≥18 and ≤80 years of age with T2DM	• History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy • Repeated FPG and/or fasting SMBG glucose measurements ≥270 mg/dL (15 mmol/L) during the pre-treatment phase • Myocardial infarction, unstable angina, revascularization procedure, or cerebro-vascular accident within 3 months before screening, or planned revascularization procedure i, or subject has a history of New York Heart Association (NYHA) Class III-IV cardiac disease • Serum creatinine ≥1.4 mg/dL (124 µmol/L) for men and ≥1.3 mg/dL (115 µmol/L) for - women; or eGFR <55 mL/min/1.73m^2 (or <60 mL/min/1.73m^2 if based upon restriction of metformin use in the metformin local label)
CANTATA-SU Trial NCT00968812 (DIA3009)	Different criteria • On metformin monotherapy at stable protocol-specified doses a for at least 12 weeks prior to screening, with an HbA1c of ≥7% and ≤9.5% at screening • On metformin monotherapy at a dose <2,000 mg/day with an HbA1c of ≥7.5% and ≤10% at screening and an HbA1c of ≥7.0% and ≤9.5% after at least 10 weeks on a stable protocol-specified dose of metformin • On metformin at a stable protocol specified dose in combination with one other oral non-thiazolidinedione (TZD) AHA with an HbA1c of ≥6.5% and ≤9.0% at screening and has a Week -2 visit HbA1c of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose* of metformin at least 10 weeks • On metformin at a dose <2,000 mg/day in combination with one other oral non-TZD AHA with an HbA1c of ≥6.5% and ≤9.0% at screening and had a Week -2 visit HbA1c of ≥7.0% and ≤9.5%, after discontinuing the AHA and on a stable protocol-specified dose* of metformin at least 10 weeks	Different criteria • History of >1 severe hypoglycaemic episode, defined as an episode that requires the help of another person, or resulting in seizure, or loss of consciousness, within 6 months before screening. • History of an ongoing eating disorder or significant weight loss or weight gain, defined as an increase or decrease of 5% in body weight (based on subject report) within 3 months before screening • History of prior bariatric surgical procedures • Alanine aminotransferase level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening • Have taken TZD therapy in the past 16 weeks before screening

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CANTATA-D Trial NCT01106677 (DIA3006)	Different criteria • On metformin IR monotherapy at a stable protocol-specified dose* for at least 8 weeks before screening and had an HbA1c of ≥7.0% and ≤10.5% at screening • On metformin XR monotherapy at a protocol-specified dose* with an HbA1c of ≥7.0% and ≤10.5% at screening • On metformin monotherapy (IR or XR) at a dose <2,000 mg/day with an HbA1c of ≥7.0% and ≤11.0% at screening • On metformin (IR or XR) in combination with an SU with an HbA1c of ≥6.5% and ≤9.5% at screening • With an HbA1c of ≥7.0% and ≤10.5% at week -2 • FPG <270 mg/dL (15 mmol/L) at Week -2. • Centre fasting fingerstick glucose of ≥110 mg/dL (6.1 mmol/L) and <270 mg/dL (15 mmol/L) on Day 1	Different criteria • On either a thiazolidinedione (pioglitazone or rosiglitazone), ongoing insulin therapy, another SGLT-2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine within 12 weeks before the screening visit • Findings on 12-lead ECG that required urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance) • Uncontrolled hypertension at Week -2
DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D)		

Table 12. Eligibility criteria in the RCTs – triple therapy and add-on to insulin therapy

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Triple therapy: patients on baseline metformin plus SU		
Common criteria	• Man or woman ≥18 and ≤80 years of age with T2DM • On metformin and an SU at protocol-specified doses for at least 8 weeks prior to screening, with an HbA1c of ≥7.5% and ≤10.5% at screening On metformin and an SU, either or both at doses below protocol-specified, with an HbA1c of ≥7.5% at screening and of and HbA1c of ≥7.0% and ≤10.5% at Week -2	• History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy • Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or planned revascularization procedure i, or subject has a history of New York Heart Association (NYHA) Class III-IV cardiac disease • Serum creatinine ≥1.4 mg/dL (124 µmol/L) for men and ≥1.3 mg/dL (115 µmol/L) for - women; or eGFR <55 mL/min/1.73m^2 (or <60 mL/min/1.73m^2 if based upon restriction of metformin use in the metformin local label) • Uncontrolled hypertension at Week -2 • Findings on 12-lead ECG that required urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)
CANTATA-D2 Trial NCT01137812 (DIA3015) Met+SU+	N/A	Different criteria • Repeated FPG and/or fasting SMBG glucose measurements ≥300 mg/dL (15 mmol/L) during the pre-treatment phase. Note ≥270 mg/dL (16.75 mmol/L) in all other studies. • On either a thiazolidinedione (pioglitazone or rosiglitazone), ongoing insulin therapy, another SGLT-2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine within 12 weeks before the screening visit
CANTATA-MSU Trial NCT01106625 (DIA3002)	N/A	Different criteria • Treatment with either a PPARγ agonist, ongoing insulin therapy, another SGLT2-i, or any other AHA (other than specified in inclusion criteria) within 12 weeks before screening
Triple therapy: patients on baseline metformin plus pioglitazone		
CANTATA-MP Trial NCT01106690 (DIA3012)	• Man or woman ≥18 and ≤80 years of age with T2DM • FPG <270 mg/dL (15 mmol/L) at Week -2	• History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CANTATA-MP Trial NCT01106690 (DIA3012)	• Fasting fingerstick glucose of ≥110 mg/dL (6.1 mmol/L) and <270 mg/dL (15 mmol/L) on Day 1 • On either a dual combination of metformin and pioglitazone, a dual combination of metformin and a TZD (pioglitazone or rosiglitazone), a dual combination of a TZD and another oral AHA , or a triple combination of metformin, a TZD and an SU (or meglitinide) or a DPP-4-i • With an HbA1c of ≥7.5% and ≤10.5% at screening (stable doses for at least 8 weeks prior to screening), and/or HbA1c of ≥7.0% and ≤10.5% at Week -2, after at least 8 weeks on stable protocol-specified doses of metformin and pioglitazone	• Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or planned revascularization procedure i, or subject has a history of New York Heart Association (NYHA) Class III-IV cardiac disease • Serum creatinine ≥1.4 mg/dL (124 µmol/L) for men and ≥1.3 mg/dL (115 µmol/L) for - women; or eGFR <55 mL/min/1.73m^2 (or <60 mL/min/1.73m^2 if based upon restriction of metformin use in the metformin local label) • Uncontrolled hypertension at Week -2 • Alanine aminotransferase level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening • Ongoing eating disorder or significant weight loss or weight gain (±5%) within 12 weeks • Contraindication to the use of metformin or pioglitazone or sitagliptin
Add-on to insulin therapy: Patients on insulin ± OAD		
CANVAS Add-on to insulin sub-study NCT01032629 (DIA3008)	• Man or woman ≥18 and ≤80 years of age with T2DM • HbA1c level ≥7.0% to ≤10.5% at screening and be either not on AHA therapy or on AHA monotherapy or combination therapy with any approved agent; e.g., sulphonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1-a, dipeptidyl peptidase-4 inhibitor, or insulin at screening • History or high risk of CV disease	• History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy • Serum creatinine ≥1.4 mg/dL (124 µmol/L) for men and ≥1.3 mg/dL (115 µmol/L) for women • Alanine aminotransferase level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening • Fasting fingerstick glucose of ≥270 mg/dL (15 mmol/L) on Day 1 (and for subjects on a sulphonylurea agent or on insulin: fasting fingerstick glucose <110 mg/dL (<6 mmol/L) on Day 1) • On an AHA and not on a stable regimen for at least 8 weeks before the screening visit and through the screening/run-in period • eGFR <30 mL/min/1.73m^2 at screening

DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU); DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP); DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study (CANVAS insulin sub-study);

6.3.4 **Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.**

We have presented the patient characteristics of the RCTs in dual, triple and add-on to insulin therapy in three separate tables (see Tables 10 to 12 in Section 10.4.3. - Appendix 4).

Overall, patients were well matched across arms within studies and were representative of the T2DM population in terms of demographics, baseline characteristics and duration of T2DM for each line of therapy

Patients in the dual therapy studies (DIA3009 and DIA3006) all received baseline metformin. Patients were well matched across the two studies. Aged in their mid-50s, around one-half of patients were men, 70% white and mean baseline HbA1c 7.8% to 8% (62 to 64mmol/mol). The duration of diabetes ranged from 6.5 years to 7.1 years and was slightly higher in DIA3006 compared with DIA3009.

Patients in the triple therapy studies were also aged in their mid-50s and around one-half were men, most were white, although the percentages varied by study (around 64% in DIA3015, 82% in DIA3002 and 63% in DIA3012) and mean baseline HbA1c was approximately 8% (64mmol/mol). The duration of diabetes was similar in the two studies in patients on baseline metformin and SU (DIA3015 and DIA3002) at 9-10 years and slightly higher in the study in patients on baseline metformin and pioglitazone (DIA3012).

As would be expected, patients in the add-on to insulin sub-study were older, in their early 60s, with a duration of diabetes of 16 years and mean baseline HbA1c of 8.3% (67mmol/mol). Around two-thirds of patients were men (67%) and most were white (78%). This patient group also had a high risk for CVD and were therefore different from the populations in the other lines of therapy study

Outcomes

6.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

The primary end-point of all efficacy studies is the change from baseline in HbA1c (%), defined as LS mean changes in HbA1c. Change in HbA1c is the primary aim of

treating T2DM patients with AHAs and is used in clinical practice to determine if a treatment should be continued.

The secondary outcomes are listed below in Table 13. A more detailed table specifying the end-points for each trial may be found in Table 8 of Appendix 4.

Table 13. Secondary outcomes and reliability/validity/current use in clinical practice.

Secondary outcome(s) and measures	Reliability/validity/current use in clinical practice
• Change in HbA1c from baseline to week X* post primary analysis • Durability of glycaemic control	Change in HbA1c is the primary aim of treating T2DM patients with AHA and is used in clinical practice to determine if a treatment should be continued.
• Proportion of subjects with HbA1c <7.0% and <6.5% at week X*	[redacted]
• Change in FBG from baseline to week X*	FBG is a one-off measure of blood glucose and is a limited indication of outcomes relevant for the management of T2DM patients. This secondary end-point was not presented in this submission but information can be found in the clinical trial reports (CSRs).
• Change in body weight from baseline to week X* • Change in body composition from baseline to week X* • The proportion of subjects with at least 5% or 10% body weight reduction from baseline was also evaluated.	People with T2DM tend to be overweight, increase weight over time and welcome support to induce a weight reduction, especially when related to fat loss rather than a reduction in lean mass.
• Incidence of hypoglycaemia between baseline to week X*	Major side-effects associated with AHAs, which can generate high level of non-elective admissions in clinical practice
• Change in SBP and DBP from baseline to week X* • Change in fasting triglycerides, fasting HDL-C, and other fasting lipid levels from baseline to week X*	BP and fasting lipid levels are indicators of risk of developing longer term CV diseases and are important outcomes for T2DM patients in clinical practice
Use (and time to initiation) of rescue medication prior to week X*	Reflects treatment stopping rule due to glycaemic failure
Discontinuation rates	Reflects AEs leading to discontinuation

** Week X is used in this table as duration varied by study*

Statistical analysis and definition of study groups

6.3.6 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.**

Table 14. Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Dual therapy: patients on baseline metformin				
DIA3009	Primary objective was to demonstrate the non-inferiority of canagliflozin versus glimepiride. If this was shown then canagliflozin potential superiority to glimepiride was examined. The primary efficacy variable was the treatment difference in HbA1c LS means between canagliflozin minus glimepiride at week 52.	The analysis of the primary end-point was based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin 0.3%. Superiority of canagliflozin versus glimepiride was concluded when the upper bound of the 2-sided 95% CI of the treatment difference in LS means between canagliflozin minus glimepiride from the ANCOVA model was less than 0. The p-values for the testing of superiority in terms of HbA1c were calculated by comparing the LS means.	The planned sample size of 427 patients in each treatment group provided a power of 90% to demonstrate a group difference of 0.0% and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 1-sided t-test with Type I error rate of 0.0125 for the comparison of each canagliflozin dose with glimepiride.	Analyses were carried out using mITT principles and included randomised subjects who took at least 1 dose of double-blind study drug The primary analysis and the analysis of major secondary efficacy end-points was performed using the mITT analysis set. Analyses based on the PP analysis set were performed as supportive analyses. Only mITT results are reported in the submission.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
DIA3006	Primary objective was to demonstrate the superiority of canagliflozin to placebo on the reduction of HbA1c from baseline. The primary efficacy variable as the treatment difference in HbA1c LS means between canagliflozin minus placebo at week 26. Secondary endpoint of non-inferiority to sitagliptin 100mg based on difference of LS mean HbA1c at 52 weeks	The analysis of the primary end-point was based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin 0.3% of canagliflozin vs. sitagliptin at 52 weeks.	The planned sample size of 360 patients in each treatment group provided a power of 90% to demonstrate a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05.	As per DIA3009
Triple therapy: patients on baseline metformin plus SU				
DIA3015	Primary objective was to demonstrate the non-inferiority of canagliflozin 300mg versus sitagliptin and then potential superiority. The primary efficacy variable as the treatment difference in HbA1c LS means between canagliflozin minus sitagliptin at week 52. Secondary objectives were to demonstrate a reduction in body weight, SBP, triglycerides and HDL-C of canagliflozin versus sitagliptin.	The analysis of the primary end-point was based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin 0.3%.	The planned sample size of 360 patients in each treatment group provided a power of 90% to demonstrate a group difference of 0.0% and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 1-sided t-test with Type I error rate of 0.025 for the comparison of canagliflozin with sitagliptin.	Analyses were carried out using mITT principles and included randomised subjects who took at least 1 dose of double-blind study drug The primary analysis and the analysis of major secondary efficacy end-points was performed using the mITT analysis set. Analyses based on the PP analysis set and analyses using MMRM were performed as supportive analyses. Only mITT results are reported in the submission.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
DIA3002	Primary objective was to demonstrate that canagliflozin 300mg reduces HbA1c relative to placebo at week 26. The primary efficacy variable as the treatment difference in HbA1c LS means between canagliflozin minus placebo at week 26. Secondary objectives were: • Demonstrate that canagliflozin 100mg reduces HbA1c relative to placebo at week 26 • Demonstrate that both doses of canagliflozin reduce the secondary efficacy end-points relative to placebo	The analysis of the primary end-point was based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. The treatment differences (between each canagliflozin group minus placebo) in the LS means and their 2-sided 95% CIs will be estimated based on this ANCOVA model. The p-values for testing the superiority will be calculated by comparing the LS means.	The planned sample size of 150 patients in each treatment group provided a power of 90% to demonstrate a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05.	As per DIA3015
Triple therapy: patients on baseline metformin plus TZD				
DIA3012	Primary objective was to demonstrate that canagliflozin 300mg reduces HbA1c relative to placebo at week 26. The primary efficacy variable as the treatment difference in HbA1c LS means between canagliflozin minus placebo at week 26. Secondary objectives were: • Demonstrate that canagliflozin 100mg reduces HbA1c relative to placebo at week 26 • Demonstrate that both doses of canagliflozin reduce the secondary efficacy end-points relative to placebo	The analysis of the primary end-point was based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. The treatment differences (between each canagliflozin group minus placebo) in the LS means and their 2-sided 95% CIs will be estimated based on this ANCOVA model. The p-values for testing the superiority will be calculated by comparing the LS means.	The planned sample size of 120 patients in each treatment group provided a power of 90% to demonstrate a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c, using a 2-sample, 2-sided t-test with type I error rate of 0.05.	As per DIA3009

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Add-on to insulin: patients on baseline insulin ± OAD				
DIA3008 (add on to insulin sub-study)	Primary objective was to assess the lowering efficacy on HbA1c (change from baseline in HbA1c) of canagliflozin 100mg and 300mg relative to placebo after 18 weeks of treatment, and to assess the safety and tolerability of canagliflozin.	The treatment differences (between each canagliflozin group minus placebo) in the LS means and their 2-sided 95% CIs will be estimated based on an ANCOVA model with treatment and stratification factors as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set using LOCF approach. P values for testing the superiority will be calculated by comparing the LS means. A sequential testing procedure was applied in testing the treatment differences of the primary and secondary end-points such that the family-wise error rate can be strongly-controlled at the 5% significance level.	The planned sample size of 86 patients in each of the three treatment group provided a power of 90% to demonstrate a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 0.75% with respect to the change in HbA1c.	Analyses were carried out using mITT principles and included randomised subjects who took at least 1 dose of double-blind study drug The primary analysis and the analysis of major secondary efficacy end-points was performed using the mITT analysis set. Analyses based on the PP analysis set and completers' analysis set were performed as supportive analyses. Only mITT results are reported in the submission.
DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU); DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP); DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study (CANVAS insulin sub-study);				

6.3.7 Provide details of any sub-group analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-specified sub-group analyses were undertaken to assess the differences in change in HbA1c between canagliflozin 300mg and 100mg and comparators (sitagliptin and glimepiride) or placebo according to different baseline patient and disease characteristics (see Table 15 below).

Post-hoc analyses of change in HbA_{1c} between baseline and week 52 according to baseline HbA_{1c} (> 9%; 75mmol/mol), have been completed for all trials which did not specify this sub-group analysis.

The results of the sub-group analyses based on baseline HbA1c are reported in Section 7.9.4.

To assess whether or not the treatment effect was consistent across various sub-groups, descriptive statistics, including the 95% CI for the change from baseline, were presented by treatment group for each subgroup (if the number of subjects was at least 60 subjects or more per subgroup).

Table 15. Sub-group analyses for each study presented in this submission.

	DIA3009	DIA3006	DIA3015	DIA3002	DIA3012	DIA3008
Analysis carried out	Week 52	Week 52	Week 52	Week 26	Week 26	Week 18
Sex: male or female	✓	✓	✓	✓	✓	✓
Age: <65, >65 years old	✓	✓	✓	✓	✓	✓
Race: white, black or African-American, Asian, other	✓		✓	✓	✓	✓
Ethnicity: Hispanic or Latino, not Hispanic or Latino, not reported	✓	✓	✓	✓	✓	✓
Baseline HbA1c: <8.0%, ≥8.0 or <9.0%, >9.0% *		✓	✓	✓	✓	✓
Undergoing the AHA adjustment period : yes or no			✓	✓	✓	
Baseline BMI: <30, ≥30 kg/m^{2}**		✓	✓	✓	✓	✓
Baseline HOMA2-%B: ≤the overall median, >the overall median			✓	✓	✓	
Baseline HOMA2-IR: ≤the overall median, >the overall median			✓	✓		
Baseline eGFR: <90, ≥90 ml/min/1.73m^{2}			✓	✓		
Dose of pioglitazone at randomisation					✓	
Baseline eGFR: <60, 60 to <90 , ≥90 ml/min/1.73m^{2}					✓	✓
Insulin randomisation stratum						✓
Baseline insulin type: subjects on basal insulin alone, bolus insulin alone, or combination basal + bolus insulin						✓

DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU); DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP); DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study (CANVAS insulin sub-study);

Participant flow

6.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

Consort flow charts for the six studies of interest for this appraisal are presented in Figures 7 to 12 and tables 9 to 11 in Section 10.4.5 - Appendix 4.

6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.**

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.**

The complete quality assessment for each of the six RCTs used as part of this submission is presented in Table 16 below.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

All studies meet the quality appraisal standards. Table 16 contains the results of critical appraisal of all included studies.

Table 16. Quality assessment results for relevant RCTs: dual therapy, triple therapy, and add-on to insulin studies

Line of therapy	**Dual Therapy**		**Triple therapy**			**Add-on to insulin**
Background therapy	**Met**		**Met+SU**		**Met+TZD**	**Ins ± SoC**
Trial no. (acronym)	**DIA3009**	**DIA3006**	**DIA3015**	**DIA3002**	**DIA3012**	**DIA3008 insulin sub-study**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes

DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU trial); DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D Trial); DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2 Trial); DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU Trial); DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP Trial); DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study (CANVAS insulin sub-study); Met+: in combination with metformin; SU+: in combination with sulfonylurea: Met+SU+: in combination with metformin and sulfonylurea; Met+TZD+: in combination with metformin and a thiazolidinedione; Ins±SoC+: in combination with insulin other and potentially other anti-diabetics.

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

6.5.3 **For each outcome for each included RCT, the following information should be provided.**

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

6.5.3.1. Dual therapy in combination with metformin

In this submission, two dual therapy studies in combination with MET (DIA 3006 and DIA3009) provided evidence the efficacy of canagliflozin compared to an active comparator. A consistent reduction in HbA1c was observed with both canagliflozin doses in dual therapy studies and a dose-dependent effect was generally observed.

In summary the studies in dual therapy demonstrate that canagliflozin 300mg resulted in significantly improved glycaemic control compared to glimepiride and sitagliptin, and that canagliflozin 100mg was non-inferior to these comparators.

Canagliflozin at both doses was superior to sitagliptin and glimepiride in terms of the key secondary metabolic endpoints of change in BP and weight. The details of these results are presented below.

Detailed results of all secondary endpoints can be found in Section 10.6 - Appendix 6 (Tables relative to the Results of the relevant RCTs - Section 6.5.).

6.5.3.1.1. Dual therapy – primary outcome

DIA3009 demonstrates that canagliflozin 300mg (in combination with MET) resulted in statistically superior reduction in HbA1c than glimepiride+ MET at Week 52: with a difference of mean change in HbA1c at week 52 for canagliflozin 300mg (minus glimepiride) of -0.12% (-24.8mmol/mol) [95% CI: -0.217;-0.023, p<0.001. (2) Canagliflozin 100mg (+ MET) was non-inferior to glimepiride (+ MET) at week 52 in terms of mean change in HbA1c: -0.01% (-0.1mmol/mol) [95% CI: -0.217;-0.023].

DIA3006 demonstrates that canagliflozin 300mg and 100mg resulted in improved glycaemic control compared to sitagliptin at week 26. Canagliflozin 100mg and 300mg (in combination with MET) reduced HbA1c (difference in mean change minus placebo) by −0.627% (-6.8mmol/mol) and –−0.77% (-8.4mmol/mol) respectively, compared with -0.66% (-7.4mmol/mol) for sitagliptin; p < 0.001 versus placebo for all active treatment arms.

The details of these results are presented in Table 17.

Table 17. Change in HbA1c in the dual therapy trials (DIA3006 and DIA3009) at the primary time point, mITT – LOCF. (2;6;73;81)

Trial no. (acronym)	Canagliflozin 100mg	Canagliflozin 300mg	Placebo	Active comparator
DIA3009	**(n = 483)**	**(n = 485)**		**Glimepiride (n = 482)**
HbA1c value at baseline (%) N Mean (SD)	 478 7.78 (0.787)	 474 7.79 (0.779)		 473 7.83 (0.795)
Value at Week 52 LOCF Mean (SD)	 7.00 (0.769)	 6.90 (0.806)		 7.04 (0.984)
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;0.085)	-0.12 (0.050) (-0.217;-0.023)		
DIA3006	**(n = 368)**	**(n = 367)**	**(n = 181)**	**Sitagliptin (n = 366)**
HbA1c value at baseline (%) N Mean (SD)	 365 7.94 (0.879)	 360 7.95 (0.931)	 181 7.96 (0.896)	 354 7.92 (0.875)
Value at Week 26 / 52 LOCF Mean (SD)	 7.13 (0.861)	 6.98 (0.819)	 7.76 (1.216)	 7.08 (0.970)
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) P-Value 95%CI	-0.62 (0.071) <0.001 (-0.758;-0.481)	-0.77 (0.071) <0.001 (-0.914;-0.636)		-0.66 (0.071) N/A (-0.795;-0.516)

DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); DIA3009:: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SD: standard deviation; SE: standard error;

6.5.3.1.2. Dual therapy – secondary outcomes

Change in HbA1c from baseline to the end of trial

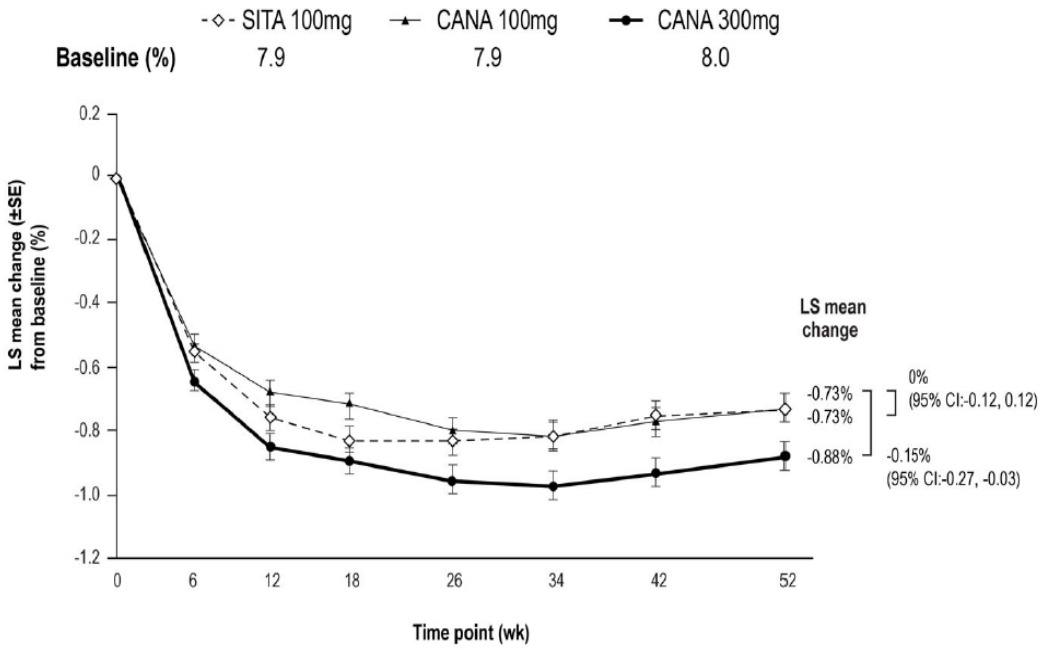
One of the key secondary end-points for both trials was change in HbA1c from baseline to the end of the trial (week 52 for DIA3006 and week 104 for DIA3009).

A sustained reduction in HbA1c was observed with both doses of canagliflozin:

In DIA 3006 at week 52, canagliflozin 100mg (+MET) demonstrated non-inferiority, and canagliflozin 300mg (+MET) demonstrated statistical superiority to sitagliptin 100mg (+MET) in lowering HbA1c from baseline (−0.73%, –0.88%, –0.73%, respectively); differences in mean change (95% CI) minus sitagliptin were 0% (95% CI: −0.12, 0.12) for canagliflozin 100mg and −0.15% (-1.7 mmol/mol) [95% CI: −0.27, –0.03] for canagliflozin 300mg (see Figure 6). (81)

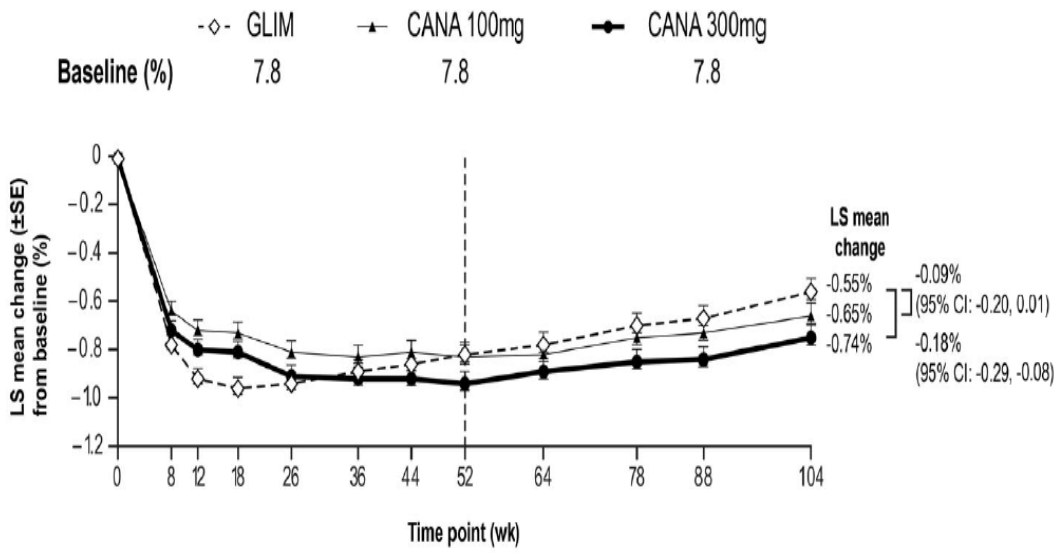
In DIA 3009 at 104 weeks, canagliflozin 300mg maintained statistically superior reductions in HbA1c versus glimepiride with differences in mean HbA1c change from baseline (minus glimepiride) of -0.09% (-24.48mmol/mol), 95% CI: (-0.2;-0.01) for canagliflozin 100mg and -0.18% (-25.46mmol/l), 95% CI: (-0.29;-0.08) for canagliflozin 300mg. (See Figure 7). Pre-specified hypothesis testing was not conducted at week 104 of DIA3009, therefore p values are not reported. (80)

Figure 6. LS mean (±SE) change from baseline in HbA1c (%) to week 52 (DIA3006), LOCF (mITT). (82;83)



Legend; DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Figure 7. LS mean (±SE) percentage change in HbA_{1c} from baseline up to week 104 (DIA3009), LOCF (mITT). (80)



Legend; DIA3009:: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Coefficient of durability in HbA1c change over time (DIA3009 only)

Both doses of canagliflozin demonstrated better durability than glimepiride.

The coefficient of durability represents the rate of rise of HbA1c over time. The coefficient of durability (rate of HbA1c increase) is a measure of how well an agent controls HbA1c over time. A low coefficient of durability indicates that the agent maintains an effect on HbA1c over time and therefore extends the period before another add-on agent is required.

In DIA3009, the coefficient of durability (rate of HbA1c rise) was examined from Week 26 to Week 104.

The coefficient of durability was lower with canagliflozin 100mg and 300mg than with glimepiride (0.16% 0.16% and 0.37% respectively); LS mean differences versus glimepiride were -0.21% [-21.2mmol/mol] for both doses of canagliflozin, indicating that canagliflozin provided durable control of HbA1c over a two year period and that the durability was superior to glimepiride. (80)

Change in blood pressure

Tables detailing the changes in SBP (secondary endpoint) and DBP (additional secondary endpoint) in the dual therapy studies can be found in Tables 16 and 17 in Appendix 6.

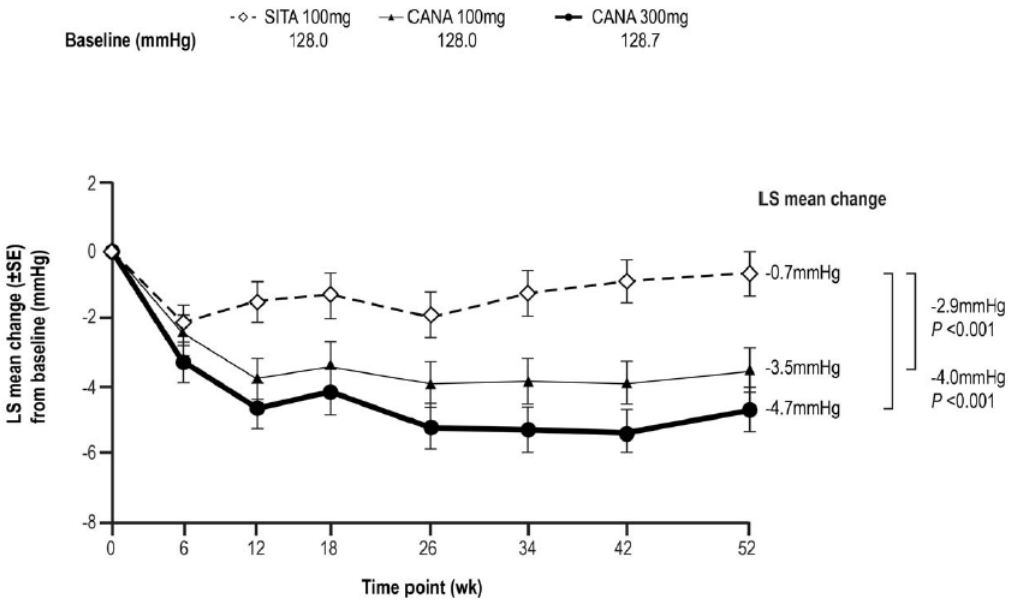
Both doses of canagliflozin, when used in combination with metformin, consistently resulted in a significant reduction in SBP compared with sitagliptin 100mg (DIA3006) or glimepiride (DIA 3009).

In DIA3006 at 26 weeks, canagliflozin 300mg and 100mg resulted in improved SBP with a difference in mean SBP change from baseline (minus placebo) of -6.58 mmHg (95%CI: -8.504;-4.653), and -5.36 mmHg (95%CI: -7.280;-3.439) respectively (p<0.001 for both canagliflozin doses versus placebo), compared to -3.54 mmHg (-5.273;-1.413) in the sitagliptin arm. (81) These reductions in SBP were sustained up to week 52 (see Figure 8).

In DIA3009 at 52 weeks, canagliflozin 300mg and 100mg resulted in improved SBP vs. glimepiride with a mean difference in SBP reduction minus glimepiride of -4.8 mmHg (95%CI: -6.2 to -3.4) and -3.5 mmHg (95%CI: -4.9 to -2.1), respectively. (2) These reductions in SBP were sustained up to week 104 (see Figure 9).

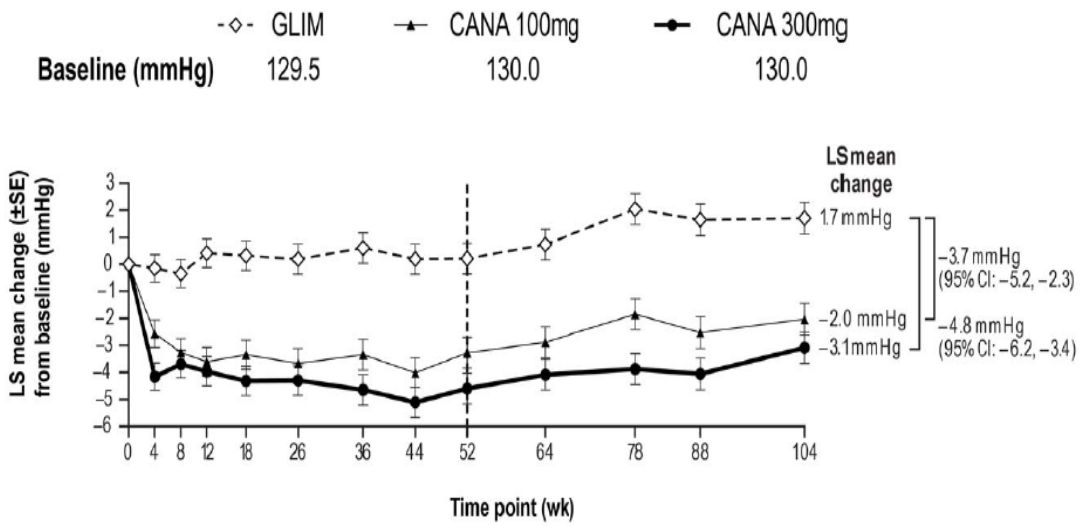
The effect was dose-dependent, with canagliflozin 300mg resulting in greater reductions than canagliflozin 100mg (see Figure 8 and Figure 9).

Figure 8. LS mean change (+SE) in SBP (mmHg) from baseline to week 52 in DIA3006 – mITT (LOCF) (83)



Legend; DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Figure 9. LS mean change (+SE) in SBP (mmHg) from baseline to week 104 in DIA3009 – mITT (LOCF) (80)



Legend; DIA3009:: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Change in body weight

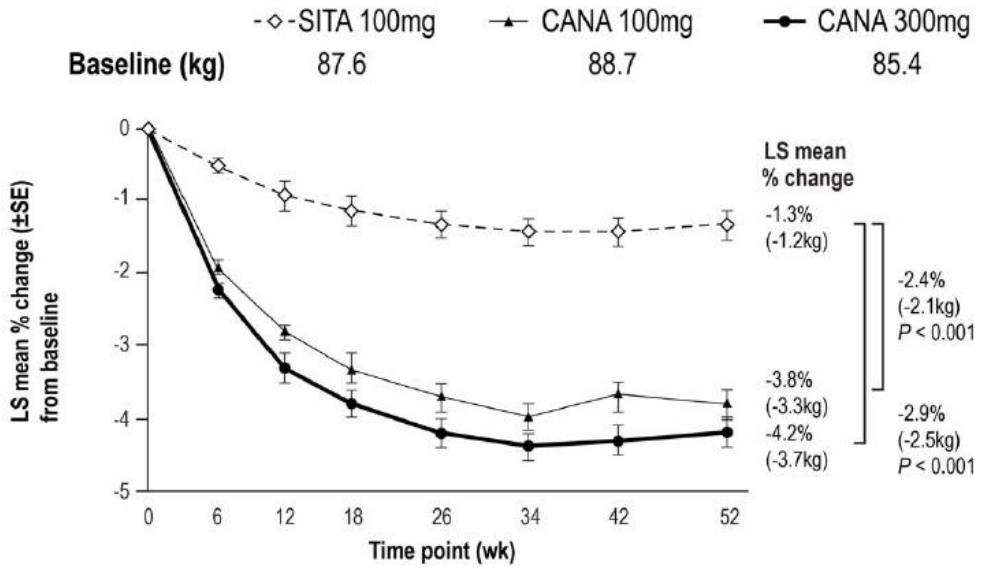
Both doses of canagliflozin, when used in combination with metformin, consistently resulted in significant reductions in body weight. Reductions in weight appear dose dependent, with canagliflozin 300mg resulting in greater reductions than canagliflozin 100mg.

In DIA 3009 at week 52, a weight loss of -4.2kg [SE: 0.2] and -4.7kg [SE: 0.2] was observed for canagliflozin 100mg and 300mg respectively, compared with a slight increase in weight with glimepiride +1.0kg [SE: 0.2]). Both doses of canagliflozin demonstrated statistical superiority to glimepiride with a difference in mean weight change (minus glimepiride) of -5.2kg (95% CI: -5.7;-4.7) and -5.7kg (95% CI: -6.2; -5.1) for canagliflozin 100mg and 300mg respectively. Weight loss in the canagliflozin arms was maintained at 104 weeks (see Figure 11).

In DIA 3006 at week 26, a weight loss of 4.2 kg [SE: 0.2] and -3.7 kg [SE: 0.2] was observed with canagliflozin 300mg and 100mg, respectively, compared to a slight decrease in weight with sitagliptin (mean change of -1.2kg [SE: 0.2]) at 52 weeks. Both doses of canagliflozin demonstrated statistical superiority to sitagliptin in terms of weight reduction up to week 52 with a difference in mean weight reduction (minus sitagliptin) of -2.4% (-2.1kg) and -2.9% (-2.5kg) for canagliflozin 100mg and 300mg respectively, p<0.001 for both doses (See Figure 10).

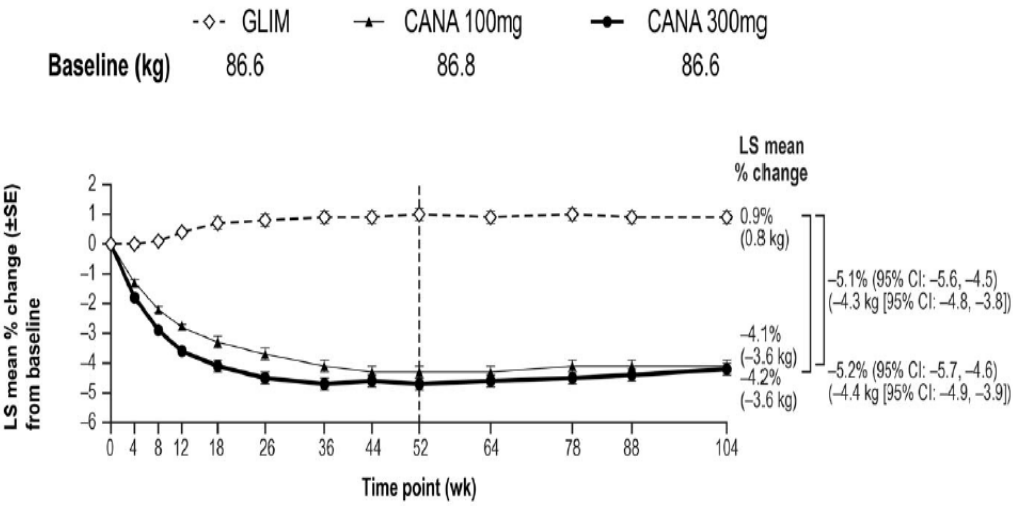
Detailed results about change in body weight for the dual therapy studies at the primary time point are reported in Table 18 of Appendix 6 (section 10.6.)5.

Figure 10. LS mean (±SE) percentage change in body weight from baseline over time in DIA3006 trial.(83)



Legend; DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Figure 11. LS mean (±SE) percentage change in weight from baseline (DIA3009), LOSF (mITT). (80)



Legend; DIA3009: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

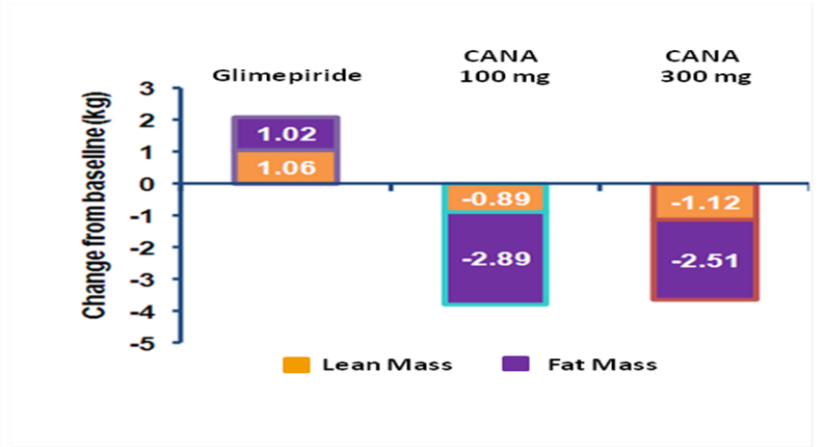
Change in body composition (DIA3009 only)

In study DIA3009, body composition was determined in a sub-group of patients by using dual-energy X-ray absorptiometry (DXA) to measure total body adiposity and Computed Tomography (CT) to measure visceral adiposity.

The sub-group included 96 patients receiving glimepiride, 111 receiving canagliflozin 100mg and 102 receiving canagliflozin 300mg. Results from DXA are available for 68, 71 and 69 patients respectively. (2)

In the body composition group, patients had similar baseline characteristics and weight changes compared to the main study population. Greater changes in body weight from baseline at Week 52 compared with glimepiride were observed in the body composition subgroup with both doses of canagliflozin. Body composition results from assessment of DXA show that weight loss observed with canagliflozin is due roughly two-thirds from fat mass and one third from lean mass (see Figure 12).

Figure 12. Change in body weight composition (DXA Analysis sub-group) at week 52 (DIA3009), LOCF (mITT). (76)



Legend; DIA3009:: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); LOCF: last observation carried forward; mITT: modified intent-to-treat;

Change in lipid levels

Details regarding change in HDL-cholesterol, triglycerides and LDL-cholesterol from baseline to primary time point for DIA3006 and DIA3009 trials are reported in Tables 19, 20 and 21 of Appendix 6 (Section 10.6.), respectively.

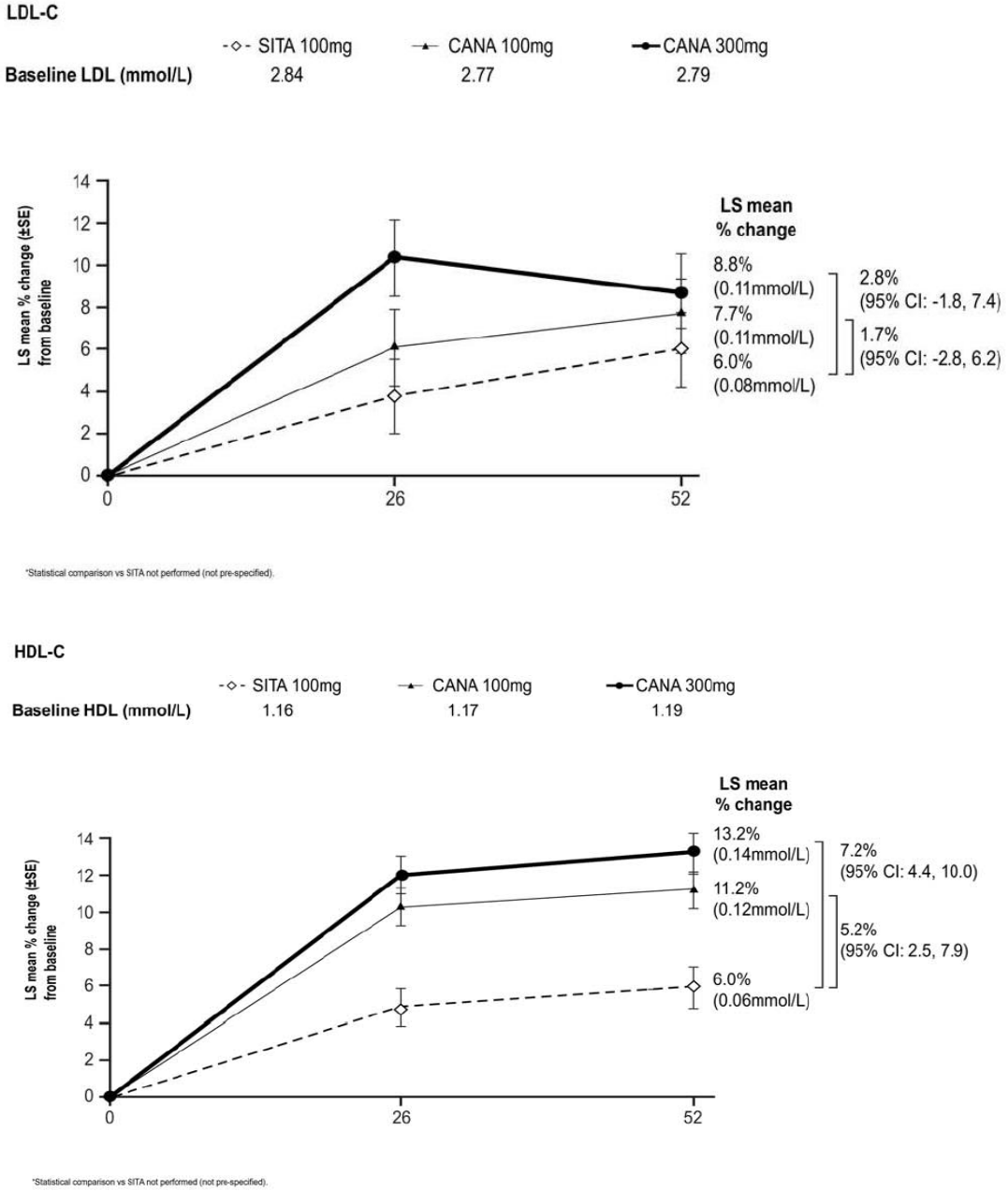
Canagliflozin resulted in changes to the lipid profile over time including moderate increases in both HDL-C and LDL-C. The changes in lipid levels were dose dependent.

In DIA3006 at 26 weeks, canagliflozin 300mg and 100mg (in combination with metformin) resulted in an increase in mean LDL-C change (minus placebo) of +12.2mmol/L(95%CI: 6.6;17.8) and +7.9mmol (95%CI: 2.4;13.5) respectively compared to +5.5mmol 95%CI: (95% CI: -0.1;11.2) for sitagliptin 100mg, and an increase in mean HDL-C change (minus placebo) of +8.4 (95%CI: 5.3;11.5) and +6.6 (95%CI: 3.6;9.7), respectively compared with +1.3 (95%CI: -1.8;4.3) for sitagliptin 100mg. (6;81) These changes in lipid levels plateaued between week 26 and week

52 as observed in Figure 13. These simultaneous increases in LDL-C and HDL-C have little impact on the overall LDL-C/HDL-C ratio.

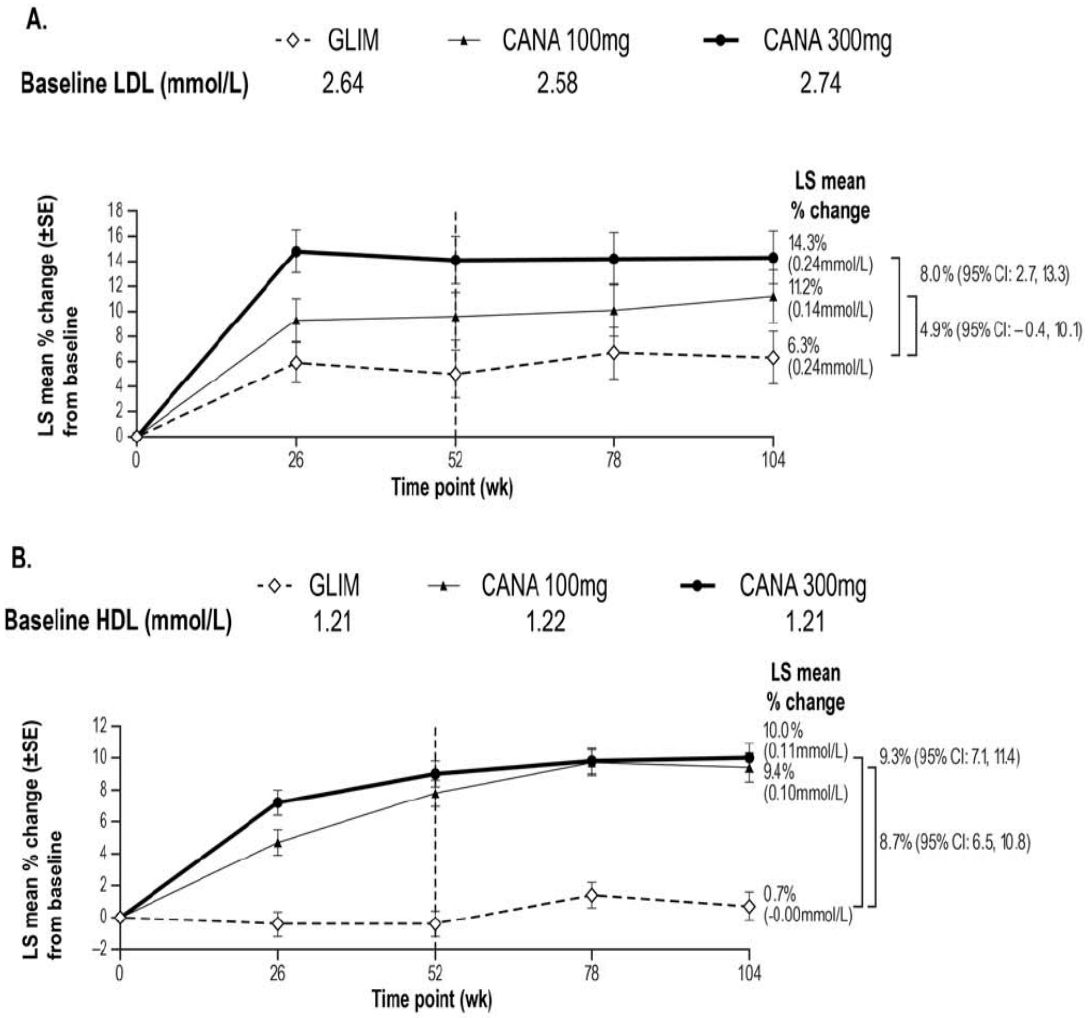
In DIA3009 at 52 weeks, canagliflozin 300mg and 100mg resulted in an increase in LDL-C (minus glimepiride) of 9.0mmol/L (95%CI: 4.4;13.7) and 4.5mmol/L (95%CI: -0.0;9.1) and an increase in HDL-C (minus glimepiride) of 8.6 (95%CI: 6.7;10.6) and 7.5 (95%CI: 5.6;9.5), respectively. (2;73) These changes in lipid levels plateaued after 52 weeks (see Figure 14), indicating that canagliflozin's main effect on lipids is observed within the first year of therapy.

Figure 13. LS mean (±SE) percentage change in LDL-C (top) and HDL-C (bottom) from baseline in DIA3006, LOCF (mITT). (83)



Legend; DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial (CANTATA-D);CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Figure 14: LS mean (±SE) percentage change in LDL-C (top) and HDL-C (bottom) from baseline in DIA3009 , LOCF (mITT). (80)



Legend; DIA3009:: CANagliflozin Treatment And Trial Analysis-Sulfonylurea SGLT2 Add-on to Metformin Versus Glimepiride (CANTATA-SU); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error;

Achievement of HbA1c targets

Both DIA 3006 and DIA 3009 had a predefined secondary endpoint of the percentage of patients achieving HbA1c of less than 7% (53mmol/mol) and less than 6.5% (48mmol/mol) at week 52. These results may be found in the respective CSRs. (73;81)

However, due to alternative HbA1c targets being considered relevant by the NHS in England, a post-hoc analysis of the percentage of patients achieving HbA1c of less than 7.5% (59mmol/mol) at week 52 is reported in this submission (see Table 22 in Appendix 6). It should be noted that no statistical tests were conducted as part of these post-hoc analyses. This threshold was chosen as they reflect NHS targets in the QOF.

Figure 15 below shows the proportion of patients achieving HbA1c of less than 7.5% (59mmol/mol) in the dual therapy studies. [redacted]

[redacted]

Figure 15. [redacted]

[redacted]

6.5.3.2. Triple therapy in combination with MET+SU or MET+TZD

In this submission, there were three relevant studies that evaluated the efficacy of canagliflozin in triple therapy. One triple therapy study in combination with MET+SU (DIA3015) provides evidence of the efficacy of canagliflozin compared to an active comparator, sitagliptin. The other two placebo-controlled studies assessed the efficacy of adding canagliflozin to MET + SU (DIA3002) and MET + TZD (DIA3012). Across all there triple therapy studies, a consistent reduction in HbA1c was observed with both canagliflozin doses and the magnitude of effect was dose-dependent.

DIA3015 demonstrates that canagliflozin 300mg (in combination with MET+SU) resulted in significantly improved glycaemic control compared to sitagliptin. Canagliflozin 300mg was also superior to sitagliptin in terms of the key secondary metabolic endpoints of change in BP and weight.

Both doses of canagliflozin when used in combination with MET+SU or MET+TZD demonstrated superior reduction in HbA1c and improvements in key secondary metabolic endpoints (change in weight and SBP) compared to placebo. The details of these results are presented below. All of these results were sustained over time, for up to two years.

6.5.3.2.1. Triple therapy - primary outcome

Detailed results of the triple therapy trials' primary endpoint can be in Table 18.

In study DIA3015, treatment with canagliflozin 300mg resulted in a significantly greater reduction in HbA1c compared with sitagliptin 100mg at Week 52; with a difference of mean change in HbA1c for canagliflozin 300mg (minus sitagliptin) of -0.37% [-4mmol/mol], 95% CI:-0.25 to -0.50. (7)

Studies DIA3002 and DIA3012 were against placebo and also showed a significant reduction in HbA1c at the primary endpoint (at 26 weeks for both studies) for both doses of canagliflozin. The mean reduction in HbA1c at week 26 with canagliflozin 100mg (minus placebo) was -0.71% (-7.8mmol/mol), 95% CI:-0.904; -0.524 ($p<0.001$), in DIA3002 and -0.62% (-6.8mmol/mol), 95% CI: -0.811;-0.437 ($p<0.001$), in DIA3012. The mean reduction with canagliflozin 300mg was -0.92% (-10mmol/mol), 95% CI: -1.114; -0.732 ($p<0.001$), in DIA3012 and -0.76% (-8.3mmol/mol), 95% CI: -0.951;-0.575 ($p<0.001$), in DIA3002. (89;93)

Table 18. Change in HbA1c in the triple therapy trials (DIA3002, DIA3012, DIA3015) at the primary time point, mITT – LOCF. (7;85;89;93)

Trial no. (acronym)	Canagliflozin 100mg	Canagliflozin 300mg	Placebo	Active comparator
Triple therapy: treatment on a background of metformin and SU				
DIA3015		**(n = 377)**		**Sitagliptin (n = 378)**
HbA1c value at baseline (%), N		374		365
Mean (SD)		8.1 (0.9)		8.1(0.9)
Value at Week 52 LOCF - Mean (SD), %		7.12 (0.875)		7.50 (1.083)
Change from baseline - LS Mean (SE)		-1.03 (0.048)		-0.66 (0.049)
Diff. of LS Means (SE) (minus sitagliptin)		-0.37 (0.064)		
95%CI		(-5.0 to -2.5)		
DIA3002	**(n = 157)**	**(n = 156)**	**(n = 156)**	
HbA1c value at baseline (%), N	155	152	150	
Mean (SD)	8.13 (0.926)	8.13 (0.942)	8.12 (0.896)	
Value at Week 26 LOCF - Mean (SD)	7.21 (0.922)	7.01 (0.906)	7.93 (1.106)	
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)	-0.71 (0.097)	-0.92 (0.097)		
95%CI, P-value	(-0.904; -0.524), <0.001	(-1.114; -0.732), <0.001		
Triple therapy: treatment on a background of metformin and TZD				
DIA3012	**(n =113)**	**(n = 114)**	**(n =115)**	
HbA1c value at baseline (%), N	113	112	114	
Mean (SD)	7.99 (0.940)	7.84 (0.911)	8.00 (1.010)	
Value at Week 26 LOCF - Mean (SD)	7.06 (0.737)	6.84 (0.803)	7.69 (1.146)	
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)	-0.62 (0.095)	-0.76 (0.096)		
95%CI, P-Value	(-0.811;-0.437), <0.001	(-0.951;-0.575), <0.001		

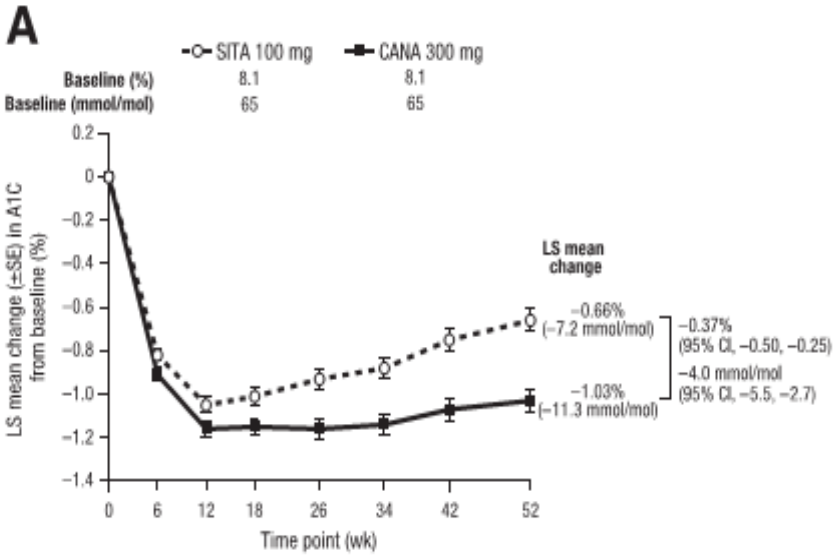
DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP); DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU),
CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SD: standard deviation; SE: standard error

6.5.3.2.2. Triple therapy - secondary outcomes

Change in HbA1c from baseline to the end of the trial

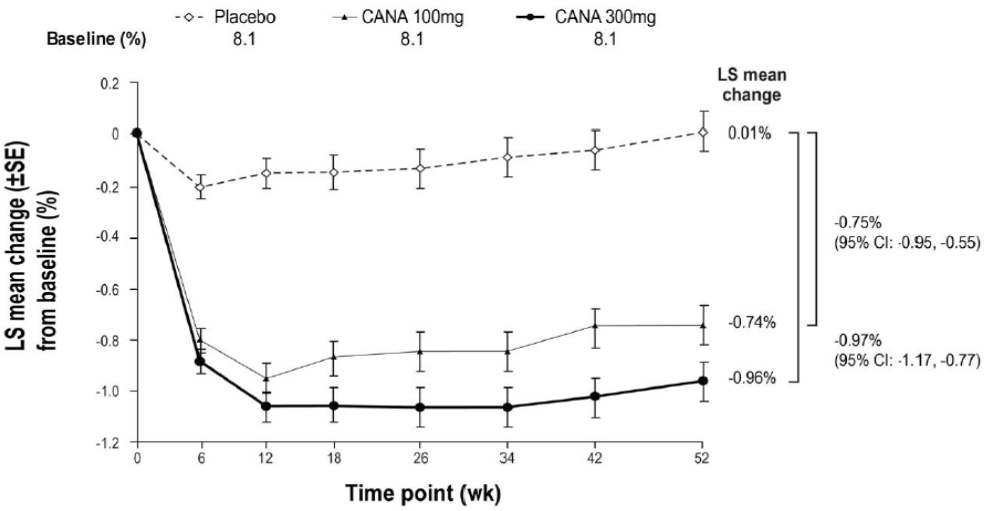
When used as triple therapy with either MET+SU (DIA3015 and DIA3002]) or MET+TZD (DIA3012), both doses of canagliflozin resulted in sustained reduction in HbA1c after 52 weeks as shown in Figure 16 to Figure 18.

Figure 16. LS mean (±SE) change from baseline in HbA1c (%) to week 52 in DIA3015 (85)



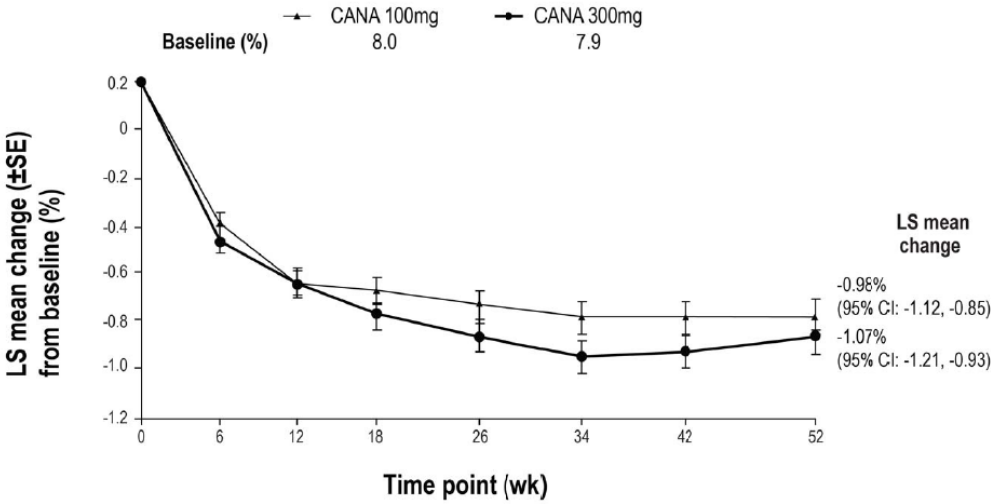
Legend: DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 17. LS mean (±SE) change from baseline in HbA1c (%) to week 52 in DIA3002 (92)



Legend: DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU),; CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 18. LS mean (±SE) change from baseline in HbA1c (%) to week 52 in DIA3012. (29)



Legend: DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP);CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Change in blood pressure

Consistent with the findings from the dual therapy studies, both doses of canagliflozin, when used as triple therapy, resulted in a significant reduction in SBP compared with sitagliptin or placebo.

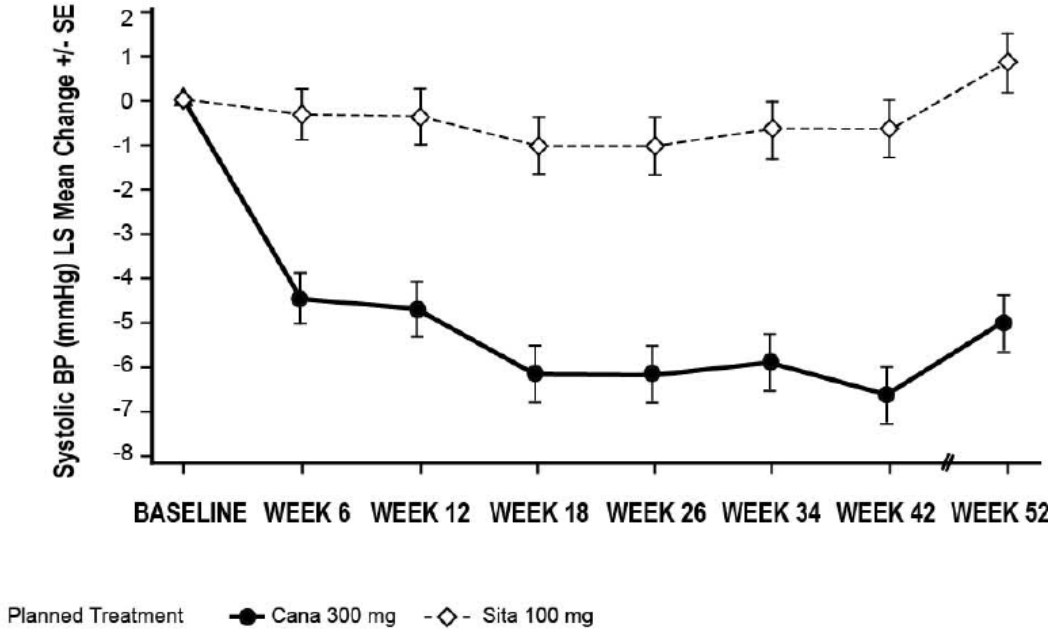
Tables detailing the changes in SBP and DBP can be found in Table 23 and Table 24 of Appendix 6 (Section 10.6.2.).

Generally, the reduction in BP was dose-dependent. However, in DIA3002 (triple therapy in combination with MET+TZD) a larger reduction in SBP and DBP was observed with the 100mg dose of canagliflozin compared to the 300mg dose.

In DIA3015, canagliflozin 300mg significantly decreased SBP compared with sitagliptin 100mg (5.1 and 0.9mmHg respectively), with the difference in mean change (minus sitagliptin) in SBP at week 52 of 5.9mmHg, 95% CI: -7.642;-4.175, p<0.001. (7;85)

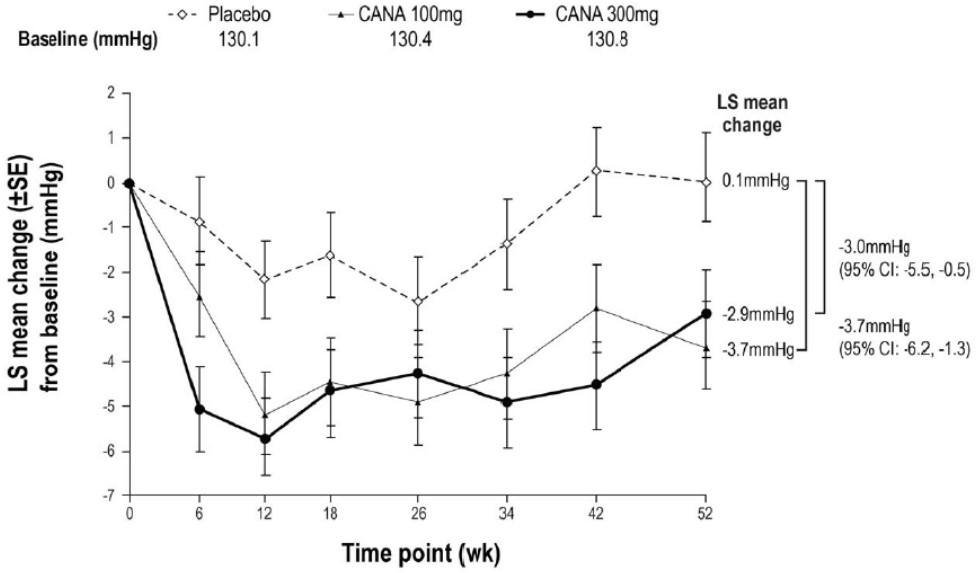
Figure 19 to Figure 21 below show the change in SBP throughout the duration of the studies and demonstrate that the reduction is sustained for one year with canagliflozin.

Figure 19. LS mean (±SE) change in SBP (mmHg) from baseline to week 52 (DIA3015) – mITT (LOCF). (85)



Legend: DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

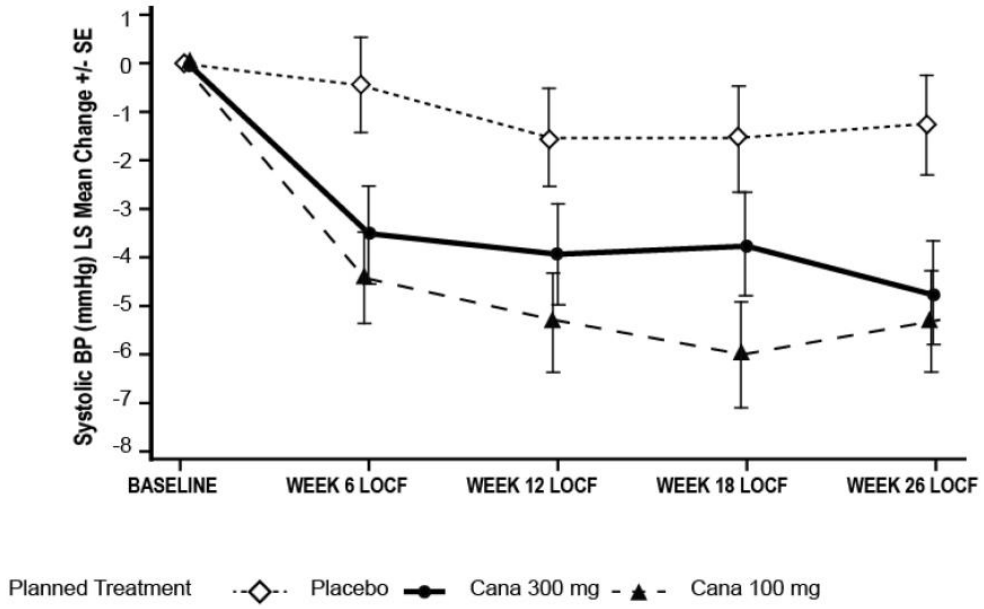
Figure 20. LS mean (±SE) change in SBP (mmHg) from baseline to week 52 in DIA3002) – mITT (LOCF). (92)



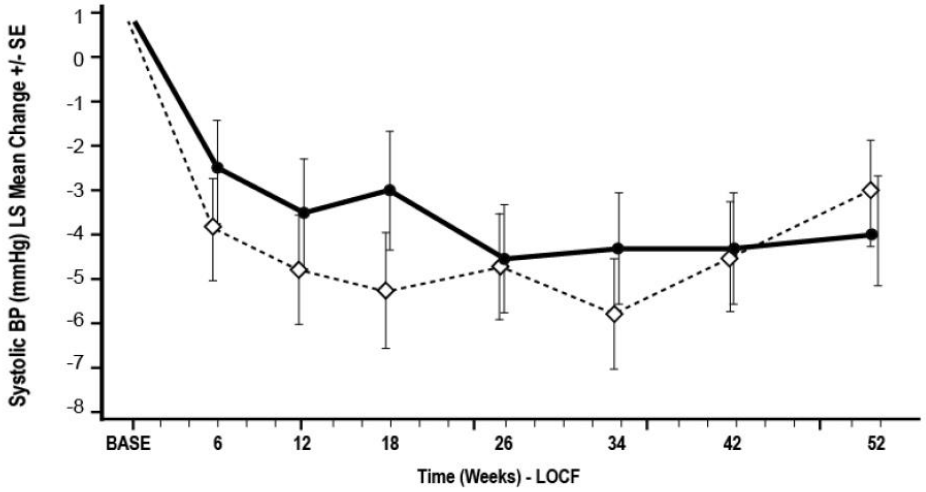
Legend: DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU),; CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 21. LS mean (±SE) change in SBP (mmHg) from baseline to week 26 (A) and from baseline to week 52 (B) in DIA3012 – mITT (LOCF). (93;94)

A



B



Legend: DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP); LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Change in body weight

Consistent with the results observed in dual therapy studies, both doses of canagliflozin, when used in triple therapy, consistently resulted in reductions in body weight despite a background of AHA therapies that are known to cause weight gain, i.e. SU and TZD. The effect on body weight was dose-dependent, with canagliflozin 300mg resulting in greater reductions in weight than canagliflozin 100mg. In all studies weight loss was maintained for the 52 week duration of the study

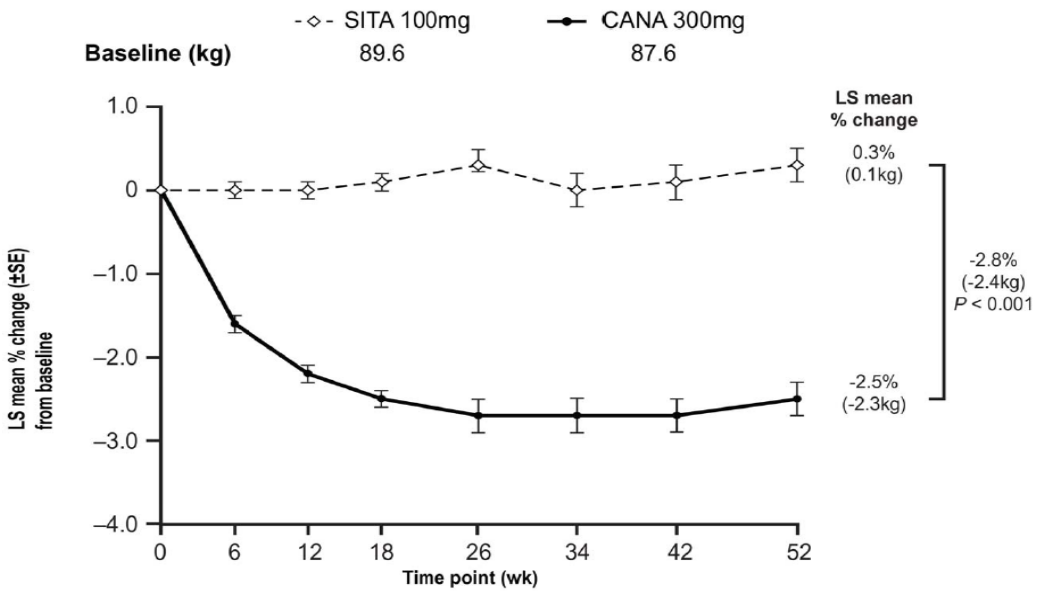
In DIA3015 at week 52, canagliflozin 300 mg treatment resulted in significant reductions in body weight relative to sitagliptin 100 mg of -2.8kg, 95%CI: -3.3;-2 (p<0.001). This change in body weight was maintained up to week 104 as reported in Figure 22. (7)

In DIA3002 at week 26, canagliflozin 100mg and 300mg (in combination with MET+SU) results in a reduction in weight of -2.1kg (SE:0.3)and -2.6kg (SE: 0.3) respectively on a baseline of 93.5kg. The placebo arm saw a reduction in weight of -0.7kg (SE: 0.3) loss. This changes in body weight were maintained at week 52 with a difference in mean weight change (minus placebo) of -1.0kg (95%CI: -1.8;-1.2) and -2.1kg (95% CI: -2.9;-1.2) for canagliflozin 100mg and 300mg, respectively (see Figure 24). (89)

In DIA3012 at week 26, a change in weight of -2.7kg [SE: 0.3] and -3.8kg [SE: 0.3] was observed for canagliflozin 100mg and 300mg (in combination with MET+TZD) respectively from a baseline of approximately 94kg (see Figure 24). (93)

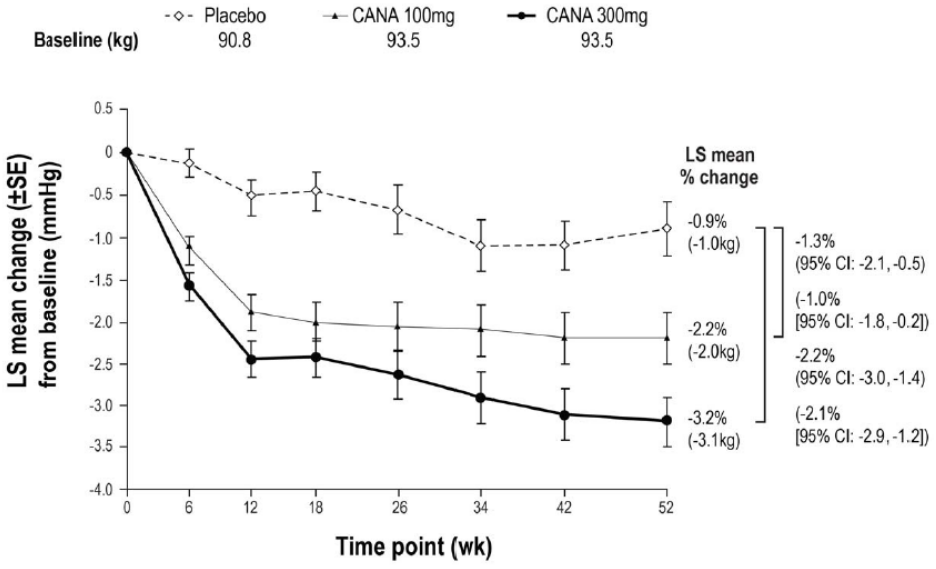
The mean changes in body weight from baseline for the triple therapy studies at the primary time point are reported in Table 25 of Appendix 6 (Section 10.6.2) and can be seen in Figure 22 to Figure 24.

Figure 22. LS mean (±SE) percentage change in body weight from baseline over time in DIA3015. (87)



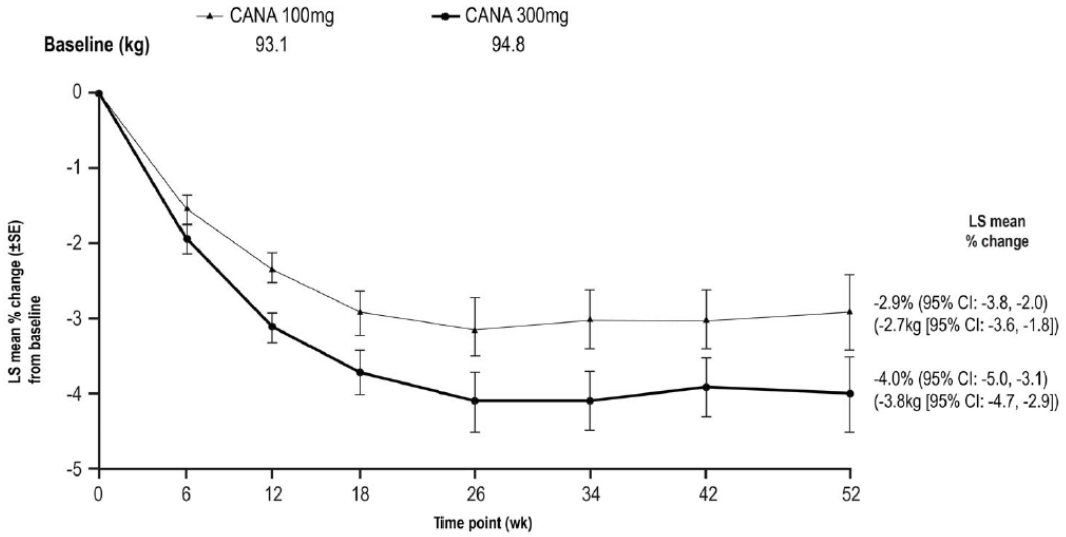
Legend: DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 23. LS mean (±SE) percentage change in body weight from baseline over time in DIA3002. (92)



Legend: DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU),; CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 24. LS mean (±SE) percentage change in body weight from baseline over time in DIA3012. (29)



Legend: DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP);CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Change in lipid levels

Both doses of canagliflozin resulted in changes to the lipid profile over time; increased HDL-C and LDL-C and moderate change in triglycerides. The changes in lipid levels appeared to be dose-dependent in most studies and were generally consistent across all three studies between baseline and week 52 (see Figure 25, Figure 26 and Figure 27, for DIA3015, DIA3002 and DIA3012, respectively).

Change in HDL-C, triglycerides and LDL-C from baseline to the primary time point for the triple therapy studies are reported in Table 26, 27 and 28 in Appendix 6 (Section10.6.2), respectively.

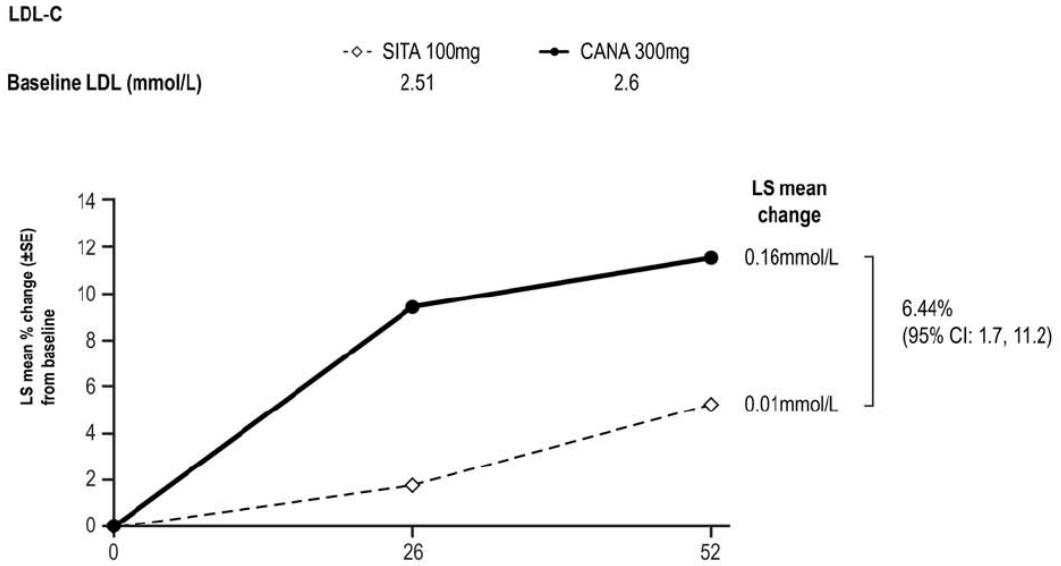
In DIA3015 at week 52, canagliflozin 300mg in combination with MET+SU resulted in an increase in LDL-C (minus sitagliptin) of +6.4mmol/L (95%CI: 1.7; 11.2) and an increase in HDL-C of +7.0mmol/L (95%CI: 4.6; 9.3). (85)

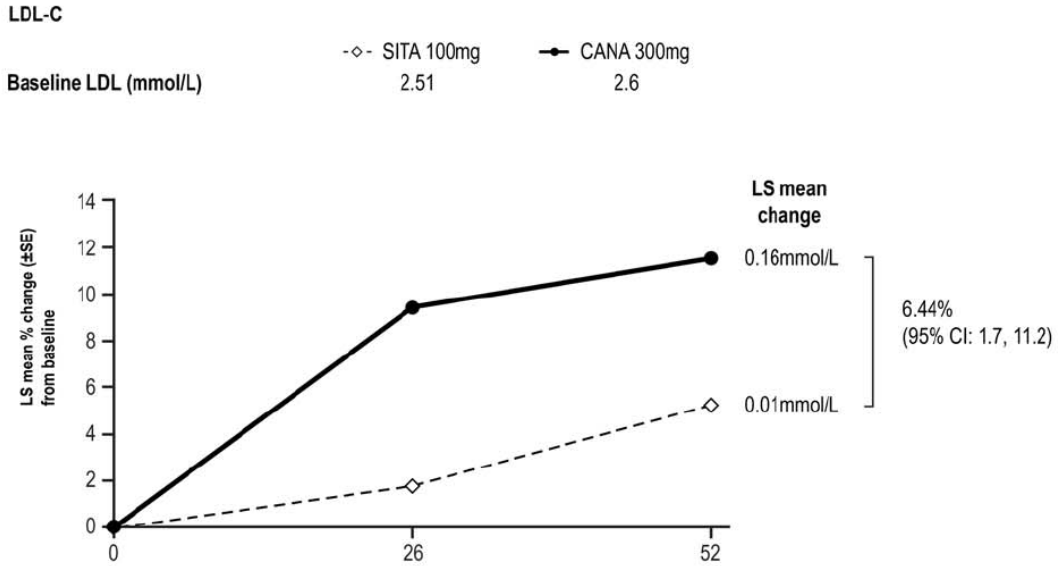
In DIA3002 at 26 weeks, canagliflozin 300mg and 100mg (in combination with MET+SU) resulted in an increase in LDL-C (minus placebo) of +4.6mmol/L (95%CI: -1.8; 10.9) and +0.5mmol/L (95%CI: -5.8; 6.8) respectively, and an increase in HDL-C (minus placebo) of +3.5mmol/L (95%CI: 0.1; 7.0) and 2.6 (95%CI: -0.8; 6.0), respectively. (89)

In DIA3012 at 26 weeks, canagliflozin 300mg and 100mg (in combination with MET+TZD) resulted in an increase in LDL-C (minus placebo) of 4.6mmol/L (-1.8; 10.9) and +0.5mmol/L (3.2) (-5.8; 6.8) respectively, and an increase in HDL-C (minus placebo) of 6.5mmol/L (95%CI: 2.8;10.2)and 4.8mmol/L (95%CI: 1.1;8.5) respectively. (93)

The changes in plasma lipids plateaued at week 26 to week 52. With the exception of LDL-C in the DIA3015 and DIA3002 trials which continued to rise after 26 weeks, although the gradient was shallower than between baseline and 26 weeks (see Figure 26, Figure 27 and Figure 27).

Figure 25. LS mean (±SE) percentage change in LDL-C (top) and HDL-C (bottom) from baseline in DIA3015 . (85)

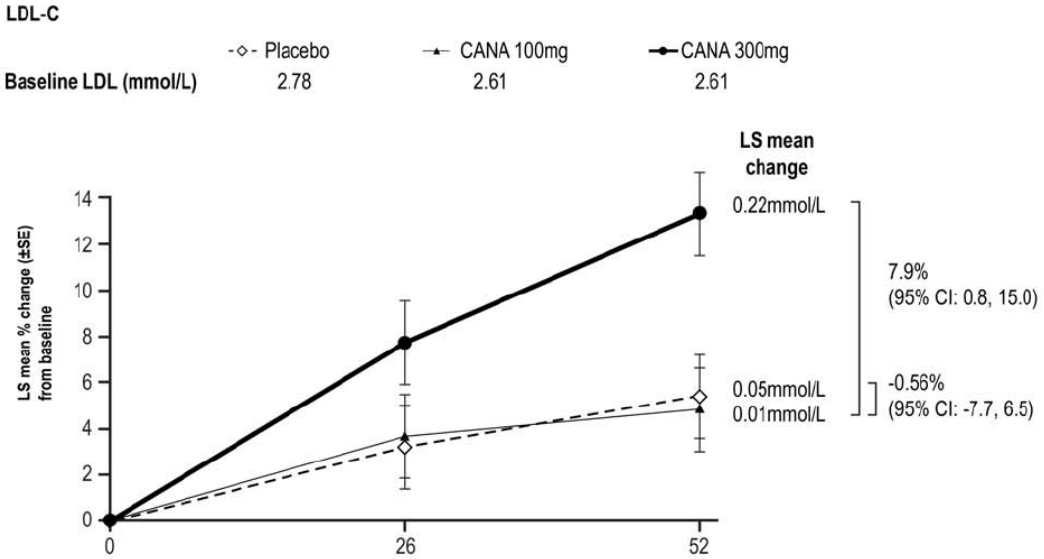




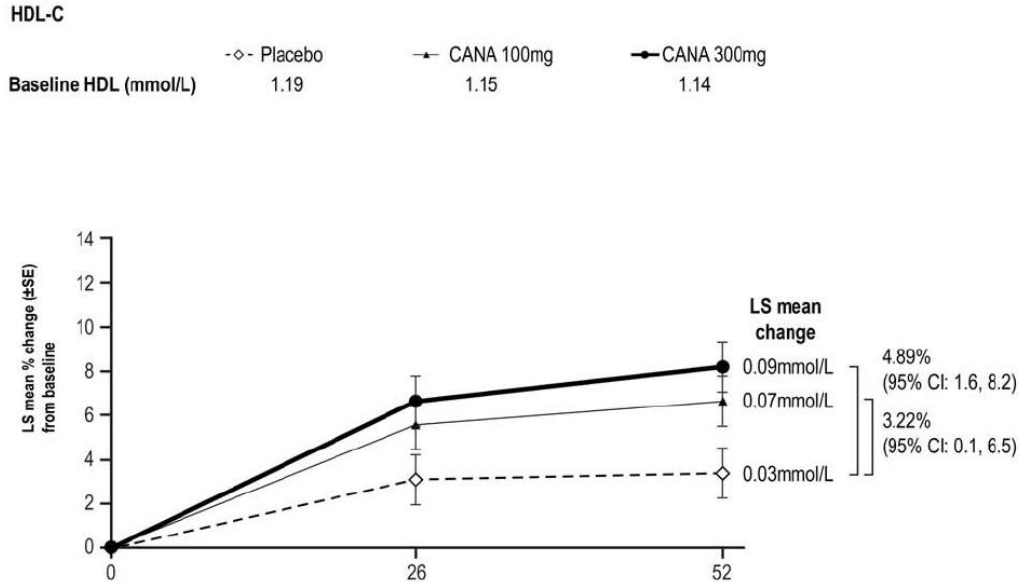
Legend: DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial (CANTATA-D2); CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 26. LS mean (±SE) percentage change in LDL-C (top) and HDL-C (bottom) from baseline in DIA3002]. (90)

LDL-C



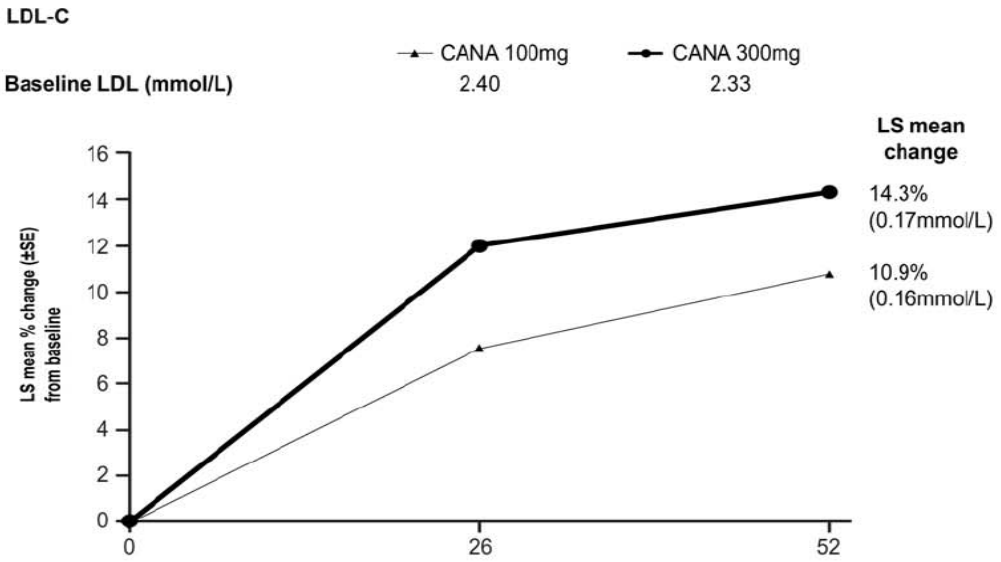
HDL-C



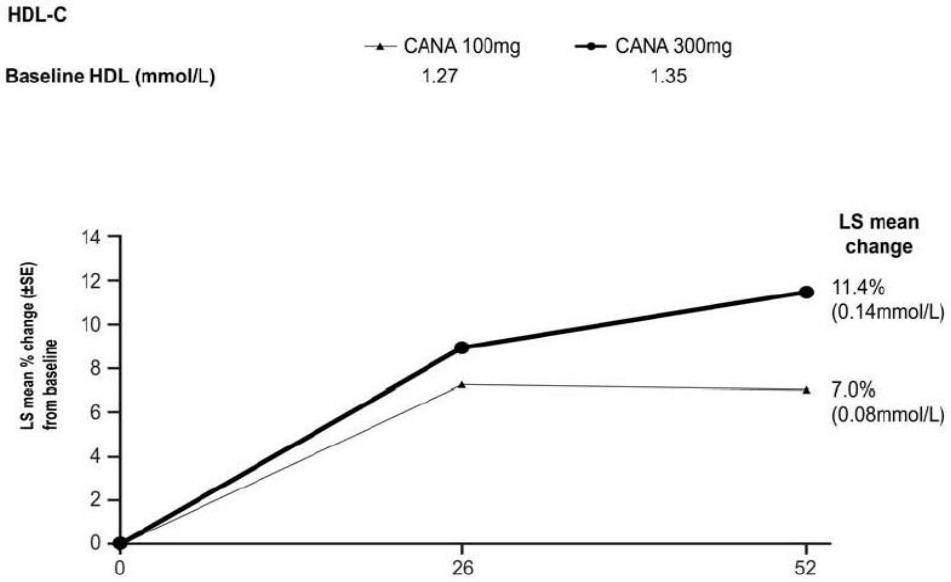
Legend: DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea (CANTATA-MSU),; CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Figure 27. LS mean (±SE) percentage change in LDL-C (top) and HDL-C (bottom) from baseline in DIA3012. (29)

LDL-C



HDL-C



Legend: DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone (CANTATA-MP);CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error.

Achievement of HbA1c targets

The studies assessed the percentage of patients achieving HbA1c of less than 7% (53mmol/mol) and less than 6.5% (48mmol/mol) at week 52. These are not presented in this dossier.

However, due to alternative HbA1c targets being considered by the NHS in England, a post-hoc analysis of the percentage of patients achieving HbA1c of less than 7.5% (59mmol/mol) at week 52 is reported in this submission (see Table 29 in Section 6.10.2. for Appendix 6). It should be noted that no treatment comparisons were

conducted as part of these post-hoc analyses. This threshold was chosen since they reflect NHS targets in the QOF.

[redacted]

[redacted]

[redacted]

6.5.3.3. Add-on to insulin (insulin ± OAD)

DIA3008 insulin sub-study demonstrates that canagliflozin 300mg and 100mg (in combination with INS+SoC) resulted in significantly improved glycaemic control and key secondary metabolic endpoints of change in BP and weight compared to placebo. The details of these results are presented below.

6.5.3.3.1. Add-on to insulin – primary outcome

In DIA3008 insulin sub-study at week 18, treatment with both doses of canagliflozin resulted in a significantly greater reduction in HbA1c than placebo at Week 18, although this appeared to be dose dependent. (30) The difference in mean change in HbA1c (95% CI) versus placebo was -0.65% [-30.6mmol/mol], 95% CI: -0.73 to -0.56, in canagliflozin 100mg arm and -0.73% [-31.48mmol/mol], 95% CI: -0.82 to -0.65, in canagliflozin 300mg arm, p<0.001. (30;84) It is worth noting that the sub-study was 18 weeks in duration and therefore maximal effect of canagliflozin may not have been realised. (84)

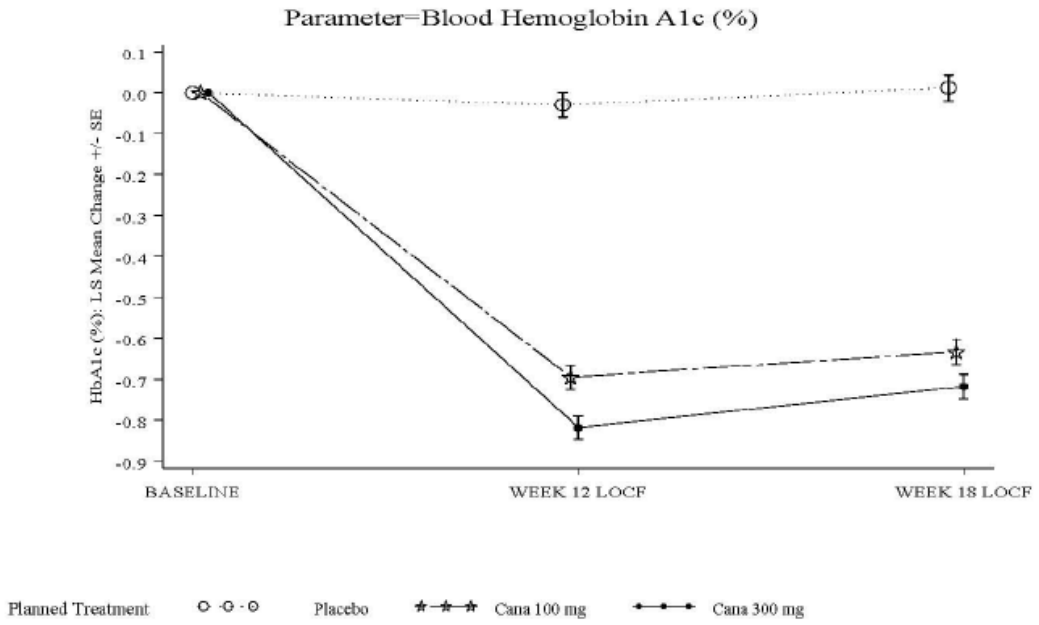
Table 19. Change in HbA1c at primary time point in CANVAS Add-on to insulin sub-study (DIA3008 insulin sub-study) – population 2 (≥30 IU) - mITT (LOCF). (84)

Trial no. (acronym)	Canagliflozin 100mg	Canagliflozin 300mg	Placebo
DIA3008 Insulin sub-study	**(n =566)**	**(n =587)**	**(n =565)**
HbA1c value at baseline (%), N Mean (SD)	540 8.33 (0.905)	562 8.27 (0.894)	517 8.20 (0.837)
Value at Week 18 LOCF Mean (SD)	7.67 (0.860)	7.54 (0.885)	8.23 (0.992)
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)	-0.65 (0.044)	-0.73 (0.043)	
P-Value	<0.001	<0.001	
95%CI	(-0.731;-0.559)	(-0.815;-0.645)	
DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study; Ins±OAD+: in combination with insulin other and potentially other anti-diabetics (CANVAS Insulin sub-study). *CI: confidence interval; LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SD: standard deviation; SE: standard error*			

6.5.3.3.2. Add-on to insulin – Secondary outcomes

Both doses of canagliflozin, when used as add-on to insulin resulted in sustained reduction in HbA1c after 18 weeks as shown in Figure 28 below.

Figure 28. LS mean (±SE) change from baseline in HbA1c (%) to week 18 CANVAS Add-on to insulin sub-study (DIA3008 insulin sub-study) – population 2 (≥30 IU) - mITT (LOCF)]. (30;96)



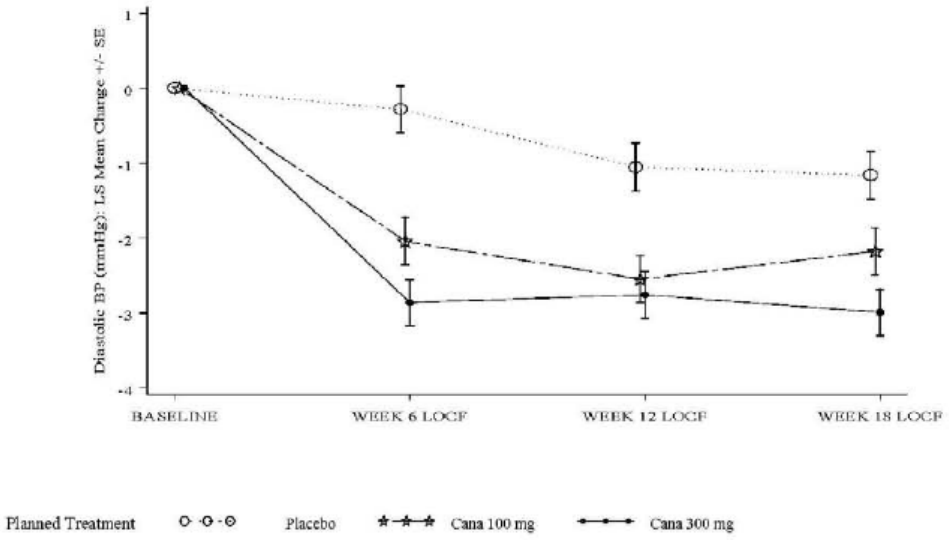
Legend: DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study; Ins±OAD+: in combination with insulin other and potentially other anti-diabetics (CANVAS Insulin sub-study). LOCF: last observation carried forward; LS: least square; mITT: modified intent-to-treat; SE: standard error

Change in blood pressure

Both doses of canagliflozin resulted in a significant reduction in SBP (p<0.001) compared with placebo. The effect was dose-dependent, with canagliflozin 300mg resulting in greater reductions than canagliflozin 100mg; difference in mean SBP change (minus placebo) of -2.58mmHg (95% CI: -4.060;1.091) and -4.38mmHg (95% CI:-5.850; -2.903), respectively - from a baseline of approximately 137mmHg (see Figure 29). (30)

Tables 30 and 31 of Appendix 6 (Section 10.6.3.) provide detailed data regarding changes in SBP and DBP for the DIA3008 insulin sub-study.

Figure 29. LS mean change (+SE) in SBP (mmHg) from baseline to week 18 CANVAS Add-on to insulin sub-study (DIA3008 insulin sub-study) – population 2 (≥30 IU) - mITT (LOCF). (84)

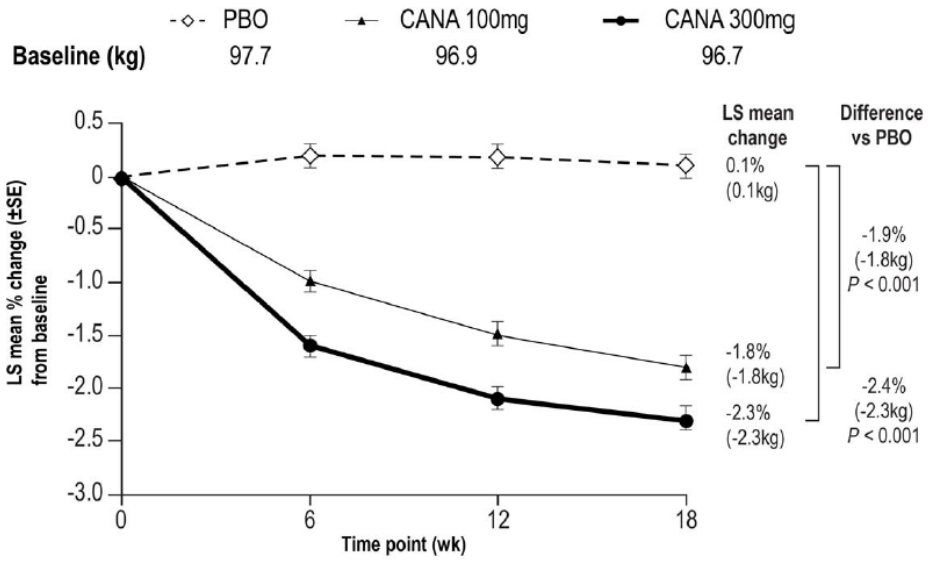


Change in body weight

Both doses of canagliflozin resulted in significant reductions in body weight despite a background of insulin which is known to cause weight gain. A reduction in weight (minus placebo) of-1.8kg (95%CI: -2.2;-1.6) was reported for canagliflozin 100mg and -2.3kg (95%CI: -2.7;-2.1) for canagliflozin 300mg, p<0.001 at week 18 (see Figure 30). As this study was only 18 weeks in duration, maximal weight loss with canagliflozin had likely not been achieved. (84)

Table 32 of Appendix 6 (Section 10.6.3.) provides details about the changes in body weight, demonstrating that patients in the canagliflozin arms steadily lost weight during the study period. (84)

Figure 30. LS mean (±SE) percentage change in body weight from baseline over time in the CANVAS add-on to insulin trial (DIA3008 insulin sub-study) – population 2 (≥30 IU) - mITT (LOCF). (96)

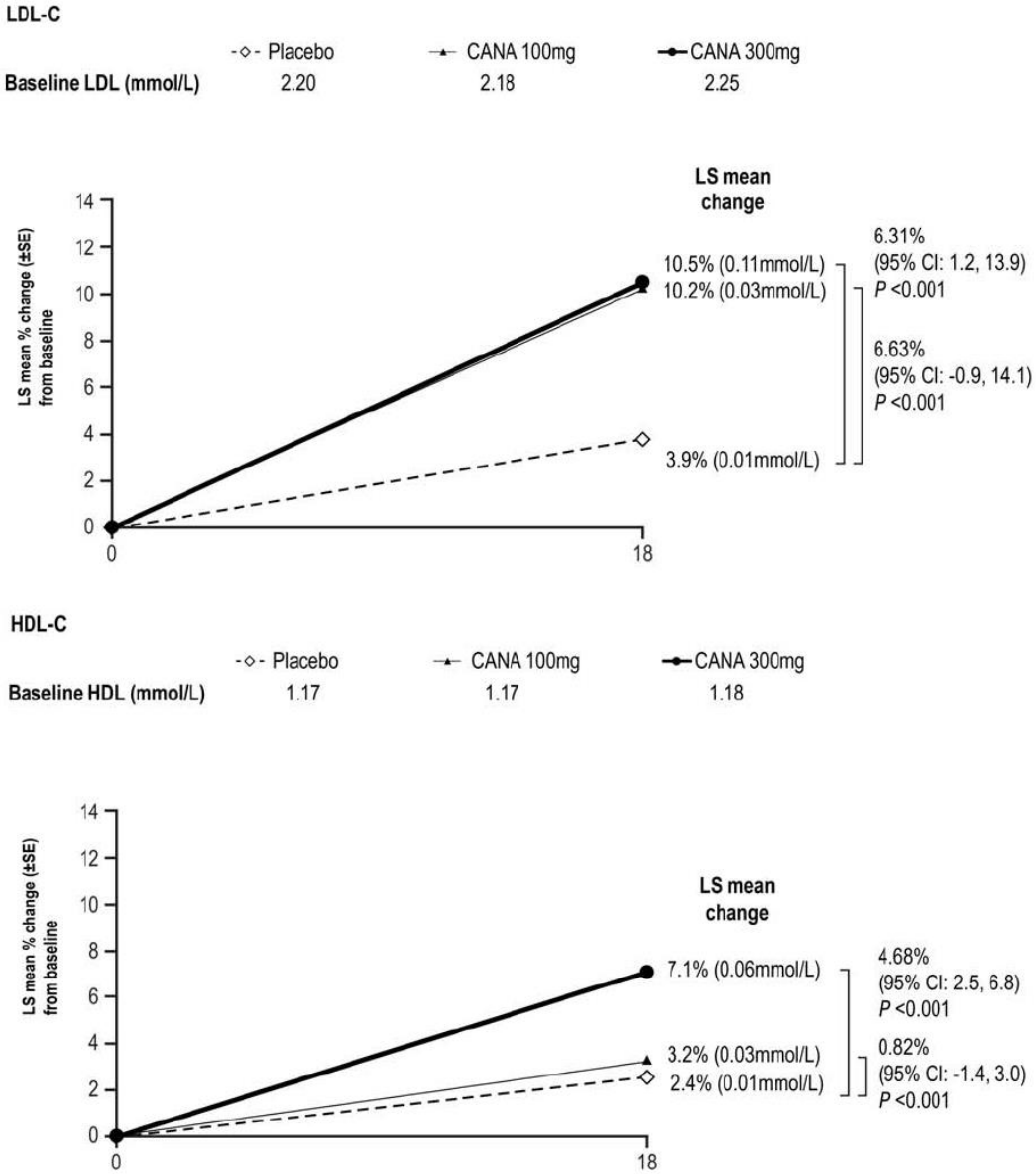


Change in lipid levels

Change in HDL-cholesterol, triglycerides and LDL-cholesterol from baseline to primary time point for add-on to insulin study are shown in Tables 33 to 35 in Appendix 6 (Section 10.6.3.).

Both doses of canagliflozin resulted in changes to the lipid profile over time; increased HDL-C and LDL-C. The change in HDL-C was dose-dependent, while the change in DLD-C was similar for both canagliflozin groups (see Figure 31).

Figure 31. LS mean (±SE) percentage change in blood lipids (LDL-C and HDL-C) from baseline over time in the CANVAS add-on to insulin trial (DIA3008 insulin sub-study), mITT LOCF. (84)



Achievement of HbA1c targets

Detailed results of the post-hoc analysis of the percentage of patients achieving HbA1c of less than 7.5% (59mmol/mol) at week 18 are reported in this submission.

More patients treated with canagliflozin in combination with INS+SoC achieved their HbA1c target than with placebo (see Figure 32) at week 18.

Figure 32. [redacted]

Sub-groups Analyses

Only the sub-group analyses by baseline BMI and baseline HbA1c thresholds are discussed in this submission, as per the decision problem (See Table 7).

While there were no difference in terms of change in mean HbA1c over time by BMI groups, change in mean HbA1c was affected by the level of baseline HbA1c. The difference between treatments were maintained for each of the trials, but larger absolute reductions in HbA1c were observed in patients with baseline HbA1c ≥ 9% vs. patients with a baseline HbA1c <8%.These results were expected and are comparable to the ones reported by other AHAs.

The results of sub-group analyses by baseline HbA1c thresholds (baseline HbA1c <8% [59mmol/mol], 8% to <9% [59mmol/mol to <64mmol/mol] and ≥ 9% [≥64mmol/mol]) by study are presented in Table 35 to 37 in Appendix 5.

In DIA3006, sub-group analyses by HbA1c threshold showed a significant difference in placebo-subtracted LS mean change (95% CI) from baseline at week 26 (mITT-LOCF) for canagliflozin 100mg and 300mg and sitagliptin 100mg, with difference in mean HbA1c change (minus placebo) of:

[redacted]

In DIA3015, numerically greater reductions from baseline in HbA1c were observed in the canagliflozin arm versus the sitagliptin arm for subjects with higher baseline HbA1c values. (7)

- For canagliflozin 300mg, mean changes from baseline in HbA1c were -1.99%, -1.15%, -0.57% in subjects with baseline HbA1c values ≥9.0%, 8.0 to <9.0 %, and <8.0%.
- For sitagliptin 100mg mean changes from baseline in HbA1c were-1.44%, -0.73%, and -0.31% respectively.
- The corresponding between-treatment differences were -0.26%, -0.41%, and -0.54% favouring canagliflozin in patients with baseline HbA1c <8%, between 8% and <9%, and ≥ 9%, respectively.

In DIA3002 and DIA3012, substantially greater reductions from baseline HbA1c at Week 26 were observed in both canagliflozin groups in subjects with higher baseline HbA1c values. Notably, clinically important reductions with canagliflozin doses were observed even in subjects with baseline HbA1c values <8%.

[redacted]

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

6.6.2 **If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.**

Network meta-analyses were conducted as described in section 6.7.

6.6.3 **If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

Not appropriate

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

Summary of section 6.7

A SLR was conducted to identify randomised controlled trials in T2DM patients inadequately controlled on OAD therapies and/or insulin. NMAs were conducted by background therapy, i.e. metformin at 26 weeks +/- 4 weeks and 52 weeks +/- 4 weeks, and MET+SU, MET+TZD and insulin at 26 weeks +/- 4 weeks. Doses of SUs and metformin were pooled as doses are adjusted on a per-patient basis in most clinical trials. Other treatments (i.e. SGLT-2-i, TZD, GLP-1-a and DDP-4-i) were dose-specific. The NMA was conducted using the Bayesian framework. The selection between fixed and random effects models was in line with the NICE recommendations (i.e. using the Deviance Information Criterion (DIC) to select the model associated with the best goodness of fit).

Results from the network meta-analysis indicated that canagliflozin 300mg was associated with similar or higher HbA1c reductions compared to exenatide 10µg, sitagliptin 100mg, pioglitazone 30mg and dapagliflozin 10mg across background therapies, and performed at least as well as glimepiride and gliclazide in the analysis of the metformin background at 52 weeks. Canagliflozin 100mg was associated with similar HbA1c reductions compared to dapagliflozin 10mg (metformin and insulin background therapies) and glimepiride and gliclazide (metformin background therapy).

Canagliflozin 300mg and 100mg were associated with similar or higher weight and/or BMI reductions compared to liraglutide 1.2mg, sitagliptin 100mg and pioglitazone 30mg across all background therapies, and higher weight and BMI reductions compared to glimepiride in the analysis of the metformin background. Canagliflozin 300mg and 100mg performed at least as well as dapagliflozin 10mg in the analysis of the metformin and insulin background therapies in terms of weight loss.

Canagliflozin 300mg and 100mg were associated with higher SBP reductions compared to liraglutide 1.2mg and glimepiride (metformin background therapy) and sitagliptin 100mg (metformin and MET+SU background therapies). Canagliflozin 300mg and 100mg performed at least as well as exenatide 10µg and dapagliflozin 10mg in the analysis of the insulin background therapy.

Canagliflozin 300mg and 100mg were associated with a lower risk of hypoglycaemic events compared to glimepiride and gliclazide in the analysis of the metformin background therapy. Canagliflozin 100mg was associated with a similar risk of hypoglycaemic events compared to sitagliptin 100mg in the analyses of MET+SU and MET+TZD background therapies.

6.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.**

6.7.1.1. Study question

A SRL was conducted to identify randomised controlled trials conducted in adults with T2DM with inadequate glycaemic control on anti-diabetic therapies and/or insulin assessing one intervention of interest versus an active comparator of interest or versus placebo on at least one study outcome. Interventions of interest are reported by background therapy in Table 20 below (in line with the NICE scope).

Study outcomes included efficacy estimates (HbA1c/glycaemic control, BMI, changes in CV risk factors, including BP and/or serum lipids, weight change, complications of diabetes and mortality, safety parameters (adverse effects of treatments, including frequency and severity of episodes of hypoglycaemia) and HRQL (in line with the NICE scope).

Table 20. Interventions and comparators of interest

	Background therapy	Comparators
Dual therapy	Metformin	SUs, TZD, DPP-4-i, GLP-1-a, dapagliflozin
	SU	TZD, DPP-4-i, GLP-1-a, dapagliflozin
Triple therapy	MET+SU	TZD, DPP-4-i, GLP-1–a , dapagliflozin, insulin*
	MET+TZD	DPP-4-i, GLP-1-a, insulin*
Add-on to insulin	Insulin + SoC	SUs, TZD, DPP-4-i, GLP-1-a, dapagliflozin, metformin

* The following classes of insulin were used: NPH insulin (intermediate acting), long acting insulin (glargine, detemir), biphasic/pre-mixed insulin and short acting insulin (lispro, aspart). These classes were defined in line with the NICE guidelines for the management of type 2 diabetes .

However, it should be noted that only outcomes of relevance to the economic model (i.e. change in HbA1c, weight, BMI and SBP, and incidence of hypoglycaemia) and the comparators considered in the economic simulations (see Section 7.3) will be presented in this submission. The full results of the SRL and the NMA can be found in the final report. (72)

6.7.1.2. Search strategy

The search strategy is described in Section 6.1.1.

6.7.1.3. Screening

The selection criteria were pre-specified and related to the population characteristics, interventions, outcomes measures, comparators, publication type, and the language

of publication. In addition, studies of less than 12 weeks in duration were excluded based on clinical expert opinion. More information regarding the screening criteria can be found in section 6.2.1.

6.7.1.4. Data abstraction

The methodology followed for data extraction is presented in Section 6.1.1 and in Appendix 2 (Section 10.2). In total, 85 RCTs were included for data extraction.

A tabular summary was developed in Microsoft Excel® to extract the data from the selected papers. The following information was extracted from the selected publications: publication details, study design, study population, study type, baseline characteristics, collected outcomes, subgroup analyses. A quality assessment of each study was performed in line with the NICE Guide to the methods of technology appraisal (103) and is presented in Appendix 7 in Section 10.7.1 (Clinical SRL – search strategy).

6.7.2 **Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.**

6.7.2.1. Study selection

Studies were identified using the systematic literature review described in section 6.1.1 and Appendix 7 in Section 10.7.1 (Clinical SRL – search strategy).

In order to pool data which are comparable across trials, additional criteria were defined for the inclusion of trials in the network meta-analysis (NMA):

- According to clinical experts, background therapies are an important treatment effect modifier. Therefore, analyses were conducted by background therapy. Trials assessing treatments on top of a “mixed” background were therefore excluded from the NMA.
- Analyses were conducted at 26 weeks (for all background therapies) and 52 weeks (for the metformin background only) to match the times of assessment of the canagliflozin trials. Based on clinical expert opinion, trials reporting results at 26 or 52 weeks ± 4 weeks were included in the base case analysis and trials reporting results at 26 or 52 weeks ± 10 weeks were included in a sensitivity analysis. Therefore, trials not reporting results within these ranges were excluded from the NMA.
- Based on clinical expert opinion, nodes of the NMA were treatment- and dose-specific except for insulin, metformin and SU.
- Treatments not recommended in the UK (i.e. by NICE or the SMC) were excluded from the NMA (e.g. insulin degludec and liraglutide 1.8 mg).
- Trials focusing on specific populations (i.e. patients with renal impairment, CVD or at risk of CVD) were not included in the NMA to reduce heterogeneity between trials in the analysis of metformin, MET+SU and MET+PIO background therapies. The only trial assessing canagliflozin added to insulin was conducted in patients with or at risk of

CVD, this criterion was not applied to the analysis of the insulin background.

6.7.2.2. Data sources

The list of data sources is reported in Appendix 7 in section 10.7.2. (Clinical SRL – data source)

6.7.2.3. Complete list of relevant RCTs

The complete list of relevant RCTs is reported in Appendix 7 in section 10.7.3. (Clinical SRL – list of relevant RCTs).

6.7.2.4. List of relevant non-RCTs

Not applicable (only RCTs were identified).

6.7.2.5. Summary of methodology of relevant RCTs

Tables presenting a summary of methodology of trials are reported in Appendix 7 in section 10.7.4 (Clinical SRL – Methods)

Thirty-eight trials were included in the base case NMA featuring a metformin background therapy. The maximum duration reported in these trials was approximately two years (with results reported at six months and/or one year). In the base case analysis, a total of 28 trials reported results at 26± 4 weeks and 17 trials reported results at 52± 4 weeks. Twenty-eight trials were double blinded and four trials were open-label. DPP-4-i were the most common interventions added to a background therapy of metformin, with these treatments featured in a total of 22 trials. GLP-1-a and SU were the next most frequently assessed class of treatments, followed by pioglitazone and SGLT-2-i. The primary outcome was change from baseline in HbA1c in all but four trials.

Ten trials were included in the base case NMA featuring a background therapy of MET+SU. The maximum study duration was approximately one year (with results reported at six months). Three trials were open-label and the remaining seven were double-blind trials. Insulin was the most frequent treatment class (in five trials) added on to the MET+SU background therapies, followed by the GLP-1-a (four trials), DPP-4-i (three trials) and SGLT-2-i (two trials) treatment classes. The primary outcome in all ten trials was change in HbA1c from baseline.

Two trials were included in the base case NMA featuring a background of MET+PIO. One trial had a study duration of 26 weeks while the study duration of the other trial was approximately one year (with results reported at six months). Both trials were double-blinded and both assessed HbA1c change from baseline as the primary outcome. One trial assessed an SGLT-2-i and the other a DPP-4-i.

Fourteen trials were included in the base case NMA featuring insulin background therapy. Three of these trials had a duration of approximately one year (with results reported at six months). All trials were double-blinded except one open-label trial

(Jacobs 2007). MET+PIO were the most common interventions added to an insulin background therapy, followed by DPP-4-i, SGLT-2-i and GLP-1-a.

6.7.2.6. Participants

The eligibility criteria of each trial are reported in Appendix 7 in section 10.7.5 (Clinical SRL – Participants).

6.7.2.7. Outcomes

Primary and secondary outcomes of each trial are reported in Appendix 7 in section 10.7.4 (Clinical SRL – Methods)

6.7.2.8. Statistical analysis and definition of study groups

A summary of statistical analyses is reported in Appendix 7 in section 10.7.6 (Clinical SRL – Statistical Analysis).

6.7.2.9. Participant flow

The sample size by treatment arm is reported in Appendix 7 in section 10.7.7 (Clinical SRL – Summary of data used in the analysis). Any unexpected imbalances in drop-outs between groups was assessed as part of the quality assessment, as reported in Appendix 7 in section 10.7.8 (Clinical SRL – Quality assessment).

6.7.2.10. Critical appraisal of relevant RCTs

The critical appraisal of RCTS is reported in Appendix 7 in section 10.7.8 (Clinical SRL – Quality assessment).

6.7.2.11. Results of the relevant RCTs

The results of the relevant RCTS are reported in Appendix 7 in section 10.7.9 (Clinical SRL –Summary of the trials used to conduct the indirect/mixed treatment comparison).

<u>Dual therapy</u>

In trials with a metformin background and results at a time point of 52 weeks ± 4 weeks included in the base case meta-analysis, the magnitude of the mean change in HbA1c from baseline, ranged from -2.10% to -0.30% (both glimepiride treatment arms) across treatment arms. The mean weight change ranged from -8.0 kg (exenatide) to 4.3 kg (glibenclamide) in these trials. Mean change in BMI ranged from -2.1 kg/m^2 (vildagliptin) to 1.5 kg/m^2 (glibenclamide) and the mean change in SBP ranged from -4.65 mmHg (canagliflozin) to 3.24 mmHg (glimepiride) in these trials. The proportion of patients experiencing hypoglycaemic events ranged from 2% (vildagliptin) to 40% (glipizide).

<u>Triple therapy</u>

In trials with a MET+SU background included in the base case meta-analysis, the magnitude of the mean change in HbA1c from baseline ranged from -2.76% (Insulin Aspart) to +0.30% (placebo) across treatment arms. The mean weight change ranged from -2.52 kg (canagliflozin 300mg) to +4.1 kg (Insulin Aspart). Mean change in BMI ranged from -0.90 kg/m^2 (canagliflozin 300mg) to 0.06 kg/m^2 (sitagliptin) and the mean change in SBP ranged from -6.21 mmHg (canagliflozin 300mg) to 0.54 mmHg (insulin glargine). The proportion of patients experiencing any hypoglycaemic event ranged from 1% (placebo) to 61% (insulin aspart).

In trials with a MET+TZD background included in the base case meta-analysis, the magnitude of the mean change in HbA1c from baseline ranged from -1.10% (sitagliptin) to -0.26% (placebo) across treatment arms. The proportion of patients experiencing a hypoglycaemic event ranged from 3% (placebo and canagliflozin arms) to 5% (canagliflozin).

Add-on to insulin therapy

In trials with an insulin background included in the base case meta-analysis, the magnitude of the mean change in HbA1c from baseline ranged from -4.00% (pioglitazone) to 1.82% (placebo) across treatment arms. The proportion of patients with HbA1c <7% in these trials ranged from 5.0% (placebo) to 60% (exenatide). The mean change in FPG ranged from -3.60mmol/l to +0.68mmol/l (both placebo arms) and the mean weight change ranged from -2.56 kg (canagliflozin) to +7.80kg (metformin). Mean change in SBP ranged from -7.57 mmHg (canagliflozin) to 1.70 mmHg (placebo).

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A summary of trials by background therapy used to conduct the indirect/mixed treatment comparisons is reported in Appendix 7 in section 10.7.9 (Clinical SRL – summary of the trials used to conduct the indirect/mixed treatment comparison).

The networks of evidence for the metformin background at 26 weeks and 52 weeks (see Figure 33 and Figure 34) included the following treatment classes: SU, TZD (pioglitazone only), DPP-4-i, GLP-1-a, and SGLT-2-i (canagliflozin and dapagliflozin).

Figure 33 Network of evidence - metformin background at 26 weeks

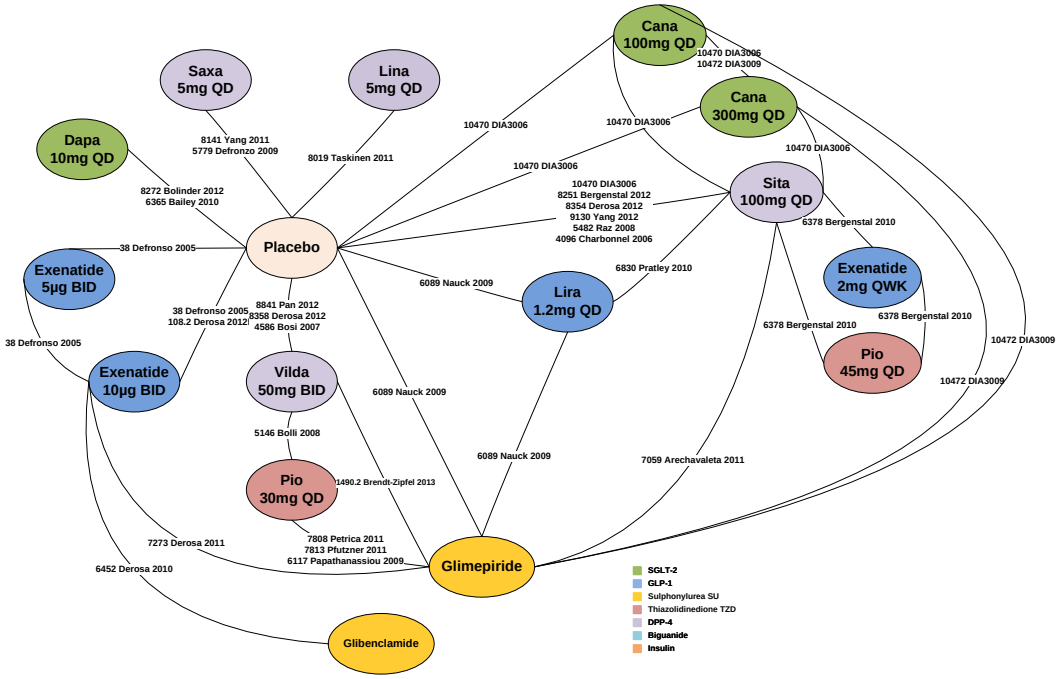
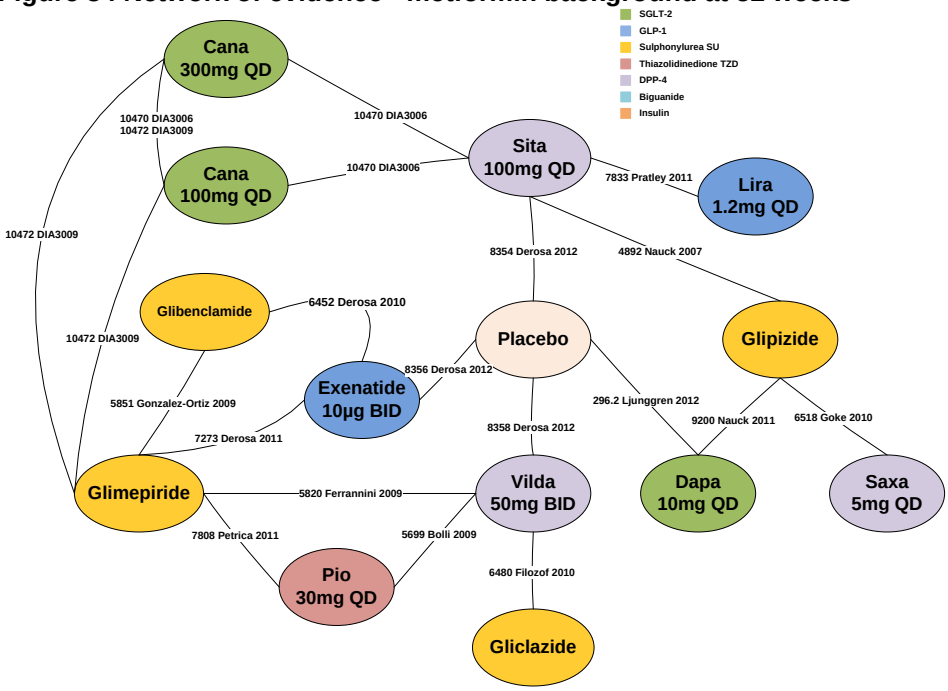
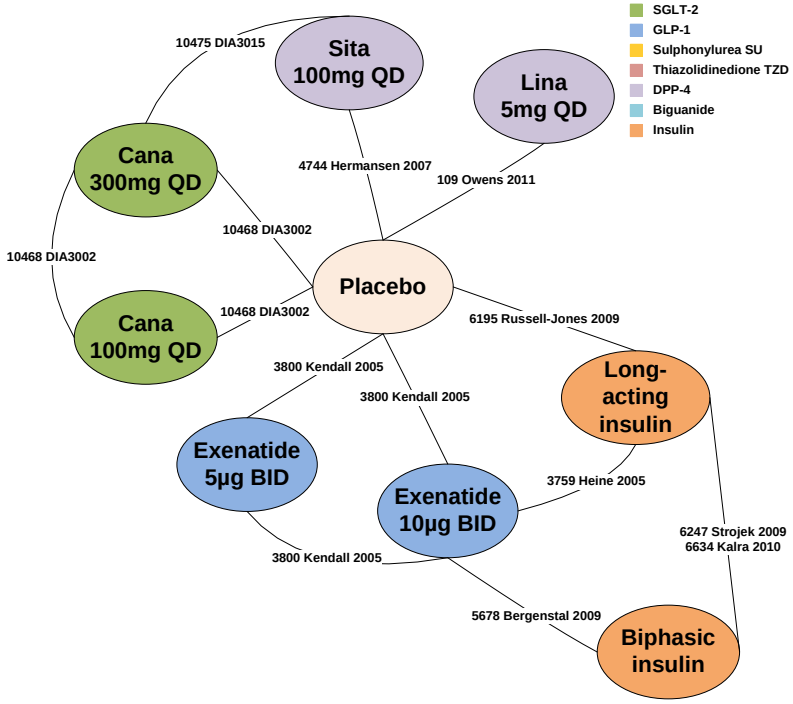


Figure 34 Network of evidence - metformin background at 52 weeks



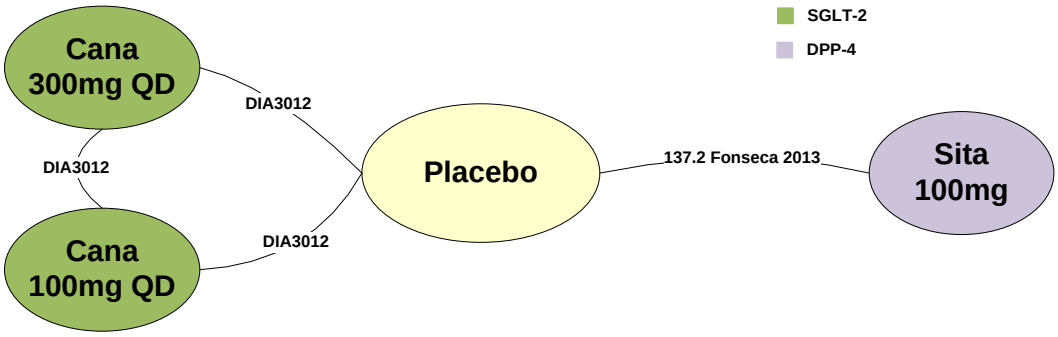
The network of evidence for the MET+SU background at 26 weeks (See Figure 35) included the following treatment classes: DPP-4-i, GLP-1-a, insulin regimens and SGLT-2-i (canagliflozin). Pioglitazone was not connected to the network in the base case analysis, as there was no direct or indirect link between canagliflozin and pioglitazone. However pioglitazone was included in the sensitivity analysis assuming class effects and was connected to the network through insulin. (104)

Figure 35 Network of evidence - MET+SU background



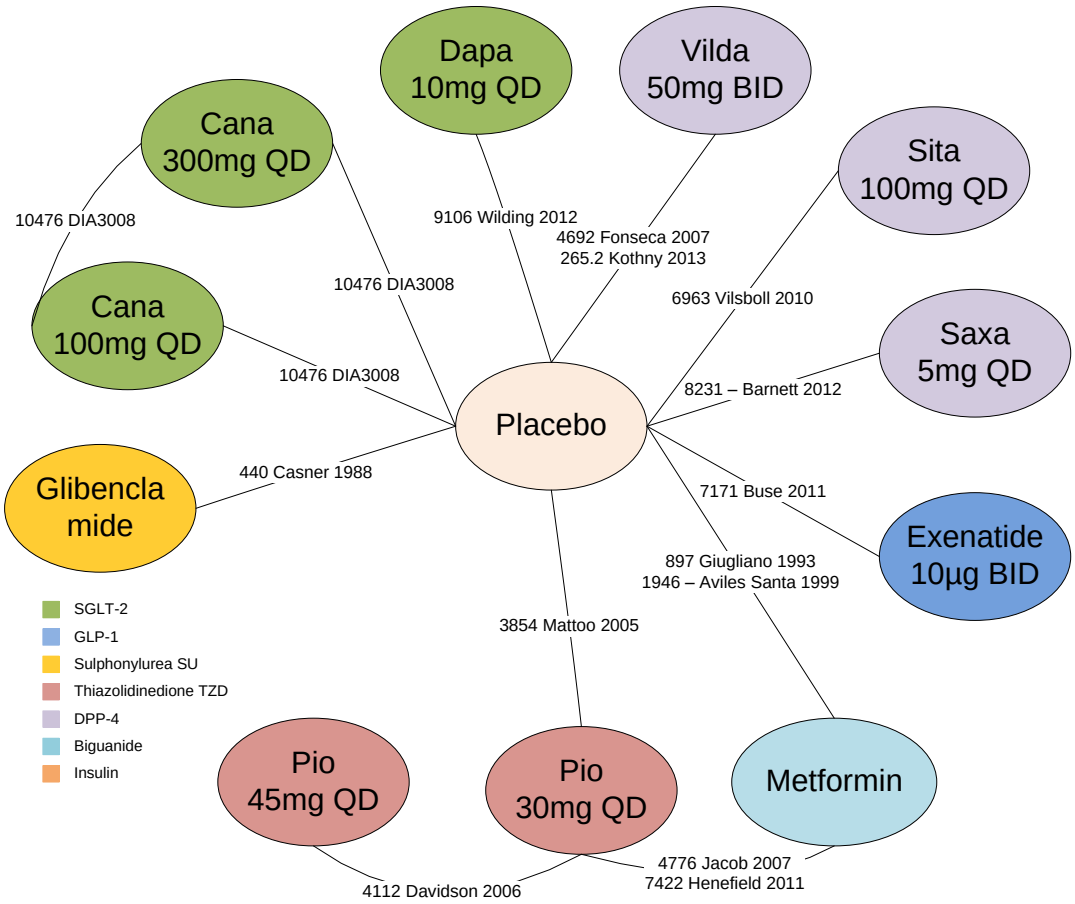
The network of evidence for the metformin plus pioglitazone background (See Figure 36) included the DPP-4-i sitagliptin. GLP-1-a and insulin were not included in this network of evidence as no trials assessing these treatments combined with metformin plus pioglitazone were identified as part of the systematic literature review.

Figure 36 Network of evidence - metformin plus pioglitazone background



The network of evidence for the insulin background at 26 weeks (See Figure 37) included the following treatment classes: pioglitazone, DPP-4-i, GLP-1-a, SGLT-2-i (canagliflozin and dapagliflozin) and metformin.

Figure 37 Network of evidence - insulin background



On the basis of the outcomes reported in the selected trials (see Appendix 7 in section 10.7.6 [Clinical SRL – statistical analyses]), and those used as part of the economic modelling, the following outcomes are reported in this submission for the NMA:

- HbA1c change from baseline (%)
- Weight change from baseline (kg)
- BMI change from baseline (kg/m^2)
- SBP change from baseline (mmHg)
- Proportion of patients with at least one hypoglycaemic event. “Any” hypoglycaemic events were pooled, defined as either symptomatic events (with or without biochemical confirmation) or asymptomatic events (with biochemical confirmation).
- Proportion of patients with at least one major hypoglycaemic event, defined as an event requiring external assistance, or associated with loss of consciousness or seizure.

Information relating to the proportion of patients reaching HbA1c <7% and FPG change from baseline (mmol/L) are presented in the NMA report only. (72)

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

A summary of data used in the analysis is reported in Appendix 7 in section 10.7.9 (Clinical SRL – Summary of trials used to conduct the indirect/mixed treatment comparison). An overview of these results is reported in section 6.7.2.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

6.7.5.1. Data inputs

For binary outcomes, the number of events and total number of patients in each treatment arm were used as inputs for the statistical model.

For continuous outcomes, the mean change from baseline in each treatment arm and the standard error were used as inputs for the statistical model. (105)

6.7.5.2. Handling of missing data

In case of missing data inputs for the meta-analysis, some data were estimated based on other results provided in the publications (depending on data availability) as follows.

For continuous outcomes, if the mean change from baseline was not reported, it was estimated as the difference between the final value and the value at baseline in each arm.

The variance of this mean change from baseline was estimated as follows:

$$\sigma_{change}{}^2 = \sigma_{final}{}^2 + \sigma_{baseline}{}^2 - 2\rho\sqrt{\sigma_{final}{}^2 * \sigma_{baseline}{}^2}$$

With σ^2 the variance reported for the outcome and ρ the within-patient correlation. As recommended in the NICE DSU evidence synthesis series, a value of 0.5 was used for ρ in the base case analysis (conservative approach) and a different value (0.7) was tested as a sensitivity analysis. (106)

6.7.5.3. Direct comparisons

Meta-analyses based on direct comparisons were carried out between each pair of treatments when possible, i.e. when the two treatments have been compared in two or more clinical trials. A frequentist model was used as described by Whitehead (2002). (107)

The inverse variance-weighted method was used to analyse binary and continuous outcomes. (108) The weights used to pool the different studies were the inverse of the variance of the study outcomes. Moreover, the weighted least squares method was used to estimate the between study variance in random effect models.

In case of binary outcomes, the inverse variance-weighted method cannot be implemented if one or more arms in one or more studies reported zero event. The presence of zero(s) in the analysis of an outcome was handled using the Mantel-Haenszel method, as recommended in the Cochrane handbook.. (105)

For each pairwise comparison, the Cochran's Q test and the I^2 statistic were calculated. Heterogeneity was suspected if:

- The Cochran's Q test was significant with a significance level of 10%, or
- I^2 was higher than 50%. (109)

The forest plot was generated to illustrate a suspected heterogeneity (if I^2> 50% or p-value of the Cochran's Q test < 10%).

6.7.5.4. Network meta-analysis

A Bayesian hierarchical model was used for the network meta-analysis. (110)

For the modelling of binary outcomes, it was assumed that the number of events in each treatment arm follow a binomial likelihood where parameters are the probability of events under each treatment and the number of patients in each arm. As the probabilities can only vary between 0 and 1, a transformation was used to map these probabilities into a continuous measure. For a binomial likelihood, a logit function was used, which is based on the assumption of the linearity of effects. The logit link function is commonly used according to the NICE DSU evidence synthesis series. (106)

With continuous outcome data, the meta-analysis was based on the sample means which can be assumed as being approximately normally distributed. Moreover, this parameter is not constrained in an interval, as consequence identity was used as link function.

6.7.5.5. Model selection

The relative goodness of fit of the models was assessed using the Deviance Information Criterion (DIC). The fixed effects (FE) and random effects (RE) models were developed and the one associated with the lowest DIC was selected (with a difference of at least three points in DIC . (111) The model with the smallest DIC is the model with the best compromise between adequacy and complexity: The BUGS Project. (112)

$$DIC = \overline{D} + P_D$$

Where $\overline{D}$ is the posterior mean residual deviance and P_D is the effective number of parameters.

When a random effects model was selected, results from the corresponding fixed effects model were also reported as a sensitivity analysis.

6.7.5.6. Multi-arm trials

In case trials compared more than two treatments of interest, the statistical approach was adjusted for the correlation between treatment effects from the same trials. The approach recommended by the NICE DSU was used, which is based on a conditional distribution formulation of the multivariate normal distribution (106)

6.7.5.7. Crossover trials

Based on statistical expert opinion, only the first phase of crossover trials was included in the meta-analysis due to the potential bias associated with carryover effect.

According to the Cochrane handbook for systematic reviews of interventions, (105) crossover trials are generally associated with a risk of bias (e.g. carryover effect, risk of incorrect analysis, treatment sequences which are not randomised). In addition, results from a crossover trial may not be comparable to results from a parallel-group study. Therefore, a sensitivity analysis excluding crossover trials was conducted to assess the impact on the results.

6.7.5.8. Inconsistency assessment

For each loop of the network, an indirect comparison (based on the Bucher at al. approach) (113) was conducted and compared to the direct evidence from the network meta-analysis. (114) The ratio of the point estimates obtained from indirect versus direct evidence was calculated, together with the 95% confidence interval (CI). Inconsistency was suspected if the CI excludes 1.

6.7.5.9. Rank probabilities

For each treatment, the probability of ranking first, second, etc was calculated and the SUCRA (Surface Under the Cumulative Ranking) was estimated for treatment j as follows ("a" being the total number of treatments and "$cum_{j,b}$" being the probability for treatment j to be in the first b treatments). (115)

$$SUCRA_j = \frac{\sum_{b=1}^{a-1} cum_{j,b}}{a-1}$$

The SUCRA is expressed as a percentage and ranges between 0% and 100%. A SUCRA of 100% indicates that the treatment always ranks first, whereas a SUCRA of 0% indicates that a treatment always ranks last.

6.7.5.10. Implementation

Non-informative prior distributions were used for unknown parameters to get results driven by the data. The following priors were used for the base case analysis:

Normal distributions with a mean of 0 and a variance of 10,000 for treatments effects. (106)

Uniform distribution for the between-trial standard deviation, with a range of [0,2] for binary outcomes. For continuous outcomes, the range was selected based on the scale of the outcome. In case of convergence issues, the posterior distribution of the between-trial standard deviation was accounted for to select the appropriate prior distribution. (106)

The network meta-analysis was performed with Winbugs V1.4 using MCMC (Markov Chain Monte Carlo) simulation method. Three chains (106) were simulated and their convergence was assessed by examining the history and the Gelman-Rubin plots. (116) When possible, starting values required for the three chains were generated automatically by WinBUGS. If not, starting values were arbitrarily selected for each chain as widely different.

A total of 20,000 iterations were used as burn-in followed by 20,000 iterations to monitor the parameters for fixed effects model, and 100,000 iterations as burn-in and 100,000 to monitor the parameters for random effects models. The number of iterations was increased in case the convergence was not reached.

6.7.5.11. Main assumptions (for the base case analysis)

Based on clinical expert opinion, separate analyses were conducted at 26 weeks +/- 4 weeks and 52 weeks +/- 4 weeks (for the metformin background) to increase comparability between trials and reflect the analyses conducted in the canagliflozin trials.

All analyses were conducted by background therapy (metformin, MET+SU, MET+TZD, insulin) as background therapies are important treatment effect modifiers in T2DM.

Nodes of the NMA were treatment- and dose-specific except for insulin, MET+SU. Doses of MET+SU were pooled to reflect dose adjustments on a per-patient basis. In addition, class effects were assumed for insulin in line with the NICE guidelines for the management of T2DM (NPH insulin, long acting insulin, biphasic/pre-mixed insulin, and short acting insulin). (36)

6.7.5.12. Sensitivity analyses

Sensitivity analyses were conducted to ensure robustness of the results.

- Time of assessment: trials which collected endpoints at 26 weeks +/- 10 weeks or 52 weeks +/- 10 weeks were included as a sensitivity analysis.
- Prior distributions: a gamma distribution (0.001, 0.001) was tested for the between-trial precision (i.e. inverse variance) in the random effects model.
- Any trial considered as a potential source of heterogeneity or inconsistency was excluded to further explore the validity of the similarity assumption between trials
- Trials of lower quality: trials which were not double-blinded were excluded as a sensitivity analysis
- Class effects were assumed for insulin, GLP-1-a, DDP-4-i, SU and TZD

- Handling of missing data: a sensitivity analysis was conducted regarding trials with imputed standard error (a correlation of 0.7 between the baseline and the final value was assumed).
- Conference abstracts: results published as conference abstracts only since 2010 were included as a sensitivity analysis to assess the impact on the results
- For the metformin plus pioglitazone background, due to the limited number of trials in the base case analysis, a sensitivity analysis including trials with patients receiving a mixed background therapy (i.e. metformin + TZD or TZD alone as a background therapy) was conducted.

SAS and WinBUGS programs are reported in Appendix 7 in section 10.7.10 (Clinical SRL – Winbugs and SAS programs).

6.7.6 Please present the results of the analysis.

Detailed tables of results can be found in Appendix 7 in Section 10.7.14. (Dual therapy at 26 weeks), Section 10.7.15 (Dual therapy at 52 weeks), Section 10.7.16 (triple therapy in combination with MET+SU), Section 10.7.17 (triple therapy in combination with MET+TZD), and Section 10.7.18 (Add-on to insulin).

6.7.6.1. Selection of models

The selection of fixed versus random effects model was based on the DIC as reported in Table 21. A random effects (RE) model was selected for the analysis of HbA1c change from baseline with the metformin (26 and 52 weeks) and MET+SU background therapies, the weight change from baseline with the MET+SU background and the BMI change from baseline with the metformin background (52 weeks).

Table 21 DIC for fixed and random effects models by background therapy and endpoint

Outcomes	Model	Met 26wks	Met 52wks	Met+SU	Met+Pio	INS
Hba1c	FE	-10.58	-55.41	-18.65	**-7.98**	**-14.80**
(change)	RE	**-81.18**	**-59.91**	**-25.78**	-7.91	-15.16
Weight	FE	**92.69**	**58.25**	29.68	**15.36**	**56.81**
(change)	RE	94.08	60.15	**19.32**	15.40	56.88
BMI	FE	**1.45**	16.15	**-6.10**	**	**
(change)	RE	2.61	**8.29**	-6.00		
SBP	FE	**113.13**	**32.28**	**26.43**	**	**40.17**
(change)	RE	113.99	33.42	26.44		40.11
All hypoglycaemia	FE	***	**126.20**	**133.99**	**27.01**	**
(change)	RE		127.13	131.39	27.05	
Severe hypoglycaemia	FE	****	****	****	**	****
(change)	RE					

The selection of model by background therapy and endpoint is reported in bold (i.e. selection of the model associated with the lowest DIC with a difference of at least three points)
**The RE model was the most appropriate based on the DIC, however results from the FE model are presented due to convergence issues of the RE model*
*** No analysis was conducted for these endpoints due to missing data*

****Results were not stable and led to abnormal values due to low numbers of hypoglycaemic events in some treatments arms*
*****Due to the absence of severe hypoglycaemic events in many trials (in one or several treatment arms), the analysis of severe hypoglycaemia could not be conducted (models could not run or chains did not converge)*

Only endpoints used in the cost-effectiveness model are reported in the following sections (i.e. change from baseline in HbA1c, weight, BMI and SBP and incidence of all hypoglycaemic events. However, network meta-analyses were conducted using all treatments among the pre-specified classes of treatments (depending on data availability from the literature). Results for other endpoints and comparators are reported in the NMA report. (72)

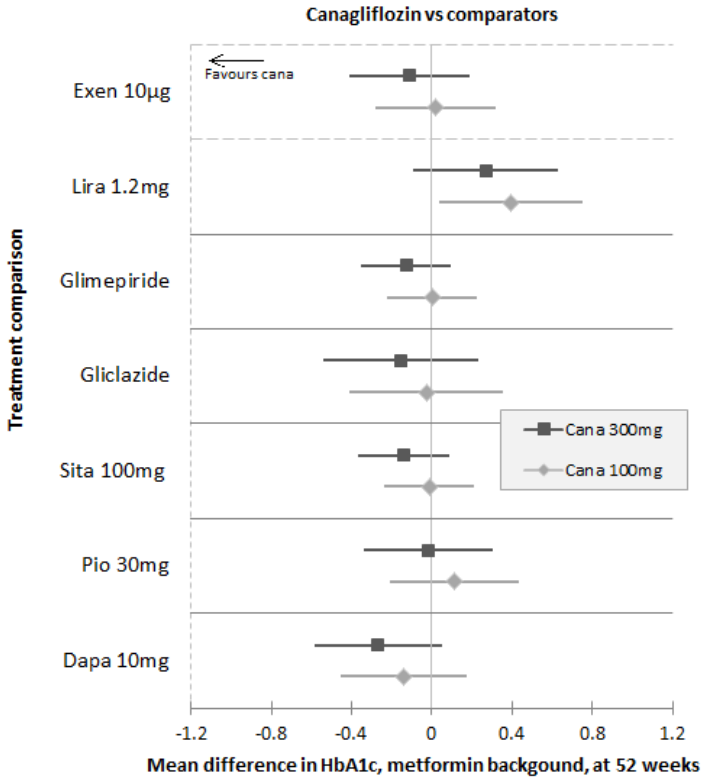
6.7.6.2. Dual therapy - Metformin background (52 weeks)

6.7.6.2.1. HbA1c change from baseline (Figure 38)

Differences in HbA1c change at 52 weeks compared to the different comparators with a metformin background are:

- Sitagliptin 100mg: difference of -0.2% for canagliflozin 300mg and -0.01% for canagliflozin 100mg.
- Dapagliflozin 10mg: difference of -0.27% for canagliflozin 300mg and -0.14% for canagliflozin 100mg.
- SU (Glimepiride and gliclazide): higher HbA1c reductions for canagliflozin 300mg and similar reduction in HbA1c for canagliflozin 100mg.
- Pioglitazone 30mg: difference of -0.112% for canagliflozin 300mg and 0.021% for canagliflozin 100mg.
- Liraglutide 1.2mg: difference of 0.27% for canagliflozin 300mg and 0.40 for canagliflozin 100mg.
- Exenatide 10µg: difference of -0.11% for canagliflozin 300mg, and 0.02% for canagliflozin 100mg.

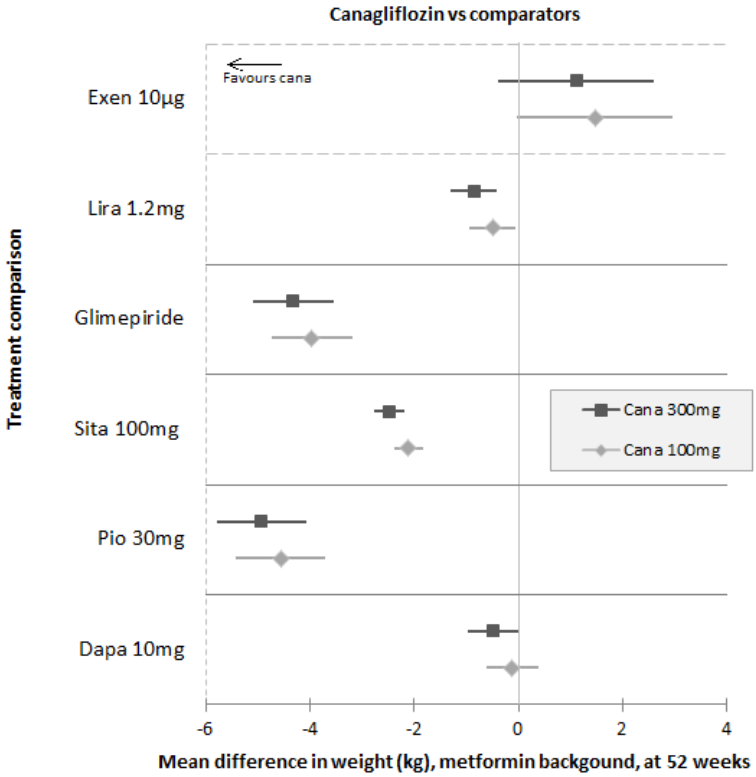
Figure 38 Mean difference in HbA1c [95%CrI], metformin background at 52 weeks



6.7.6.2.2. Weight change from baseline (Figure 39)

Canagliflozin 300mg and 100mg were associated with higher weight reductions compared to DDP-4 –i (difference in weight change vs. sitagliptin 100mg: -2.12kg and -2.48kg), SU (difference ranging from -3.97kg to -4.33kg) and pioglitazone 30mg (difference ranging from -4.57kg to -4.93kg) for canagliflozin 100mg and 300mg respectively. The reduction in weight was at least similar for canagliflozin 300mg and 100mg compared to dapagliflozin 10mg. When comparing canagliflozin with the GLP-1-a, exenatide 10µg was associated with a higher reduction in weight whereas liraglutide 1.2mg was associated with a lower reduction in weight.

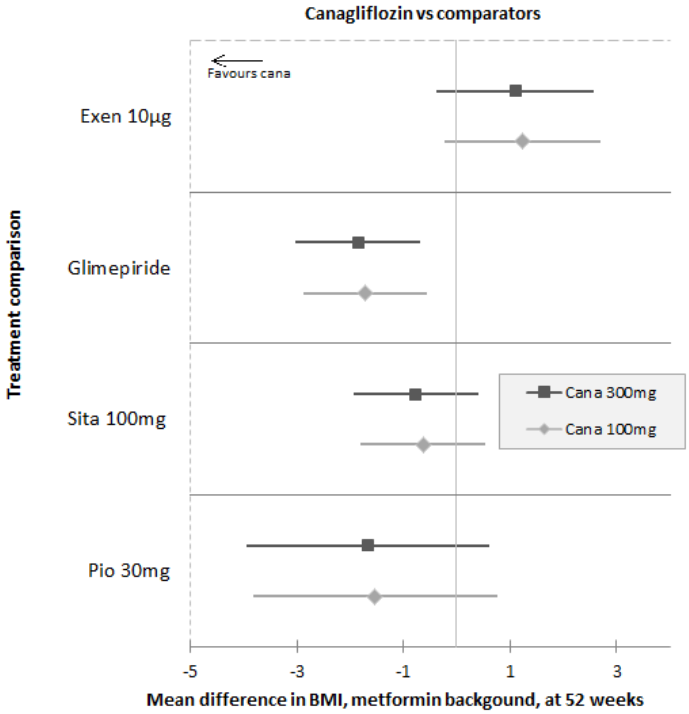
Figure 39 Mean difference in weight [95%CrI], metformin background at 52 weeks



6.7.6.2.3. BMI change from baseline (Figure 40)

Canagliflozin 300mg and 100mg were associated with higher reductions in BMI compared to SU and pioglitazone 30mg. The reduction in BMI was similar or higher for canagliflozin 300mg and 100mg compared to the DDP-4-i. Exenatide 10µg ranked first on the basis of the SUCRA and was associated with higher reductions in BMI compared to canagliflozin 300mg and 100mg.

Figure 40 Mean difference in BMI [95%CrI], metformin background at 52 weeks

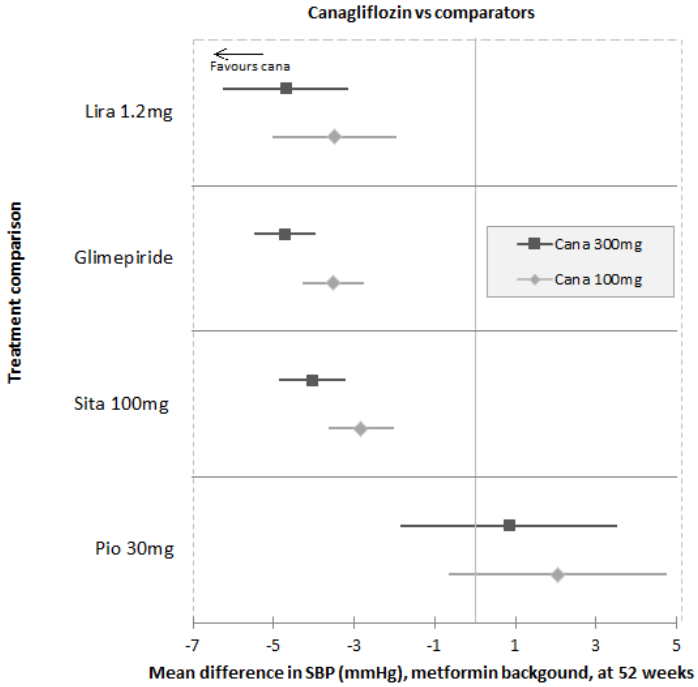


6.7.6.2.4. SBP change from baseline (Figure 41)

The placebo arm was excluded from the analysis of SBP in the metformin background at 52 weeks due to missing data (Appendix 7 in section 10.7.9. [Clinical SRL - Summary of the trials used to conduct the indirect/mixed treatment comparison]). Only results for canagliflozin versus active treatments are reported below.

Canagliflozin 300mg and 100mg were associated with higher reductions in SBP compared to glimepiride, liraglutide 1.2mg and sitagliptin 100mg, and smaller reductions in SBP compared to pioglitazone 30mg.

Figure 41 Mean difference in SBP [95%CrI], metformin background at 52 weeks

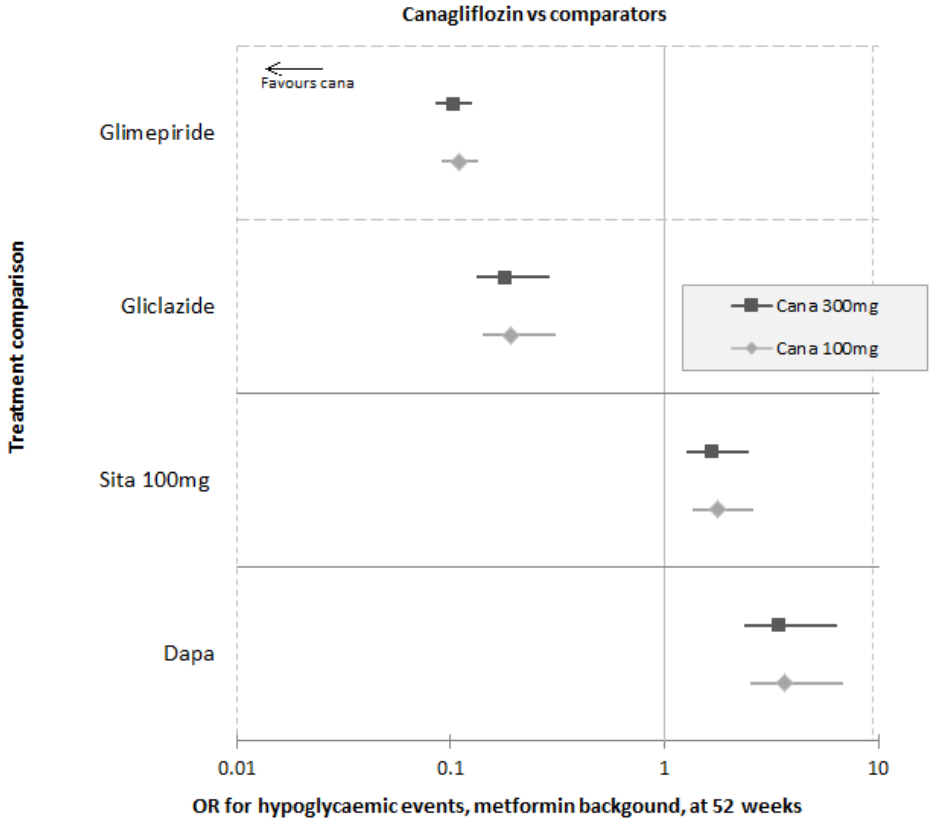


6.7.6.2.5. All hypoglycaemic events (Figure 42)

The network of evidence for the analysis of all hypoglycaemic events was almost linear leading to a high number of indirect links between some treatments.

Canagliflozin 300mg and 100mg were associated with a lower risk of hypoglycaemia compared to SU (ORs ranging from 0.10 to 0.11) and higher risk of hypoglycaemia compared to dapagliflozin 10mg (ORs ranging from 3.43 to 3.65) and the DDP-4-i (ORs ranging from 1.19 to 3.62). The difference in risk of hypoglycaemia versus dapagliflozin measured in this NMA is likely to be due to study design (i.e. different in reporting of hypoglycaemic event) only.

Figure 42 Hypoglycaemic events (OR [95%CrI]), metformin background at 52 weeks



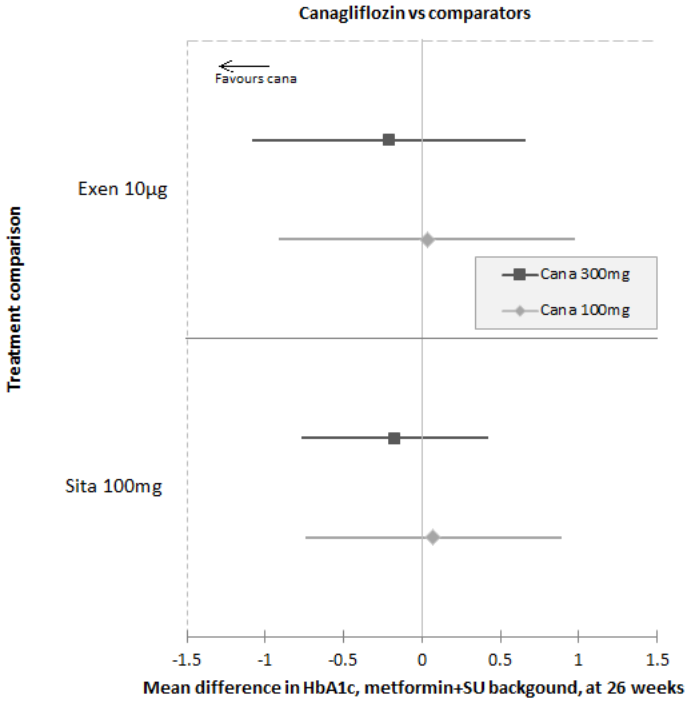
6.7.6.3. Triple therapy - metformin plus SU background

6.7.6.3.1. HbA1c change from baseline (Figure 43)

Canagliflozin 300mg was associated with higher HbA1c reductions compared to DDP-4-i (sitagliptin 100mg) with a difference in HbA1c of -0.17%. Canagliflozin 100mg was associated with similar HbA1c reductions compared to DDP-4-i with a difference in HbA1c of 0.07%.

Canagliflozin 300mg was associated with higher HbA1c reductions compared to GLP-1-a (exenatide 10µg) with a difference in HbA1c of -0.21%. Canagliflozin 100mg was associated with similar HbA1c reductions compared to GLP-1-a with a difference in HbA1c of 0.03%.

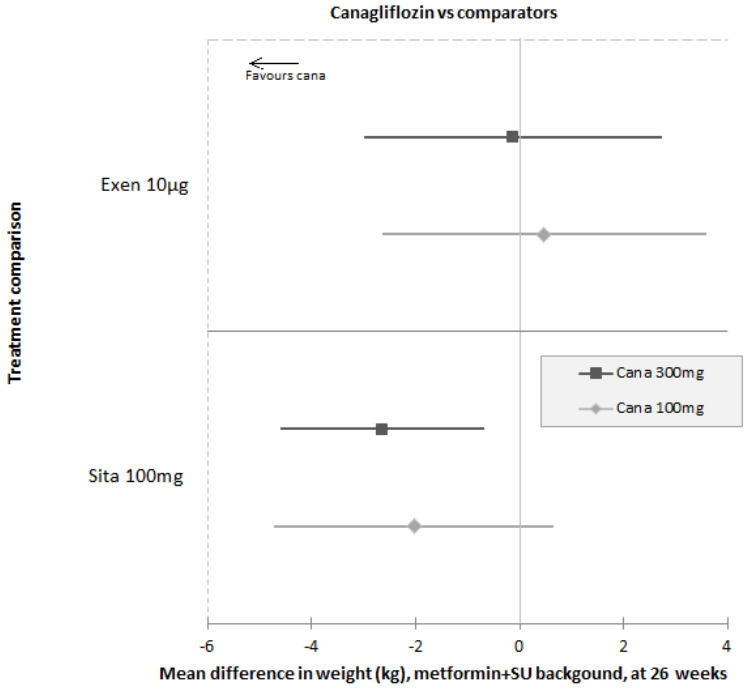
Figure 43 Mean difference in HbA1c [95%CrI], MET+SU background at 26 weeks



6.7.6.3.2. Weight change from baseline (Figure 44)

Canagliflozin 300mg and 100mg were associated with higher weight reductions compared to DDP-4-i (difference of -2.64kg and -2.03kg, respectively). The reduction in weight for canagliflozin 100mg and 300mg was similar to GLP-1-a (difference of –0.14kg and 0.47kg, respectively).

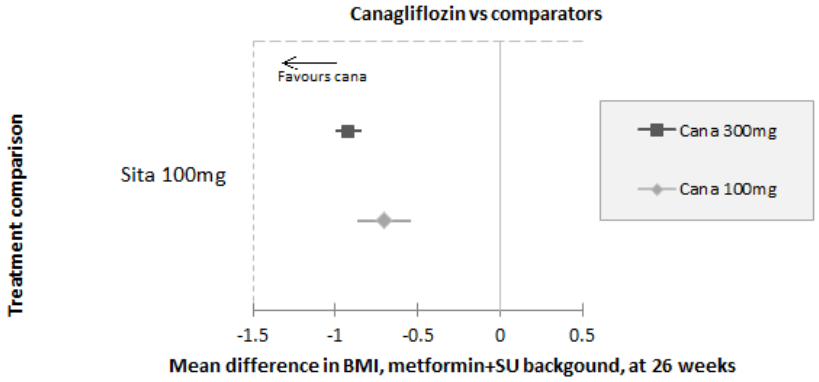
Figure 44 Mean difference in weight [95%CrI], MET+SU background at 26 weeks



6.7.6.3.3. BMI change from baseline (Figure 45)

Canagliflozin 300mg and 100mg were associated with higher reductions in BMI compared to sitagliptin 100mg (difference of -0.92kg/m^2 and -0.70 kg/m^2, respectively).

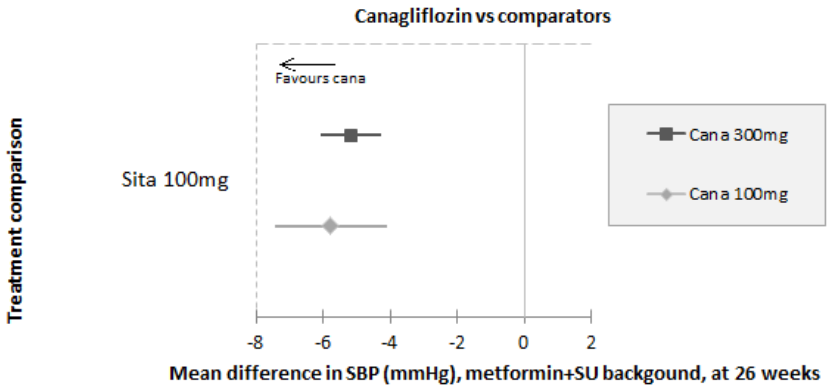
Figure 45 Mean difference in BMI [95%CrI], MET+SU background at 26 weeks



6.7.6.3.4. SBP change from baseline (Figure 46)

Canagliflozin 300mg and 100mg were associated with higher reductions in SBP compared to sitagliptin 100mg (difference of -5.16mmHg and -5.76mmHg, respectively).

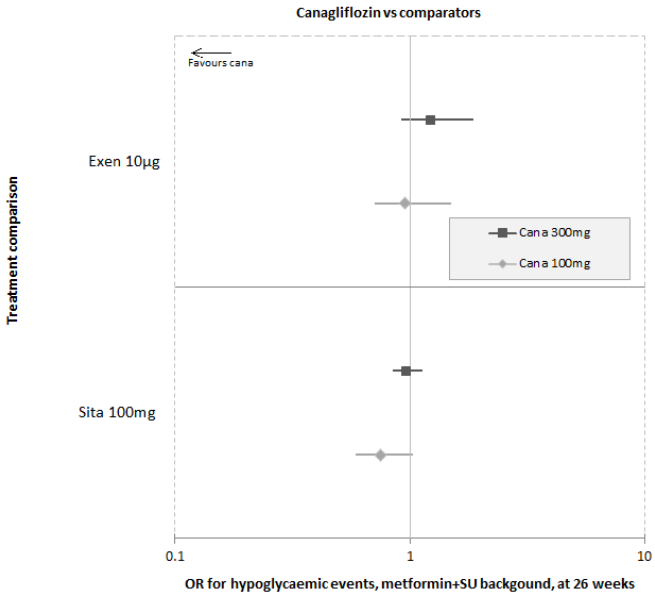
Figure 46 Mean difference in SBP [95%CrI], MET+SU background at 26 weeks



6.7.6.3.5. All hypoglycaemic events (Figure 47)

Canagliflozin 300mg and 100mg were associated with a similar risk compared to sitagliptin 100mg (ORs of 0.96 and 0.75 respectively) and a similar risk of hypoglycaemia compared to exenatide 10µg (ORs of 1.23 and 0.96 respectively).

Figure 47 Hypoglycaemic events (OR [95%CrI]), MET+SU background at 26 weeks

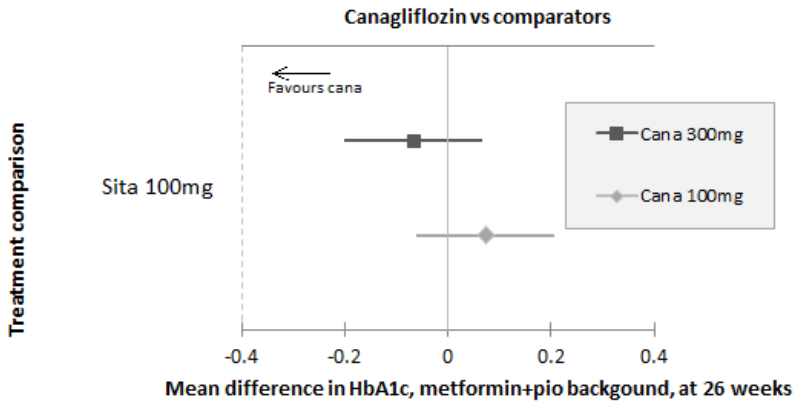


6.7.6.4. Triple therapy - MET+TZD background

6.7.6.4.1. HbA1c change from baseline (Figure 48)

Canagliflozin 300mg was associated with a reduction in HbA1c of -0.07% compared to sitagliptin 100mg.

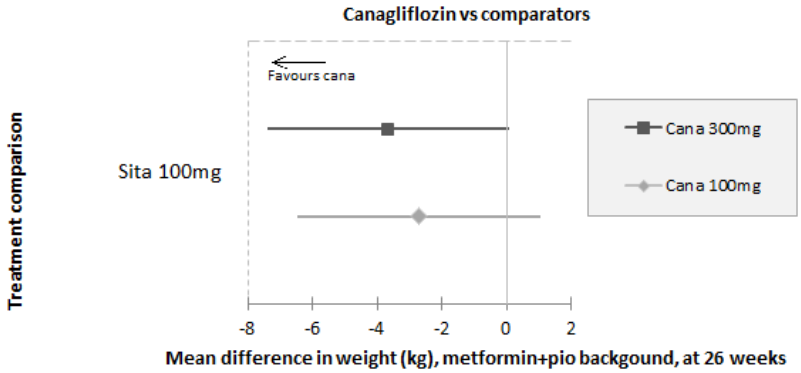
Figure 48 Mean difference in HbA1c [95%CrI], MET+TZD background at 26 weeks



6.7.6.4.2. Weight change from baseline (Figure 49)

Canagliflozin 300mg and 100mg were associated with weight reductions of -3.65kg and -2.70kg respectively compared to sitagliptin 100mg.

Figure 49 Mean difference in weight [95%CrI], MET+TZD background at 26 weeks



6.7.6.4.3. BMI change from baseline

The BMI change from baseline was not reported in the trial by Fonseca (2013), therefore the only trial included in the network of evidence was the canagliflozin trial. (93) No statistical analysis was conducted for the analysis of the BMI change from baseline.

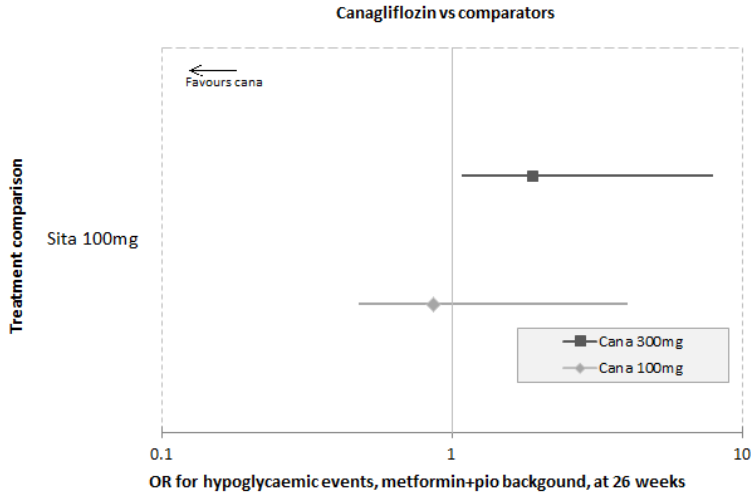
6.7.6.4.4. SBP change from baseline

The SBP change from baseline was not reported in the trial by Fonseca (2013), therefore the only trial included in the network of evidence was the canagliflozin trial. (93) . No statistical analysis was conducted for the analysis of SBP change from baseline.

6.7.6.4.5. All hypoglycaemic events (Figure 50)

Canagliflozin 100mg was associated with a risk of hypoglycaemic events similar to sitagliptin 100mg (OR of 0.86 and probability of being better of 55%). Canagliflozin 300mg was associated with a higher risk of hypoglycaemic events compared to sitagliptin 100mg (OR of 1.89 and probability of being better of 25%). Standard deviations were high leading to broad credibility intervals (CrI).

Figure 50 Hypoglycaemic events (OR [95%CrI]), MET+TZD background at 26 weeks



6.7.6.5. Add-on to insulin - Insulin ± OAD background (26 weeks)

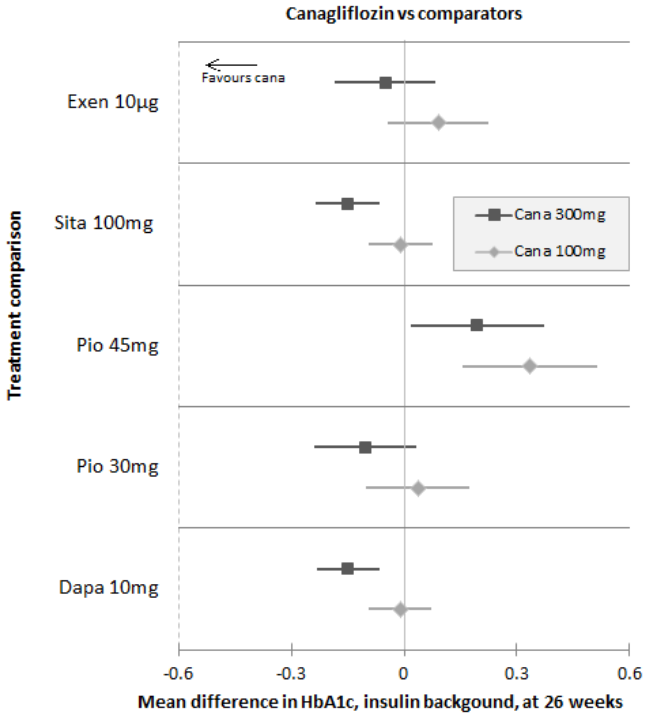
6.7.6.5.1. HbA1c change from baseline (Figure 51)

Differences in HbA1c change at 26 weeks compared to the different comparators are as follows:

- Sitagliptin 100mg: difference in HbA1c of -0.15% for canagliflozin 300mg and -0.01% for canagliflozin 100mg.
- Dapagliflozin 10mg: difference of -0.15% for canagliflozin 300mg and -0.01% for canagliflozin 100mg.
- Exenatide 10µg: difference of -0.05% for canagliflozin 300mg, and 0.09% for canagliflozin 100mg.
- Pioglitazone 30mg, with a difference of -0.10% for canagliflozin 300mg and 0.04% for canagliflozin 100mg,

Pioglitazone 45mg ranked first on the basis of the SUCRA and was associated with higher HbA1c reduction compared to canagliflozin 100mg and 300mg.

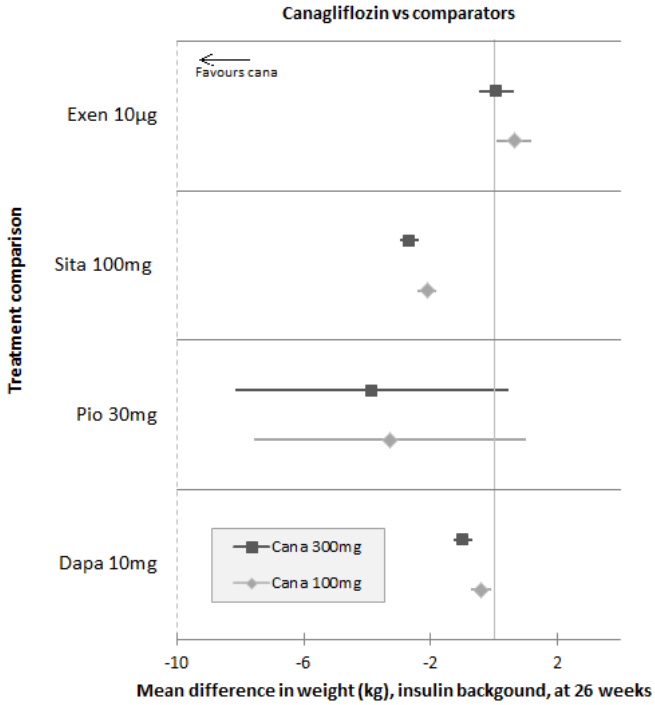
Figure 51 Mean difference in HbA1c [95%CrI], insulin background at 26 weeks



6.7.6.5.2. Weight change from baseline (Figure 52)

Canagliflozin 100mg and 300mg were associated with higher reductions in weight compared to DDP-4-i (difference of -2.10kg and -2.67kg, respectively), pioglitazone 30mg (difference of -3.28kg and -3.85kg, respectively) and dapagliflozin 10mg (difference of -0.41kg and -0.98kg, respectively). Exenatide 10µg was associated with a similar reduction in weight compared to canagliflozin 300mg and with a higher reduction in weight compared to canagliflozin 100mg.

Figure 52 Mean difference in weight [95%CrI], insulin background at 26 weeks



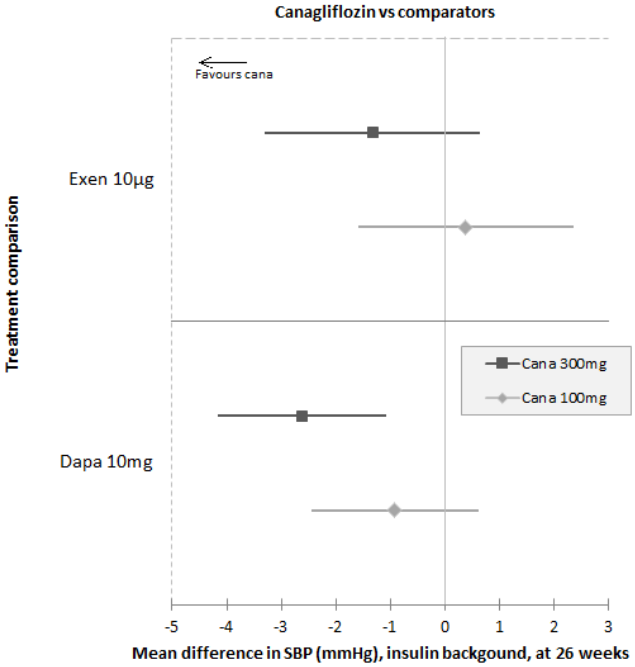
6.7.6.5.3. BMI change from baseline

Due to the absence of BMI results at 26 weeks for the canagliflozin trial, no analysis was conducted.

6.7.6.5.4. SBP change from baseline (Figure 53)

Canagliflozin 300mg and 100mg were associated with higher reductions in SBP compared to dapagliflozin 10mg (difference of -2.62mmHg and -0.92mmHg, respectively). When comparing canagliflozin and exenatide 10µg, canagliflozin 300mg was associated with higher reduction in SBP and canagliflozin 100mg was associated with similar reduction in SBP (difference of -1.33mmHg and 0.38mmHg, respectively).

Figure 53 Mean difference in SBP [95%CrI], insulin background at 26 weeks



6.7.6.5.5. All hypoglycaemic events

Due to the absence of results for all hypoglycaemic events at 26 weeks for the canagliflozin trial, no analysis was conducted.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

An assessment of heterogeneity was conducted and detailed results are presented for each line of therapy in Section 10.7.11 of Appendix 7.

No heterogeneity was identified in the analyses of the metformin, MET+SU and MET+TZD background therapies; although a moderate level of heterogeneity was detected in the analysis of the insulin background therapy. Some trials included in the analysis of the insulin background allowed patients to receive OADs as a background therapy. Among the 14 trials included in the base case analysis, five trials enrolled patients on insulin monotherapy, and nine trials enrolled patients on insulin ± OAD (including metformin, SU, TZD or a combination of two of these OADs). In particular, the trial assessing canagliflozin allowed patients to take INS+SoC. As no data were available in patients receiving insulin monotherapy as a background therapy in the canagliflozin trial, no sensitivity analysis was conducted. The heterogeneity in the analysis of the insulin network was acknowledged as a limitation.

In addition, it should be noted that the study population of the CANVAS insulin-sub-study was slightly different from the population in the other trials. the CANVAS insulin-sub-study included T2DM patients with a history of, or a high CVD risk. (84) This heterogeneity in the study population between trials could not be addressed as part of a sensitivity analysis as the canagliflozin trial was the only trial including

patients with a history of, or a high risk for, CVD. It was therefore acknowledged as a limitation of the analysis of the insulin background.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Sensitivity analyses excluding trials sources of inconsistency and/or heterogeneity were conducted to assess the impact on the results. The assessment of inconsistency and heterogeneity was reported in sections 6.7.7 and 6.7.9.

Sensitivity analyses excluding trials which were sources of inconsistency were conducted in the analyses of the metformin and MET+SU background therapies.

Conclusions remained unchanged with regards to the analysis of metformin background therapy. Conclusions from the analysis of MET+SU background therapy were slightly impacted by the sensitivity analyses: canagliflozin 300mg and 100mg were associated with similar or lower HbA1c reductions compared to exenatide 10µg in the sensitivity analysis (whereas HbA1c reductions were similar or higher to exenatide 10µg in the base case analysis). In addition, canagliflozin 300mg was associated with a larger weight reduction compared to exenatide 10µg in the sensitivity analysis (whereas weight reduction was similar to exenatide 10µg in the base case analysis).

Detailed results from the sensitivity analyses are presented in Section 10.7.12 of Appendix 7.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

As described in section 6.7.7, the analysis of heterogeneity between results of pairwise comparisons led to the identification of a potential source of heterogeneity in the insulin background as some trials allowed patients to receive OADs in addition to insulin, whereas other trials enrolled patients on insulin monotherapy.

The analysis of inconsistency was conducted within each independent loop of the networks. Detailed results are presented in Section 10.7.13 of Appendix 7.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 **If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

The clinical SRL only included RCTs with relatively consistent study design and populations to the RCTs available as part of the Phase 2 clinical programme for canagliflozin. There are non- randomised controlled studies using canagliflozin and it was therefore decided not to include any non-RCTs for comparators in the clinical SLR.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

The clinical studies outlined in the clinical evidence section were powered to detect differences in efficacy, rather than safety. However, safety data were captured in all RCTs.

The clinical SRL (section 6.7.1. to section 6.7.5). also investigated outcomes related to AEs (i.e. hypoglycaemic episode, genitourinary tract infection, CV events, AEs and death). However, all selected trials primarily assessed clinical efficacy outcomes. The assessment of safety outcomes was a secondary objective of these trials and did not include a description of all these AEs. Therefore, on the basis of the AE-related outcomes reported in the selected trials (see Section 10.7.6. of Appendix 7 [Clinical SRL – Statistical analysis]), only the proportion of patients with at least one hypoglycaemic event (i.e. "Any" hypoglycaemic events were pooled, defined as either symptomatic events [with or without biochemical confirmation] or asymptomatic events [with biochemical confirmation]) was considered as part of the NMA. The results of the NMA related to hypoglycaemic events are presented in Section 6.7.6.2.5 in dual therapy (in dual therapy in combination with metformin), Section 6.7.6.3.5 (in triple therapy in combination with MET+SU) and Section 6.7.6.4.5 in triple therapy (in triple therapy in combination with MET +TZD) and Section 6.7.6.5.5. (in add-on to insulin therapy).

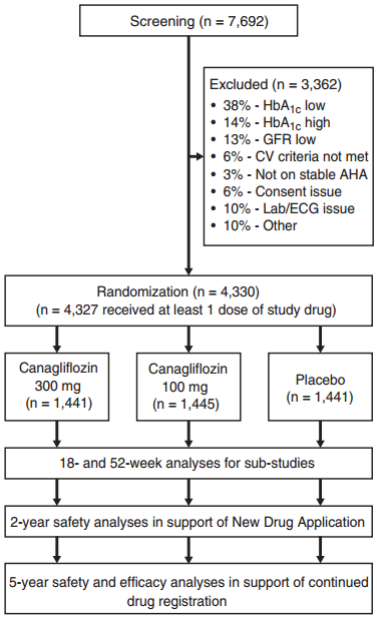
AEs were collected as part of canagliflozin clinical programme and DIA3008 (CANVAS) was designed primarily to assess CV safety outcomes).

CANVAS (DIA3008) trial

CANVAS (DIA3008) is a randomised, double-blind, placebo-controlled, parallel group, multicentre trial. The first phase includes 4,330 patients randomised on a 1:1:1 basis to placebo, canagliflozin 100mg, or canagliflozin 300mg scheduled to be followed initially for an average of approximately 2 years. (9) A planned second phase which intended to recruit and follow a further 14,000 patients to demonstrate CV protection will not be carried out.

CANVAS has yet to report as the total trial duration is expected to be approximately 4 years and the study is event-driven. The current cohort of patients (4,330) will continue to be followed, assuming 420 events are accrued at completion.

Figure 54. Study flow chart [(9)



The primary objectives of CANVAS are to evaluate the effects of treatment with canagliflozin on CV risk as measured by the hazard ratio (HR) for a composite CV end-point of MACE-plus (including CV death, non-fatal MI, non-fatal stroke, and unstable angina) and to assess safety and tolerability of canagliflozin. The primary null hypothesis to be tested was that there would be no difference in the risk of CV disease between patients treated with canagliflozin compared to patients treated with placebo.

The inclusion criteria for subjects included in CANVAS differ from the criteria for rest of the Phase 3 trials. Subjects enrolled in CANVAS were required to have a diagnosis of T2DM and a history of or high risk of CV disease defined on the basis of either:

- Age >30 years with documented symptomatic atherosclerotic CVD, including stroke, MI, hospital admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention (with or without stenting), peripheral revascularisation (angioplasty or surgery), symptomatic with documented haemodynamically significant carotid or peripheral vascular disease, or amputation secondary to vascular disease.

- Age >50 years with two or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, SBP >140mmHg (average of 3 readings) recorded at the screening visit, on at least one BP-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria or documented HDL-C of <1mmol/L (<39mg/dL).

In contrast, the exclusion criteria for the non-CANVAS studies included subjects with a previous history or high risk of CVD:

In CANVAS, background AHAs needed to have been administered at a stable dose for the 8 weeks prior to screening. Background therapy could be any approved agent(s), whether oral or injectable. Patients were required to remain on the same background therapy for 18 weeks, with rescue medication permitted if FPG was >15mmol/L after day 1 to week 6, >13.3mmol/L after week 6 to week 12 or >11.1mmol/L after week 12 to week 18.

The trial was originally designed to provide 90% power (α=0.05) to detect a relative risk reduction of 15% or greater for the effect of canagliflozin compared to placebo on the primary CV end-point across the two trial phases among a total study population of approximately 18,000. This estimate assumed an event rate of 2.25% per year and a 5% per year rate of premature discontinuation of active treatment. The 15% relative risk reduction was based on projected favourable effects of the agent on HbA1c, blood pressure and weight. To achieve this power the study was planned to continue until 1,600 MACE events had accrued. The recruitment of 4,330 individuals to phase one of the study was based on this being a sufficient number of participants to meet initial CV safety requirements when considered together with the data from other controlled trials in the canagliflozin development programme. It was projected that within about 2 years there would be more than 90% power with 160 MACE-plus events across the programme to exclude a non-inferiority margin of 1.8, assuming a point estimate of effect of 1.0.

This cohort of 4,330 individuals will continue to be followed and will contribute to the ongoing assessment of CV safety and the assessments of other outcomes as planned. Due to the decision to only enrol the initial cohort of patients there will be 80% power (2-sided α= 0.05) to detect a 25% or greater risk reduction assuming about 420 events are accrued at study completion. Analysis will be by intention-to-treat and a p value of 0.05 will be taken to indicate a significant effect.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The Phase 3 clinical trial programme evaluated the safety of canagliflozin in 10,285 people with T2DM. Data from three pre-specified pooled safety datasets is available: a broad dataset, a placebo-controlled studies dataset and a pooled renal impairment dataset, see Table 179 in Section 10.8. of Appendix 8.

The broad dataset includes data for canagliflozin 100mg and 300mg and all non-canagliflozin arms (i.e. placebo, glimepiride and sitagliptin). This dataset was set up to provide information on safety with longer exposure, and support the CV meta-

analysis. It provides a broad and robust safety assessment and is the primary focus of this section.

6.9.2.1. AEs reported

In the Broad Dataset, the incidence of subjects who experienced any adverse event was similar across groups (76.6% and 77.0%, for canagliflozin 100mg and 300mg respectively vs. 76.8% in the non-canagliflozin group), as presented in Table 22. (117)

The incidence of subjects who experienced AEs leading to discontinuation was slightly higher in the canagliflozin 300mg group (4.6%) compared with the canagliflozin 100mg (3.6%) and non-canagliflozin groups (2.11%). (117) The incidence of AEs considered related to study drug by the investigator was slightly higher in the canagliflozin 100mg and 300mg groups (33.6% and 29.4%, respectively) compared with the non-canagliflozin group (21.8%). The incidence of serious AEs and deaths was similar in the canagliflozin and non-canagliflozin groups (see Table 22). (117)

Specific AEs that were reported in at least 2% of subjects in any treatment group regardless of use of rescue medication are presented in Table 22. AEs that were common in subjects treated with canagliflozin (i.e., occurring in at least 5% of subjects in a canagliflozin group) were naso-pharyngitis, hypoglycaemia, upper respiratory tract infection, UTI, diarrhoea, arthralgia back pain, and headache.

Table 22. Overall summary of AEs - regardless of use of rescue medication (broad dataset: safety analysis set) (117)

Number (%) of subjects with a least one TEAE of the following types	Canagliflozin 100mg	Canagliflozin 300mg	All Cana	All non-Cana
	N = 3,092	N = 3,085	N = 6,177	N = 3,262
Any AEs	2,369 (76.6)	2,375 (77.0)	4,744 (76.8)	2,473 (75.8)
AEs leading to discontinuation	173 (5.6)	224 (7.3)	397 (6.4)	164 (5.0)
AEs related to study drug*	910 (29.4)	1,037 (33.6)	1,947 (31.5)	711 (21.8)
AEs related to study drug and leading to discontinuation	110 (3.6)	142 (4.6)	252 (4.1)	70 (2.1)
Serious AEs	417 (13.5)	406 (13.2)	823 (13.3)	445 (13.6)
Serious AEs leading to discontinuation	63 (2.0)	52 (1.7)	115 (1.9)	71 (2.2)
Serious AEs related to study drug	35 (1.1)	33 (1.1)	68 (1.1)	27 (0.8)
Serious AEs related to study drug and leading to discontinuation	17 (0.5)	14 (0.5)	31 (0.5)	10 (0.3)
Deaths	25 (0.8)	24 (0.8)	49 (0.8)	37 (1.1)
AEs in at least 2% of subjects in any treatment group by body system and preferred term				
Ear and labyrinth disorders	108 (3.5)	108 (3.5)	216 (3.5)	146 (4.5)
Vertigo	58 (1.9)	63 (2.0)	121 (2.0)	73 (2.2)
GI disorders	748 (24.2)	735 (23.8)	1483 (24.0)	724 (22.2)
Constipation	95 (3.1)	92 (3.0)	187 (3.0)	78 (2.4)
Diarrhoea	159 (5.1)	215 (7.0)	374 (6.1)	213 (6.5)
Nausea	92 (3.0)	108 (3.5)	200 (3.2)	90 (2.8)
Toothache	61 (2.0)	47 (1.5)	108 (1.7)	43 (1.3)

Number (%) of subjects with a least one TEAE of the following types	Canagliflozin 100mg	Canagliflozin 300mg	All Cana	All non-Cana
	N = 3,092	N = 3,085	N = 6,177	N = 3,262
General disorders and administration site conditions	412 (12.6)	416 (13.5)	438 (14.2)	854 (13.8)
Chest pain	52 (1.6)	61 (2.0)	48 (1.6)	109 (1.8)
Fatigue	81 (2.5)	87 (2.8)	83 (2.7)	170 (2.8)
Oedema peripheral	122 (3.7)	63 (2.0)	59 (1.9)	122 (2.0)
Pyrexia	51 (1.6)	66 (2.1)	117 (1.9)	58 (1.8)
Thirst	42 (1.4)	69 (2.2)	111 (1.8)	2 (0.1)
Infections and infestations	1343 (43.4)	1326 (43.0)	2669 (43.2)	1343 (41.2)
Bronchitis	129 (4.0)	116 (3.8)	111 (3.6)	129 (4.0)
Gastroenteritis	80 (2.5)	64 (2.1)	72 (2.3)	80 (2.5)
Influenza	122 (3.7)	134 (4.3)	121 (3.9)	122 (3.7)
Nasopharyngitis	328 (10.1)	313 (10.1)	298 (9.7)	328 (10.1)
Sinusitis	84 (2.6)	81 (2.6)	83 (2.7)	84 (2.6)
Upper respiratory tract infection	271 (8.3)	224 (7.2)	206 (6.7)	271 (8.3)
Urinary tract infection	194 (5.9)	217 (7.0)	210 (6.8)	194 (5.9)
Vulvovaginal mycotic infection	22 (0.7)	73 (2.4)	76 (2.5)	22 (0.7)
Blood creatine phosphokinase	64 (2.0)	30 (1.0)	28 (0.9)	64 (2.0)
Metabolism and nutrition disorders	448 (14.5)	451 (14.6)	899 (14.6)	559 (17.1)
Hyperglycaemia	51 (1.6)	44 (1.4)	95 (1.5)	113 (3.5)
Hypoglycaemia	239 (7.7)	256 (8.3)	495 (8.0)	290 (8.9)
Musculoskeletal/connective tissue disorders	700 (22.6)	691 (22.4)	700 (22.6)	732 (22.4)
Arthralgia	152 (4.9)	121 (3.9)	152 (4.9)	173 (5.3)
Back pain	169 (5.5)	196 (6.4)	169 (5.5)	165 (5.1)
Musculoskeletal pain	69 (2.2)	72 (2.3)	69 (2.2)	81 (2.5)
Osteoarthritis	71 (2.3)	64 (2.1)	71 (2.3)	67 (2.1)
Pain in extremity	106 (3.4)	83 (2.7)	106 (3.4)	115 (3.5)
Nervous system disorders	485 (15.7)	502 (16.3)	987 (16.0)	485 (14.9)
Dizziness	45 (1.5)	65 (2.1)	110 (1.8)	47 (1.4)
Headache	146 (4.7)	165 (5.3)	311 (5.0)	183 (5.6)
Renal and urinary disorders	354 (11.4)	360 (11.7)	714 (11.6)	222 (6.8)
Pollakiuria	117 (3.8)	137 (4.4)	254 (4.1)	34 (1.0)
Reproductive system and breast disorders	273 (8.8)	321 (10.4)	594 (9.6)	129 (4.0)
Balanitis	74 (2.4)	68 (2.2)	142 (2.3)	14 (0.4)
Vulvovaginal pruritus	44 (1.4)	62 (2.0)	106 (1.7)	7 (0.2)
Respiratory, thoracic / mediastinal disorders	356 (11.5)	332 (10.8)	688 (11.1)	394 (12.1)
Cough	120 (3.9)	99 (3.2)	219 (3.5)	131 (4.0)
Vascular disorders	219 (7.1)	234 (7.6)	453 (7.3)	270 (8.3)
Hypertension	84 (2.7)	68 (2.2)	152 (2.5)	152 (4.7)

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least one AE regardless of rescue medication
** related to study drug includes following relationship as determined by investigator: possibly related, probably related and very likely related.*

Table 23. AEs with 95% CI of treatment difference excluding zero with a higher incidence in the combined canagliflozin group - regardless of use of rescue medication (Broad dataset: safety analysis set) (118)

	Canagliflozin 100mg	Canagliflozin 300mg	All Cana	All non-Cana	Canagliflozin 100mg minus all Non-Cana 95%CI[a]	Canagliflozin 300mg minus all Non-Cana 95%CI[a]	All canagliflozin minus all Non-Cana 95%CI[a]
Infections and infestations	1234 (39.9)	1216 (39.4)	2450 (39.7)	1229 (37.7)	(-0.2; 4.7)	(-0.7; 4.2)	(-0.1; 4.1)
Balanitis candida	9 (0.3)	16 (0.5)	25 (0.4)	5 (0.2)	(-0.1; 0.4)	(0.0; 0.7)	(0.0; 0.5)
Urinary tract infection	191 (6.2)	185 (6.0)	376 (6.1)	164 (5.0)	(-0.0; 2.3)	(-0.2; 2.1)	(0.1; 2.0)
Vaginal infection	38 (1.2)	32 (1.0)	70 (1.1)	9 (0.3)	(0.5; 1.4)	(0.3; 1.2)	(0.5; 1.2)
Vulvitis	11 (0.4)	8 (0.3)	19 (0.3)	0	(0.1; 0.6)	(0.0; 0.5)	(0.1; 0.5)
Vulvovaginal candidiasis	43 (1.4)	40 (1.3)	83 (1.3)	5 (0.2)	(0.8; 1.7)	(0.7; 1.6)	(0.9; 1.5)
Vulvovaginal mycotic infection	70 (2.3)	72 (2.3)	142 (2.3)	21 (0.6)	(1.0; 2.2)	(1.1; 2.3)	(1.2; 2.1)
Vulvovaginitis	25 (0.8)	26 (0.8)	51 (0.8)	2 (0.1)	(0.4; 1.1)	(0.4; 1.1)	(0.5; 1.0)
Renal and urinary disorders	317 (10.3)	332 (10.8)	649 (10.5)	192 (5.9)	(3.0; 5.7)	(3.5; 6.3)	(3.5; 5.8)
Micturition urgency	17 (0.5)	15 (0.5)	32 (0.5)	6 (0.2)	(0.0; 0.7)	(-0.0; 0.6)	(0.1; 0.6)
Nephrolithiasis	21 (0.7)	6 (0.2)	27 (0.4)	18 (0.6)	(-0.3; 0.5)	(-0.7;-0.0)	(-0.4; 0.2)
Pollakiuria	110 (3.6)	132 (4.3)	242 (3.9)	31 (1.0)	(1.8; 3.4)	(2.5; 4.1)	(2.4; 3.6)
Polyuria	30 (1.0)	33 (1.1)	63 (1.0)	10 (0.3)	(0.2; 1.1)	(0.3; 1.2)	(0.4; 1.1)
Vascular disorders	181 (5.9)	191 (6.2)	372 (6.0)	228 (7.0)	(-2.4; 0.1)	(-2.1; 0.5)	(-2.0; 0.1)
Hypotension	40 (1.3)	54 (1.8)	94 (1.5)	17 (0.5)	(0.3; 1.3)	(0.7; 1.8)	(0.6; 1.4)
Orthostatic hypotension	8 (0.3)	21 (0.7)	29 (0.5)	4 (0.1)	(-0.1; 0.4)	(0.2; 0.9)	(0.1; 0.6)
Other AEs relevant to the management of T2DM patients							
Cardiac disorders	156 (5.0)	162 (5.3)	318 (5.1)	189 (5.8)	(-1.9; 0.4)	(-1.7; 0.6)	(-1.6; 0.4)
Cardiac failure	2 (0.1)	7 (0.2)	9 (0.1)	12 (0.4)	(-0.6;-0.0)	(-0.4; 0.2)	(-0.5; 0.0)
Coronary artery disease	10 (0.3)	12 (0.4)	22 (0.4)	23 (0.7)	(-0.8;-0.0)	(-0.7; 0.1)	(-0.7;-0.0)
Myocardial ischaemia	6 (0.2)	2 (0.1)	8 (0.1)	14 (0.4)	(-0.5; 0.1)	(-0.6;-0.1)	(-0.6;-0.0)
Palpitations	15 (0.5)	23 (0.7)	38 (0.6)	10 (0.3)	(-0.2; 0.5)	(0.0; 0.8)	(0.0; 0.6)

[a] Pairwise comparison: Normal approximation to binomial distribution with continuity correction.
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one AE, not the number of events.
Note: The table presents treatment-emergent AEs (preferred terms) with 95% confidence interval on treatment difference excluding zero

6.9.2.2. Hypoglycaemia[1]

As the excretion of glucose in the urine is limited when blood glucose is reduced to approximately 4 mmol/L. canagliflozin possess a low inherent risk for hypoglycaemia. Data from the canagliflozin study programme supports this. However, when subjects are treated with canagliflozin in combination with other therapies known to be associated with hypoglycaemia such as SUs or insulin, the hypoglycaemia rate reflects the action of these agents.

Hypoglycaemic events are described as part of an analysis of subjects not on the background of an AHA associated with hypoglycaemia: i.e. Placebo-controlled Studies Dataset including the monotherapy study (DIA3005), the add-on to metformin study (DIA3006), and the add-on to metformin/pioglitazone study (DIA3012), but omitting the add-on to metformin/SU study (DIA3002 & DIA3015) and add-on to insulin therapy (DIA3008 insulin sub-study). In this pooled population not receiving AHAs associated with hypoglycaemia, the incidence of hypoglycaemic episodes was overall low, slightly higher in the canagliflozin 100 mg (3.8%) and 300 mg groups (4.3%) relative to the placebo group (2.2%) (see Table 180 in Section 10.8.1 of Appendix 8). The incidence of severe hypoglycaemia was low, with 1 subject in each canagliflozin group reported to have had a severe hypoglycaemic episode. (117)

In the DIA3009 study, a significantly lower incidence of documented hypoglycaemia was observed with canagliflozin 100mg and 300mg compared with glimepiride (6.0%, 5.0% and 34.0% respectively ($p<0.0001$ for both doses)). (2) Rates of severe hypoglycaemia events (i.e. events requiring the assistance of another person, or with loss of consciousness or a seizure) were very low in all treatment groups across studies. (119)

In subjects on background agents associated with hypoglycaemia (defined as an episode with a biochemically documented event [fingerstick glucose of ≤70 mg/dL] regardless of the presence of symptoms), the incidence of hypoglycaemia was, not unexpectedly, higher across treatment groups compared with the analyses of subjects not on such agents (see Table 181 in Section 10.8.1 of Appendix 8). (119)

In subjects on background therapy of MET+SU (DIA3015), the incidence of hypoglycaemia was not meaningfully different between canagliflozin and sitagliptin, and was driven by the presence of glimepiride in the background regimen. (7) The incidence of severe hypoglycaemia episodes was low and generally similar across treatment groups. (119)

6.9.2.3. Genital mycotic infections

Due to the excretion of glucose in the urine caused by SGLT2 inhibitors, the incidence of GMI such as candida albicans (“Thrush”) is expected to be elevated in both women and men taking canagliflozin. However, it was found to be easily managed by standard therapy and rarely led to discontinuations.

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[1] Across the Phase 3 studies, documented hypoglycaemia episodes were defined as either biochemically documented events (≤3.9 mmol/L [70 mg/dL], regardless of the presence of symptoms) or severe events (requiring the assistance of another person, or with loss of consciousness or a seizure) (119)][2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

GMI in women

In the Broad Dataset, the incidence of female GMI AEs was higher in the combined canagliflozin group (14.3%) compared with the placebo group (3.1%) and with a slightly higher incidence in the canagliflozin 100 mg group (14.7%) compared with the canagliflozin 300 mg group (13.9%). (117)

There were no serious events relating to this AE and 30 (1.2%) of subjects receiving canagliflozin discontinued study drug as a result (see Table 24). Discontinuation due to these events was infrequent: 1.2% of all female subjects discontinued canagliflozin due to GMI. (117)

In the combined canagliflozin group, these events were generally treated by the health care professional (approximately 65% of treated events) or by the subject herself (approximately 35% of treated adverse events) without discontinuing study drug, using either oral/topical antifungal and/or antibacterial agents. (117)

Table 24. Summary of vulvovaginitis AEs - regardless of use of rescue medication (Broad dataset) (117)

Number (%) of subjects with at least one adverse event of following types:	All Non-CANA (N=1338) n (%)	CANA 100 mg (N=1289) n (%)	CANA 300 mg (N=1319) n (%)	All CANA (N=2608) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any vulvovaginitis	42 (3.1)	190 (14.7)	184 (13.9)	374 (14.3)	11.2	(9.5; 12.9)
Incidence rate per 1000 subject-years exposure	*26.96*	*118.90*	*112.87*	*115.85*		
Vulvovaginitis leading to discontinuation	0	13 (1.0)	17 (1.3)	30 (1.2)	1.2	(0.7; 1.6)
Vulvovaginitis related to study drug[b]	28 (2.1)	147 (11.4)	153 (11.6)	300 (11.5)	9.4	(7.9; 10.9)
Serious adverse events of vulvovaginitis	0	0	0	0	0.0	(-0.1; 0.1)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae21bvvac04msuraevv_overall_mycnos.rtf generated by raevv_overall_mycnos.sas, 02DEC2012 18:54, tae22vvac04msuraevv_mycnos1.rtf generated by raevv_mycnos1.sas, 19NOV2012 16:12

GMI in men

In the Broad Dataset (through 01 July 2012), an increased incidence of male GMI events was seen with canagliflozin treatment (7.3% and 9.3% in the 100 mg and 300 mg groups, respectively), vs. 1.6% of male subjects in the non-canagliflozin group. (117)

In general, male GMI events were mild to moderate in intensity and were not associated with interruption of study drug. Seven events of male GMI were reported as severe in intensity. (117)

Table 25. Summary of male GMIs - regardless of use of rescue medication (Broad dataset) (117)

Number (%) of subjects with at least one adverse event of following types:	All Non-CANA (N=1924) n (%)	CANA 100 mg (N=1803) n (%)	CANA 300 mg (N=1766) n (%)	All CANA (N=3569) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any male genital infections	30 (1.6)	131 (7.3)	164 (9.3)	295 (8.3)	6.7	(5.6; 7.8)
Incidence rate per 1000 subject-years exposure	*12.16*	*52.88*	*69.58*	*61.02*		
Male genital infections leading to discontinuation	0	14 (0.8)	19 (1.1)	33 (0.9)	0.9	(0.6; 1.3)
Male genital infections related to study drug [b]	22 (1.1)	110 (6.1)	145 (8.2)	255 (7.1)	6.0	(5.0; 7.0)
Serious adverse events of male genital infection	0	1 (0.1)	1 (0.1)	2 (0.1)	0.1	(-0.1; 0.2)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae01mgac04msuraemg_overall0.rtf generated by raemg_overall0.sas, 04DEC2012 10:17, tae02mgac04msuraemg1.rtf generated by raemg1.sas, 05OCT2012 09:25

In the combined canagliflozin group, male GMIs were treated by a healthcare professional for the majority of the subjects and most commonly treated with a topical antifungal agent. (117)

Overall, 1.3% of male subjects overall had more than 1 GMI event. The incidence of male GMIs increased at a generally consistent rate throughout the first year of treatment, after which the incident rate appeared to plateau. (117)

6.9.2.4. Urinary tract infections

Incidence of UTIs was expected to be elevated in both women and men taking canagliflozin, due to its MoA. However, the clinical studies have found only minimal increases in the incidence of UTIs in those taking canagliflozin and where they have occurred they have mainly been lower UTIs which have been treated with standard of care, and rarely led to discontinuation.

In the Broad Dataset, a small increase in the incidence of adverse events of UTI with the canagliflozin relative to non-canagliflozin treated subjects was observed: 8.2% and 8.1% in canagliflozin 100 mg and 300 mg groups, respectively, and 6.7% in non-canagliflozin group. (117)

Table 26. Summary of UTIs - regardless of use of rescue medication (Broad dataset) (117)

Number (%) of subjects with at least one UTI adverse event of following types:	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any adverse event	218 (6.7)	254 (8.2)	250 (8.1)	504 (8.2)	1.5	(0.4; 2.6)
Incidence rate per 1000 subject-years exposure	*54.17*	*62.32*	*62.70*	*62.51*		
Adverse event leading to discontinuation	4 (0.1)	11 (0.4)	6 (0.2)	17 (0.3)	0.2	(-0.0; 0.4)
Adverse event related to study drug[b]	106 (3.2)	152 (4.9)	148 (4.8)	300 (4.9)	1.6	(0.8; 2.4)
Serious adverse event	12 (0.4)	16 (0.5)	8 (0.3)	24 (0.4)	0.0	(-0.3; 0.3)
Upper tract UTI adverse event	11 (0.3)	20 (0.6)	10 (0.3)	30 (0.5)	0.2	(-0.1; 0.4)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae13a0401jul12raeuti1overallci.rtf generated by raeuti1overallci.sas, 03DEC2012 09:34; tae130401jul12raeutioverall.rtf generated by raeutioverall.sas, 17AUG2012 16:03;tae14uti0401jul12raeuti.rtf generated by raeuti.sas, 28AUG2012 12:17

Over 80% of UTIs were in women. Recurrence rates were also similar in the combined canagliflozin and non-canagliflozin groups for symptomatic UTI AEs: 19.9% and 23.8% of subjects, respectively, had >1 such UTI AE. (117)

6.9.2.5. Osmotic diuresis-related AEs

By increasing urinary glucose output, canagliflozin induces a mild osmotic diuresis, with an increase in urine output. The increase in urine output is expected to lead to a range of AEs, such as an increase in urinary frequency and/or volume (pollakiuria and polyuria). In addition, the increase in fluid loss may lead to symptoms reflecting such increased thirst or fluid intake.](118)

In the Broad Dataset, there was a higher incidence of osmotic diuresis-related adverse events in the combined canagliflozin group (7.6%) relative to the non-canagliflozin group (2.4%), most of which were considered related to study drug. A dose-dependent increase in incidence was not seen. (117)

No subject had a serious osmotic diuresis-related adverse event. Two subjects in the canagliflozin 100 mg group and 8 subjects in canagliflozin 300 mg group had events considered by the investigator to be severe in intensity; all other subjects had events that were mild or moderate in severity. There was a low incidence of discontinuations due to this adverse event. (117)

Table 27. Summary of osmotic diuresis-related AEs - regardless of use of rescue medication (Broad dataset) (117)

	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Total no. subjects with osmotic diuresis-related adverse events	79 (2.4)	227 (7.3)	243 (7.9)	470 (7.6)	5.2	(4.3; 6.1)
Incidence rate per 1000 subject-years exposure	*19.63*	*55.70*	*60.95*	*58.29*		
Grouped Terms:						
Polyuria/Pollakiuria	64 (2.0)	188 (6.1)	193 (6.3)	381 (6.2)	4.2	(3.4; 5.0)
Thirst	18 (0.6)	85 (2.7)	87 (2.8)	172 (2.8)	2.2	(1.7; 2.7)
Adverse event leading to discontinuation	2 (0.1)	8 (0.3)	9 (0.3)	17 (0.3)	0.2	(0.0; 0.4)
Serious adverse event	0	0	0	0		

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae69osmo0401jul12rae2osmoticci.rtf generated by rae2osmoticci.sas, 04DEC2012 10:09

In both canagliflozin treatment groups, the majority of osmotic diuresis related AEs occurred within the first 6 weeks of initiation of treatment. (118)

6.9.2.6. Volume depletion AEs

By increasing urinary glucose excretion, canagliflozin acts as an osmotic diuretic; this diuretic action may reduce intravascular volume, providing benefits such as improvements in BP control, but also the potential for AEs related to reduced intravascular volume (e.g. dizziness, hypotension, etc.). (117)

In the Placebo-controlled Studies Dataset, the incidence of volume depletion-related AEs was low across all groups (2.4% to 4.6%), although slightly higher in the canagliflozin group (see Table 28). (118) Five subjects in the canagliflozin groups vs. four in the non-canagliflozin group had volume depletion-related AEs that led to discontinuation. (117)

Table 28. Summary of volume depletion AEs - regardless of use of rescue medication (ISS Phase 3 placebo-controlled studies dataset: safety analysis set) (117)

Number (%) of subjects with at least one reduced intravascular volume-related adverse event of following types:	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any adverse event[b]	78 (2.4)	99 (3.2)	141 (4.6)	240 (3.9)	1.5	(0.8; 2.2)
Incidence rate per 1000 subject-years exposure	*19.38*	*24.29*	*35.36*	*29.77*		
Adverse event[b] leading to discontinuation	4 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)	-0.0	(-0.2; 0.1)
Adverse event[b] related to study drug[c]	16 (0.5)	25 (0.8)	51 (1.7)	76 (1.2)	0.7	(0.4; 1.1)
Serious adverse event	11 (0.3)	12 (0.4)	8 (0.3)	20 (0.3)	-0.0	(-0.3; 0.3)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the Statistical Analysis Plan (SAP).

[c] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae45b0401jul12raevol1ci.rtf generated by raevol1ci.sas, 11DEC2012 11:30

Volume depletion-related AEs occurred early in treatment with most events having been observed within the first 12 weeks after initiation of treatment, and no further increment in events in the canagliflozin relative to the non-canagliflozin group after about 26 weeks. (117)

6.9.2.7. Treatment discontinuations

Discontinuation of treatment, whether for AEs or for lack of efficacy, provides an indication of the true proportion of patients who will benefit from a treatment. Data from consort diagrams (see Figures 7 to 12 of Section 10.7.4. for Appendix 4) provides information on the number of patients who received rescue therapy or discontinued treatment. Reasons for discontinuations included AEs, reduction in eGFR, death, lack of efficacy on rescue therapy, non-compliance, physician decision, protocol deviation, withdrawal of consent, study terminated, pregnancy and unable to take protocol-defined rescue therapy.

The incidence of adverse events leading to discontinuation in the Broad Dataset was higher in the canagliflozin 300 mg group (7.3%) relative to 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 glomerular filtration rate decreased (11 [0.4%] subjects), renal impairment (11 [0.4%] subjects), and blood creatinine increased (9 [0.3%] subjects). (117) A modestly higher incidence of discontinuations related to these adverse events (e.g. adverse events of renal failure, renal impairment, blood creatinine increased, GFR decreased) was seen in the canagliflozin 300 mg group, with a similar incidence in the canagliflozin 100 mg and non-canagliflozin groups. Follow-up eGFR information was obtained in all subjects who discontinued due to renal-related adverse events: a high proportion of these subjects had follow-up eGFR values that were at baseline or only modestly below baseline levels – with a similar small proportion in the canagliflozin and non-canagliflozin groups having persistent decreases. (117)

Based on clinical evidence emerging from the trial programme, the regulatory authorities have recommended patients taking canagliflozin discontinue therapy if their eGFR<45 ml/min/1.73m^2. (25)

6.9.2.8. Serious AEs

In the broad dataset, the incidence of subjects with serious AEs (SAEs) was similar in the combined canagliflozin group (10.7%) compared with the non-canagliflozin group (11.6%), with similar incidences in the canagliflozin 100mg and 300mg groups (10.6% and 10.7%, respectively).(117;118) The incidence of subjects with SAEs that led to discontinuation was low, with similar incidences in the combined canagliflozin group and the non-canagliflozin group (1.5% and 1.8%, respectively).(117;118) The incidence of subjects with SAEs that were considered related to study drug was also low, with similar incidences in the combined canagliflozin group and non-canagliflozin group (0.9% and 0.8%, respectively). (117;118)

CV Risk

Evidence from a meta-analysis in 9,632 patients suggests that there is no increase in CV risk associated with canagliflozin. A pre-specified meta-analysis was performed to prospectively evaluate MACE (including CV death, non-fatal MI, and non-fatal stroke) and events of hospitalised unstable angina (MACE-plus). (8;117) The meta-analysis was performed in a pooled population of subjects with T2DM (n=9,632) from nine Phase 2/3 studies of ≥12 weeks in duration (excluding DIA3015 because the database lock for this study occurred after the database lock for the CV meta-analysis; however, given the small number of events, and balanced distribution of MACE, this would not have impacted on the conclusions). The ongoing CANVAS (DIA3008) study contributed 45% (n=4,327) of subjects included in the meta-analysis.

The HR of canagliflozin (both doses pooled) to non-canagliflozin from the primary analysis of time to first adjudicated MACE-plus event was 0.91 (95% CI, 0.68-1.22) (see Table 29). This meets the US FDA guidance to demonstrate an upper bound <1.8 (), indicating that there is no evidence of increased CV risk with canagliflozin in the pre-licence phase (119) It must be emphasised that this data is from an interim analysis and DIA 3008 (CANVAS) is ongoing.

Table 29. Summary of MACE-Plus Events (8;117)

	Non-CANA[a] N = 3,327	CANA 100mg N = 3,156	CANA 300mg N = 3,149	All CANA N = 6,305	HR (95% CI)
MACE-plus[b,c]					
Subjects with an event, n (%)	71 (2.1)	66 (2.1)	64 (2.0)	130 (2.1)	0.91 (0.68, 1.22)[d]
Event accounting, n (%)[e]					
CV death	16 (0.5)	11 (0.3)	10 (0.3)	21 (0.3)	
Non-fatal MI	25 (0.8)	22 (0.7)	19 (0.6)	41 (0.7)	
Non-fatal stroke	12 (0.4)	22 (0.7)	20 (0.6)	42 (07)	
Hospitalised unstable angina	18 (0.5)	11 (0.3)	15 (0.5)	26 (0.4)	

MACE, major adverse CV events; CANA, canagliflozin; HR, hazard ratio; CI, confidence interval;
[a]Placebo and/or active comparator.
[b]Preferred terms for MACE events are provided in reference(8;117).
[c]Includes events that occurred between the first dose of study drug and up to 30 days after study drug discontinuation.
[d]HR of pooled CANA subjects vs. control subjects with events determined from Cox proportional hazards model, stratified by CANVAS/non-CANVAS studies.
[e]Subjects with multiple event types are included in the event category that occurred earliest.

6.9.2.9. Deaths

In the broad dataset, 49 (0.8%) subjects in the combined canagliflozin group and 37 (1.1%) subjects in the non-canagliflozin group died. The incidence of subjects who died was similar in the two canagliflozin treatment groups. (117) The majority of adverse events with an outcome of death were in the Cardiac disorders, General disorders and administration site conditions, Infections and infestations, Nervous systems disorders, and Respiratory, thoracic and mediastinal disorders. Specific causes of death were generally balanced between the treatment groups, with no discernible pattern. (117)

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety and tolerability data collected in the Phase 2/3 studies demonstrate that many of the AEs reported were common to both the canagliflozin and non-canagliflozin groups.

Although canagliflozin is generally well tolerated, some AEs occur more frequently with the use of canagliflozin (e.g. UTIs, GMIs, osmotic diuresis and volume depletion-related AEs), although the majority of cases were mild or moderate in severity. However, these AEs are expected due to the mode of action of SGLT2 inhibitors.

GMIs are the most common AEs associated with canagliflozin. UTIs, osmotic diuresis and volume depletion-related AEs are also related to the MOA. However these adverse reactions were generally mild to moderate, responded to standard therapies, and infrequently led to withdrawal of canagliflozin therapy.

Canagliflozin is associated with a low inherent risk of hypoglycaemia and severe hypoglycaemia when used as combination therapy with other therapies not associated with hypoglycaemia. As expected, an increased incidence of hypoglycaemia was observed when canagliflozin was used in combination with insulin or agents which are known to cause hypoglycaemia, such as SU. Canagliflozin demonstrated statistically significantly lower rates of hypoglycaemia when compared with SU. Canagliflozin may advantage of benefit for patients at risk of hypoglycaemia and for whom hypoglycaemia may present a concern.

Interim data from a large meta-analysis (n=9,632) which evaluated MACE plus, demonstrated a CV risk HR of 0.91 (95% CI: 0.68, 1.22) for canagliflozin) indicating no demonstrable increase in CV risk vs. other AHAs at this time. However, additionally, a large CV risk assessment study (CANVAS) is currently underway.

Overall, canagliflozin demonstrated lower rates of discontinuation and requirement for rescue therapy than active comparators (sitagliptin and glimepiride) or placebo, demonstrating that patients are more likely to remain on canagliflozin, than switch to another OAD or add-in another therapy.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

6.10.1.1. Clinical benefits

Canagliflozin is an SGLT-2-i, causing 60-80g (240-320 calories) of glucose to be lost through the urine each day. This results in improved glycaemic control, weight (fat) loss and BP reduction (via osmotic diuresis). Canagliflozin has an insulin-independent MoA. Studies suggest that this MoA may confer a degree of β-cell protection. Furthermore, it enables canagliflozin to be used in a complementary manner with other AHAs that rely on the insulin pathway, with low levels of hypoglycaemia unless combined with an agent known to cause hypoglycaemia.

Canagliflozin has been studied in an extensive and robust clinical trial programme (> 10,000 subjects) which included active comparator trials with SU and sitagliptin, in dual and triple therapy, and in combination with metformin, SU, TZD and insulin. During the study programme canagliflozin consistently demonstrated clinically relevant reductions in HbA1c, SBP and body weight. All three end-points are key in the treatment of T2DM. Figure 55, Figure 56 and Figure 57 summarise these results for the placebo-controlled trials.

Figure 55. LS mean change in HbA1c for patients treated with canagliflozin 100mg and 300mg from baseline to primary time point in placebo-controlled Phase 3 studies (81;84;89;93)

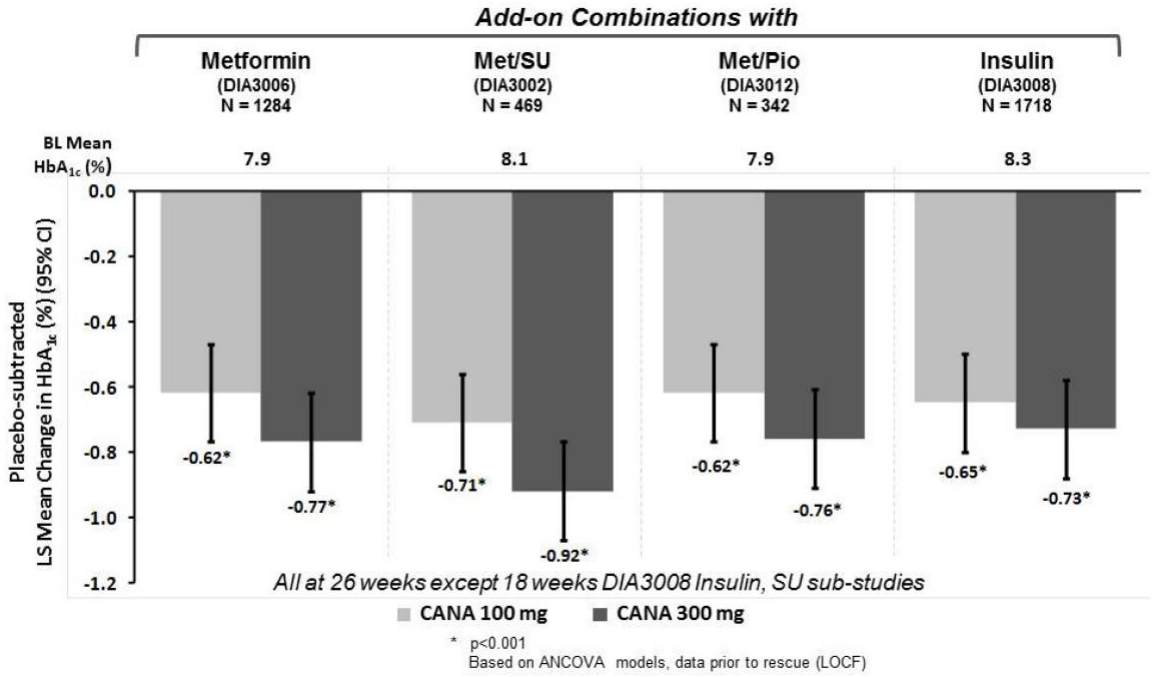


Figure 56. LS mean change in body weight for patients treated with canagliflozin 100mg and 300mg from baseline to primary time point in placebo-controlled Phase 3 studies (81;84;89;93)

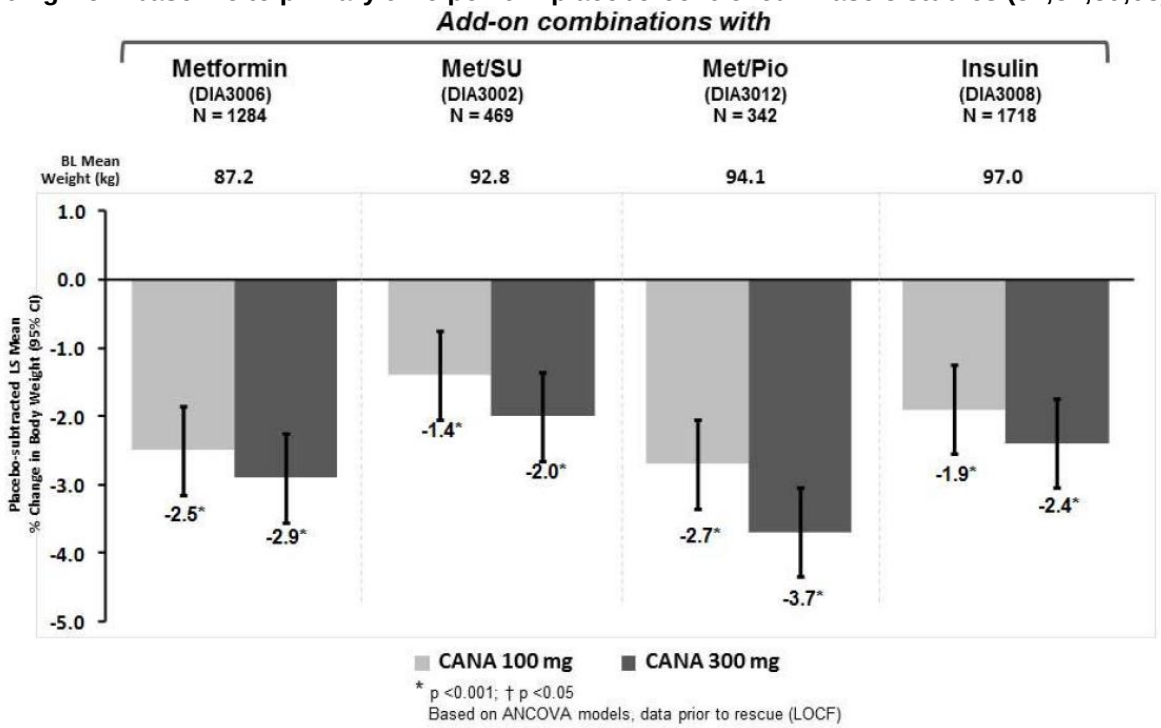
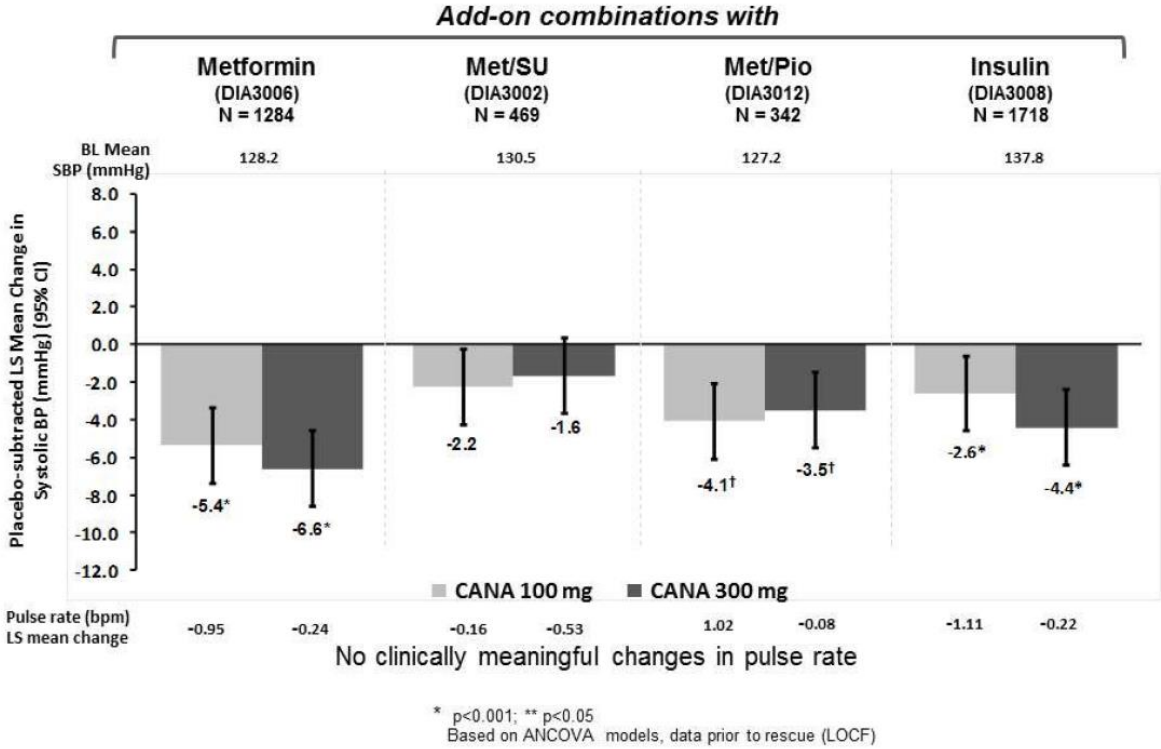


Figure 57. LS mean change in SBP for patients treated with canagliflozin 100mg and 300mg from baseline to primary time point in placebo-controlled Phase 3 studies (81;84;89;93)



For the active comparator trials in dual therapy canagliflozin 300mg at 52 weeks (plus MET) showed:

- Significantly superior reduction in HbA1c compared with glimepiride (DIA3009: Difference in mean change in HbA1c vs. glimepiride: -0.12% [-24.8 mmol/mol]; 95% CI: -0.217;-0.023, p<0.001). Canagliflozin 300mg remained superior at 104 weeks.
- Superior reduction in HbA1c compared with sitagliptin 100mg group (DIA3006: mean change from baseline for canagliflozin 300mg arm was -0.94% (SE: 0.044) and -0.82% (SE: 0.044) for sitagliptin 100mg arm).

These results are clinically relevant given that SUs and sitagliptin are currently considered "gold standard" in the treatment of T2DM. As well as the benefits in terms of glycaemic control, canagliflozin reduced weight and SBP. In comparison, SUs have a propensity to cause weight gain and hypoglycaemia and DPP-4-i do not offer the benefit of weight loss and BP reduction.

Canagliflozin 100mg was non-inferior to both glimepiride and sitagliptin 100mg at 52 weeks, and remained non inferior to glimepiride at 104 weeks, whilst offering benefits of both weight loss and BP reduction over these comparators.

At 104 weeks, both canagliflozin 100mg and 300mg doses (in combination with MET) exhibited durability, in terms of sustained reduction in HbA1c, SBP and weight.

In triple therapy, canagliflozin 300mg resulted in a significantly superior reduction in HbA1c compared with sitagliptin 100mg (DIA3015: difference in mean change in HbA1c vs. sitagliptin was-0.37% [-4 mmol/mol]). Benefits in SBP and weight loss were maintained, even on a background of SU which has a propensity to cause weight gain.

[redacted]

Both doses of canagliflozin were successfully combined with insulin (>30 IU). During this 18-week prospective sub-study, both canagliflozin arms (in combination with INS + SoC) demonstrated statistically significant improvements in HbA1c (DIA3008 difference in mean change in HbA1c was -0.65% [-30.6mmol/mol] (-0.73 to -0.56) in canagliflozin 100mg arm and -0.73% [-31.48mmol/mol] (-0.82 to -0.65) in canagliflozin 300mg arm; p<0.001), BP and weight loss vs. placebo.

Patients with a higher baseline HbA1c achieve greater reductions in HbA1c with canagliflozin than those with lower baseline HbA1c, this is a common phenomenon across all AHAs. Pre-determined sub-group analysis revealed that baseline HbA1c was the only consistent factor, other factors such as age, sex, renal function, race, ethnicity, BMI and β-cell function were not consistent across studies.

Canagliflozin has been studied in a broad T2DM patient population including patients with moderate renal impairment; and has demonstrated an efficacy benefit outweighing risk in patients with an eGFR < 45ml/min/1.73m^2, the posology of canagliflozin allows patients to continue therapy on the 100mg dose until this level of eGFR.

6.10.1.2. Harms

Overall, canagliflozin is well tolerated. However, there are a number of AE relating to the MOA that are to be expected.

The most common of these is GMI in women (approx. 12%). GMIs are also seen in men, but at a much lower level. Rates of UTI were slightly elevated with respect to placebo and other AHAs. GMIs and UTIs generally occurred early in treatment, were easily manageable, were not generally recurrent and did not result in increased discontinuation in the Phase 3 clinical study programme. AEs related to osmotic diuresis and reduced intravascular volume were generally mild-to-moderate in nature, but high risk groups such as the elderly, patients with low eGFR and those on other diuretics should be treated with caution.

Treatment with canagliflozin is associated with changes in fasting plasma lipids, including increased HDL and LDL-C levels. In the placebo-controlled dataset, the LS mean placebo-subtracted absolute change from baseline at Week 26 revealed increases in LDL-C and HDL-C levels for both canagliflozin doses. (8) The MoA for the lipid elevations has yet to be elucidated, however, a large CV risk assessment study (CANVAS) is ongoing and an interim analysis did not reveal any increase in CV risk. Furthermore, changes in lipid levels are amenable to treatment with statins in clinical practice, so clinicians are able to manage lipid profiles in the usual manner.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

6.10.2.1. Strengths

The global CANagliflozin Treatment And Trial Analysis (CANTATA) Phase 3 clinical programme, which enrolled more than 10,000 subjects, is the largest late-stage development programme for an investigational pharmacological product for the treatment of T2DM submitted to health authorities to date.

Three of the RCTs provide head-to-head evidence for two of the key decision problem comparators (SU and DPP-4-i). The programme has supplied outcomes and publications across four lines of therapy: monotherapy (not in the scope), dual therapy in combination with metformin or SU, triple therapy in combination with metformin and SU/TZD and as an add-on to insulin in combination with insulin ± OAD. In addition, canagliflozin has been studied in patients with moderate renal impairment, older patients (55-80 years) and patients with high CV risk. This provides a robust clinical evidence-base supporting canagliflozin across the full range of T2DM patients.

All of the active comparator RCTs have been published in high quality journals such as *The Lancet, Diabetologia, Diabetes Care* or *Diabetes Obesity and Metabolism*. In total, the clinical evidence for canagliflozin incorporates eight peer reviewed publications and multiple communications at scientific congresses such as EASD, ADA and CODhy (see Table 10). (2;7;18;32;34;120). Patients were enrolled into the studies if they were uncontrolled on their existing therapy, and the demographics of the patient groups in terms of age, BMI and duration of diabetes reflects real world patients. Trial subjects had to be on stable doses of their existing medication prior to inclusion into the trial, in addition there was a 2-week single-blind placebo-run in period. This ensured that the study assessed the effect of canagliflozin, rather than the background medication.

Discontinuation rates witnessed within the clinical trials are likely to represent the outcomes that would be observed in clinical practice.

6.10.2.2. Limitations

Despite the robust nature of the phase 3 programme, as in all development programmes limitations exist in the evidence base. Due to limitations on resources and time, it is not feasible to address all comparator arms in RCTs. Therefore there is a lack of granularity when it comes to comparison with different products within a class. In addition, some classes as comparators have not been examined at all in the Phase III programme, e.g. GLP-1-a. However the use of NMA helps to fill these data gaps.

On a study level, as with all RCTs, the use of exclusion criteria means that the clinical study population does not necessarily reflect the potential real world population. In this case there is limited evidence in patients with baseline HbA1c >10%, in the elderly population and the paediatric population, as most of the RCT excluded patients with moderate renal impairment and those with high CV risk with the exception of two separate studies did look at these populations (DIA3004 and CANVAS respectively).

Another limitation is the duration of the studies. T2DM is a chronic long term condition and whilst 2 year data is an acceptable duration for a clinical trial, as with other AHAs, modelling is required to estimate the longer term impact over the lifetime of the patient. Most studies were for 52 weeks in duration, with the exception of DIA3009 which has a duration of 104 weeks. However, a 4-year RCT is currently on-going (DIA3008 CANVAS) and will provide safety, tolerability and CV risk with canagliflozin plus SoC compared with placebo plus SoC in subjects with T2DM. (9)

An additional limitation is the lack of direct evidence supporting dose increase from canagliflozin 100mg to 300mg. The RCTs were designed to have 100mg and 300mg arms running in parallel. None of the studies, examined efficacy when 100mg was up titrated to canagliflozin 300mg, so assumptions have been made based upon specialist opinion following this requirement that was requested by the regulators. Some observational evidence is beginning to emerge from the US where the posology wording is similar; however, no formal analysis has yet been conducted. Furthermore, a group of clinical experts was consulted on this specific point during an advisory-board in August 2013 and a consensus was reached to determine the most optimal clinical scenario for dose increase from the canagliflozin 100mg dose to the 300mg would occur during the first year if a patient failed to reach a HbA1c threshold of 7.5%. (5)

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The insulin-independent MoA of canagliflozin suggests that it can be used at all stages of treatment. Indeed, there is either RCT data to support the efficacy of canagliflozin across all lines of therapy relevant to the decision problem, or this has been supplemented with the NMA.

The Phase 3 trials which form part of the canagliflozin clinical programme are directly relevant to the decision problem in that they all included patients who were uncontrolled in their existing therapy (thus reflecting real world practice and the decision problem)

Furthermore, three of the trials provide head-to-head comparisons with two key comparators relevant to the decision problem.

In all trials, the primary clinical efficacy outcome is the LS mean change in HbA1c from baseline to either week 18, 26 or 52, which is the primary marker of glycaemic control in clinical practice. The NICE clinical guidelines (36;37) state that the primary goal of AHAs is to reduce HbA1c levels below a threshold of 7.5% in order to control for the development of longer term micro- and macro-vascular complications, and the trials have demonstrated that this target can be met by both doses of canagliflozin, although the proportion is higher in the 300mg arm due to the dose response in efficacy.

Secondary endpoints of weight loss and BP reduction were consistently demonstrated across all studies with both doses of canagliflozin. Being overweight is a common co-morbidity with T2DM and contributes to the development of T2DM by increasing insulin resistance, and weight reduction and control is a primary goal in the holistic management of T2DM.

With respect to BP reduction, long-term study groups, such as the UK Prospective Diabetes Study (UKPDS) group, have identified that reductions in HbA1c, especially when combined with controlled BP and lipid levels, are associated with significant clinical benefit in terms of macro- and micro-vascular complications and mortality. Furthermore, UKPDS 38 identified that tight control of BP in patients with T2DM and hypertension is associated with clinically important reductions in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy and deterioration in visual acuity. (121)

Canagliflozin also has a positive impact on other contributors to CV risk, such as SBP and DBP, HDL-C and triglycerides. However, canagliflozin has a negative impact on LDL-C, with increases by 0.11mmol/L in patients receiving canagliflozin 100mg and 0.21mmol/L in patients receiving canagliflozin 300mg, as reported in the placebo-controlled dataset at 26 weeks. (8) Current evidence shows that canagliflozin does not have an increased risk of CVD. Further evidence to investigate this will emerge from the CANVAS (DIA3008) trial, the long-term CV safety study.

Hypoglycaemia has a significant clinical impact in terms of mortality, morbidity and HRQL, which correlates with the severity of the episode.(122) Canagliflozin has low rates of hypoglycaemia especially when used without an agent known to cause hypoglycaemia, as evaluated in the placebo-controlled dataset, with an overall hypoglycaemia incidence of 3.8% in the canagliflozin 100mg arm (n=676), 4.3% in the canagliflozin 300mg arm (n=678) and 2.2% in the placebo arm (n=490). The most common AEs associated with canagliflozin are GMIs, especially in women. In the clinical studies these were easily managed with topical antifungal treatments, and rarely led to discontinuation. Topical antifungal treatment can be prescribed or dispensed OTC and the treatment of this group of side effects is not expected to lie outside normal clinical practice.

Overall, canagliflozin demonstrated lower rates of discontinuation and requirement for rescue therapy than active comparators (sitagliptin and glimepiride) or placebo, demonstrating that patients are more likely to remain on canagliflozin, than switch to another OAD or add-in another therapy.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The biggest discrepancy in the trial programme versus use in clinical practice is the posology. Evidence was not generated on titrating 100mg to 300mg in the trial populations so assumptions have been made based on extrapolation of data from one dose to another and specialist opinion. Supportive evidence is beginning to emerge from the US, where the posology is the same

The trial base covers a broad range of patient populations including those with moderate renal impairment. Due to its MOA, the efficacy of canagliflozin is dependent on renal function, and reduced efficacy is expected in patients with moderate to severe renal impairment. The SmPC states that canagliflozin can be commenced in patients up to an eGFR<60 ml/min/1.73^2 (Cr/CL <60ml/min). Patients with early moderate renal impairment should only be treated with the 100mg dose and canagliflozin should be discontinued in patients when eGFR <45 ml/min/1.73^2 (Cr/Cl <45 ml/min), and not used in patients with ESRD or on dialysis, since it is not expected to be effective in such populations. (25)

Canagliflozin increases UGE which induces osmotic diuresis, which causes a decrease in BP and may reduce intravascular volume in those at risk, particularly the elderly (>75 years). The SmPC states that canagliflozin should not be used in patients taking loop diuretics or in patients who are volume depleted. (25)

Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients. However, canagliflozin may be used in patients with mild or moderate hepatic impairment. (25). Canagliflozin has not been studied in children and the safety and efficacy of canagliflozin in patients aged under 18 has not been established.

All the evidence included in this submission is for the licensed doses of canagliflozin.

7 Cost effectiveness

Key findings from the canagliflozin economic analysis

- A comprehensive economic analysis of the cost-effectiveness of canagliflozin in T2DM was conducted using ECHO-T2DM, a validated micro-simulation model of the long-term costs and disease outcomes.

- For methodological consistency, a NMA was used to estimate treatment effects for available parameters across each line of therapy vs. all relevant comparators defined in the decision problem.

- Overall, the results of the economic evaluation show a consistent picture across a range of comparisons, demonstrating that canagliflozin as an add-on therapy to other AHAs is a cost-effective treatment option.
    - For patients inadequately controlled with MET alone, use of canagliflozin in dual therapy (combination with MET) is cost-effective when compared to SU or DPP-4-i (in combination with MET). The base-case ICERs for canagliflozin 100mg are both below £1,600, and for canagliflozin 300mg are £4,899/QALY vs. SU, and £18,349/QALY vs. DPP-4-i.
    - In triple therapy, canagliflozin is cost-effective vs. DPP-4-i in combination with MET+SU, canagliflozin 100mg is both more effective and cost-saving vs. DPP-4-i. Canagliflozin 300mg vs. DPP-4-i has an ICER of £13,287/QALY. In combination with MET+TZD, the ICERS vs. DPP-4-i are £1,095 and £21,430/QALY for canagliflozin 100mg and 300mg, respectively.
    - As an add-on therapy to insulin plus SoC, canagliflozin 300mg is cost-effective when compared to DPP-4-i; (ICER of £8,925/QALY). Canagliflozin 100mg is marginally dominated (i.e. more expensive and less effective) by DPP-4-i for the base case analysis

- Clinical data for dose modification of canagliflozin 100mg to 300mg are not available, and so the clinical criteria and modelling of this step was discussed with UK clinicians. (5) Dose modification allows patients on the 100mg dose and who have a need for greater glycaemic control to increase their dose to 300mg. The clinical trial data did not specifically assess this dose modification strategy and so we have assessed the impact of this approach via modelling. The modelling of dose modification, consistent with the anticipated label suggests that canagliflozin 100mg was cost-effective against all relevant comparators. In combination with insulin+SoC, under the dose modification scenario, the canagliflozin 100mg dose was cost-effective when compared to DPP-4-i (£5003/QALY).

- The cost-effectiveness results that are reliant on the NMA are consistent with the results observed in the head-to-head randomised controlled trials which showed that canagliflozin 300mg was more effective than SU and DPP-4-i in terms of reduction of HbA1c, weight and blood pressure, whilst the 100mg dose demonstrated non-inferiority in HbA1c improvement and superiority in weight and blood pressure reduction.
- Scenario analyses showed that the structural assumptions around the ECHO-T2DM modelling are robust and that there are few assumptions that directionally impact the costs and/or QALYs.
    - Scenario analysis utilising the discontinuation threshold relevant to the final license (eGFR<45mL/min/1.73m^2), rather than the eGFR<60 mL/min/1.7m^2 in

the basecase, generated more QALYs than the base case and thus in most instances led to both doses of canagliflozin being more cost-effective.
    - Results using RCT data (where head-to-head data were available) are directionally consistent with the modelling results using the NMA and give similar ICERs.
- Two-way deterministic sensitivity analyses (DSAs) performed on the key comparisons confirm that canagliflozin is cost-effective in most analyses. The key driver from a DSA perspective was HbA1c drift.
- In conclusion, the economic evidence presented in this submission are a consistent set of results demonstrating that canagliflozin is a cost-effective treatment option for T2DM patients when combined with metformin in dual therapy, when combined with metformin plus SU or TZD in triple therapy, and in combination with insulin. These conclusions are robust to changes in assumptions across a range of deterministic sensitivity analyses and scenario analyses.

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.**

A systematic search of published economic evaluations with relevance to the decision problem was conducted. (123) Briefly, the search encompassed:

- Publically available cost-effectiveness evidence for canagliflozin, for agents in the class of SGLT-2 inhibitors (e.g., dapagliflozin), and intended comparators to canagliflozin (DPP-4-i, GLP-1-a, and SU) within the scope of this appraisal. In addition, the study also included a review of economic simulation models of T2DM (see Section 7.2.3)
- Searches were conducted on Medline (PubMed Interface), Embase, Medline® In-Process, EconLIT, NHS EED, DARE, HTA (University of York's Centre for Reviews and Dissemination [CRD] Database), ISPOR and Mt. Hood Challenge conference proceedings on their respective internet sites, and internet sites for NICE in the UK, SMC in Scotland, PBAC in Australia, and CADTH in Canada. Secondary searches of the reference lists of qualifying studies were also conducted.
- Studies were included if they:
    - Included economic evaluation that included SGLT-2-i, DPP-4-i, GLP-1-a, and/or SU derivatives
    - UK, Canada, or Australian setting
    - Less than 10 years old (i.e., after June 2003)
- Studies were excluded if they:
    - Did not concern T2DM (e.g., T1DM)

    - Were not written in English
    - Used cost-minimisation or cost-consequence methods
    - Were limited to individual complications of T2DM (e.g., retinopathy or diabetic foot ulcers)
- Usual methods were employed for selecting the studies for inclusion in the analysis. Specifically, titles were first reviewed by three trained health economists using a generous level of tolerance. Abstracts were then reviewed for those passing the title stage by the same three health economists. Full-length articles were then reviewed for those passing the abstract stage by two of the health economists. Finally, each qualifying study was downloaded to reference management software EndNote, where duplicate copies were removed.

Study content—consisting of the model employed, indications and comparisons studied, perspective, key data sources, time horizon, sub-groups and sensitivity analyses, key results, and conclusions and recommendations—was extracted and entered into a data capture form consistent with that recommended by NICE. (124) The quality of evidence was assessed using the procedure developed by Drummond and Jefferson. (125)

Description of identified studies

7.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

The search yielded 52 analyses of potential relevance to the UK setting, of which five were research abstracts/posters presented at ISPOR congresses, seven were articles published in peer-reviewed journals, and 40 were HTA reviews. No studies of canagliflozin were found that met the inclusion criteria. For complete details, see the full report. (123) Importantly, previous HTAs assessments have raised concerns about optimistic disutility values for weight gain and hypoglycaemic events, uncertainty about the underlying clinical efficacy data (including data generated with indirect methods such as NMA and mixed treatment comparison), and the handling of non-significant treatment effects. These concerns have been addressed to the extent possible in the current analysis, including use of conservative disutility weights favoured by NICE and clinical efficacy data from a comprehensive trial programme (entered into a thorough NMA to maximise consistency for scenarios where head-to-head data were unavailable).

Table 30. Summary list of other cost-effectiveness evaluations

Study	Model and Analysis	Results			Conclusions
		ΔQALYs	ΔCosts	ICER	
NICE TA 288, 2013	**1.** HTA Review **2.** Model: DES model similar to CDM and JADE (no further references made in TA 288) **3.** Indication and comparators: **A.** 2nd line add-on to MET): i) DAPA vs. SU ii) DAPA vs. DPP-4s iii) DAPA vs. TZD **B.** 2nd line (add-on to insulin) i) DAPA vs. DPP-4s **C.** 3rd line i) DAPA vs. DPP-4s ii) DAPA vs. TZDs iii) DAPA vs. GLP-1s **4.** Perspective: UK NHS **5.** Time horizon: 40 years **6.** Key data sources: **A.** Patients: RCT of DAPA vs. SU, NMAs for remaining comparators **B.** Efficacy: RCT of DAPA vs. SU, NMAs for remaining comparators. **C.** Costs: UKPDS 65 (126) **D.** Utilities: UKPDS 62 (127) (diabetes-related complications), Currie et al, 2006 (128)(hypoglycaemic events), Lane et al, 2012 (129)(BMI), sub-groups and Sensitivity Analysis: A probabilistic sensitivity analysis was performed. 2 scenario analyses with alternative BMI-related utility values, from CODE-2 (130), were presented. Sub-group analyses conducted with according to race, ethnicity, HbA1c, age, sex and BMI.	A: (i) 0.467 (ii) 0.02 (iii) 0.42 B: (i) 0.119 C: (i) N/A (ii) N/A (iii) N/A	A: (i) £1,246 (ii) -£149 (iii) -£60 B: (i) £517 C: (i) N/A (ii) N/A (iii) N/A	A: (i) £2,671 (ii) dominant (iii) dominant B: (i) £4,358 C: (i) dominant (ii) dominant (iii) dominant	DAPA dominated or had low ICER's vs. SU, DPP-4's, TZD's, and GLP-1's in 2nd and 3rd line treatment. The results were sensitive to the BMI disutility weight, with ICER's increasing 4- to 7-fold vs. SU in dual therapy and vs. DPP-4's in insulin add-on. DAPA was recommended for use in 2nd line therapy, where NICE viewed DPP-4's as the primary comparator. DAPA was not recommended for use in 3rd line therapy, citing lack of evidence and lack of robustness of results

Study	Model and Analysis	Results			Conclusions
SMC Advice No. (799/12), 2012	**1.** HTA Review **2.** Model: DES (no further information) **3.** Indication and comparators: **A.** 2nd line (add-on to MET) i) DAPA vs. SU ii) DAPA vs. DPP-4s iii) DAPA vs. PIO **B.** 2nd line (add-on to insulin) i) DAPA vs. DPP-4s **4.** Perspective: Scotland NHS **5.** Time horizon: 40 years **6.** Key data sources: **A.** Patients: 1 RCT of DAPA vs. glipizide, 3 RCTs of DAPA vs. placebo, and NMAs of DAPA vs. comparators. **B.** Efficacy: 1 RCT of DAPA vs. glipizide, 3 RCTs of DAPA vs. placebo, and NMAs of DAPA vs. comparators. **C.** Costs: UKPDS **D.** Utilities: UKPDS 62 [93] (diabetes-related complications), Currie et al, 2006 [94] (hypoglycaemic events), Lane et al, 2012 [95] (BMI), Sub-groups and Sensitivity Analysis: Sensitivity analysis performed on key model inputs and by excluding non-significant treatment effects.	A: (i) 0.50 (ii) 0.02 (iii) 0.40 B: (i) 0.126 Results after sensitivity analysis: A: (i) 0.099 (ii) 0.031 (iii) 0.098 B: (i) 0.04	A: (i) £1,335 (ii) -£143 (iii) -£80 B: (i) £538 Results after sensitivity analysis: A: (i) £1,663 (ii) £310 (iii) £448 B: (i) £294	A: (i) £2,689 (ii) dominant (iii)dominant B: (i) £4,268 Results after sensitivity analysis: A: (i) £16,786 (ii) £10,000 (iii) £4,552 B: (i) £7,333	DAPA dominated DPP-4 and PIO and had low ICER vs. SU in 2nd line treatment and had a low ICER in insulin add-on in the base case. Using CODE-2 BMI disutility and excluding non-significant treatment effects decreased the cost-effectiveness of DAPA but the resulting ICER's were each equal to or below £10,000. Assuming converging weight change over time further worsened the ICER's. DAPA was recommended as add-on therapy with MET. The use of DAPA as add-on to insulin was not recommended, citing limitations in the NMA.
Study	**Model and Analysis**	**Results**			**Conclusions**

PBAC Public Summary Documents for dapagliflozin, March 2012	**1.** HTA Review **2.** Model: Not reported, cost-minimisation analysis **3.** Indication and comparators: **A.** 2nd line (add-on to MET or SU) i) DAPA vs. SITA **B.** 2nd line (add-on to insulin) i) DAPA vs. PIO **4.** Perspective: Australian government **5.** Time horizon: **6.** Key data sources: **A.** Patients: **B.** Efficacy: 3 RCTs for DAPA and 5 RCTs for SITA. Treatment effects from 3 indirect comparisons of DAPA vs. SITA with three different common references **C.** Costs: Not reported **D.** Utilities: Not used Sub-groups and Sensitivity Analysis: Not reported	Not reported	Not reported	Not reported	The PBAC rejected DAPA in 2nd line treatment. Costs for key adverse events excluded in the analysis. The submission was rejected on the basis of uncertain comparative clinical effectiveness.

7.1.3 Quality assessment

Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004). For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

The quality of evidence was assessed in the 14 peer-reviewed publications and research posters. (131) These 14 studies were generally of acceptable quality. The main differences concerned the level of detail provided (with research posters naturally lagging behind). In particular, the degree of detail of reporting of the data used varied widely.

7.2 De novo analysis

Patients

7.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

This submission includes de novo economic analyses of adult T2DM patients suitable for therapy with canagliflozin in dual therapy (combination with metformin), in triple therapy (in combination with MET+SU and in combination MET+TZD), and as an add-on to insulin (with or without other AHAs). These populations reflect the licensed indications for canagliflozin (see Section 1.5) as well as the patients recruited into the Phase 3 clinical trial programme.

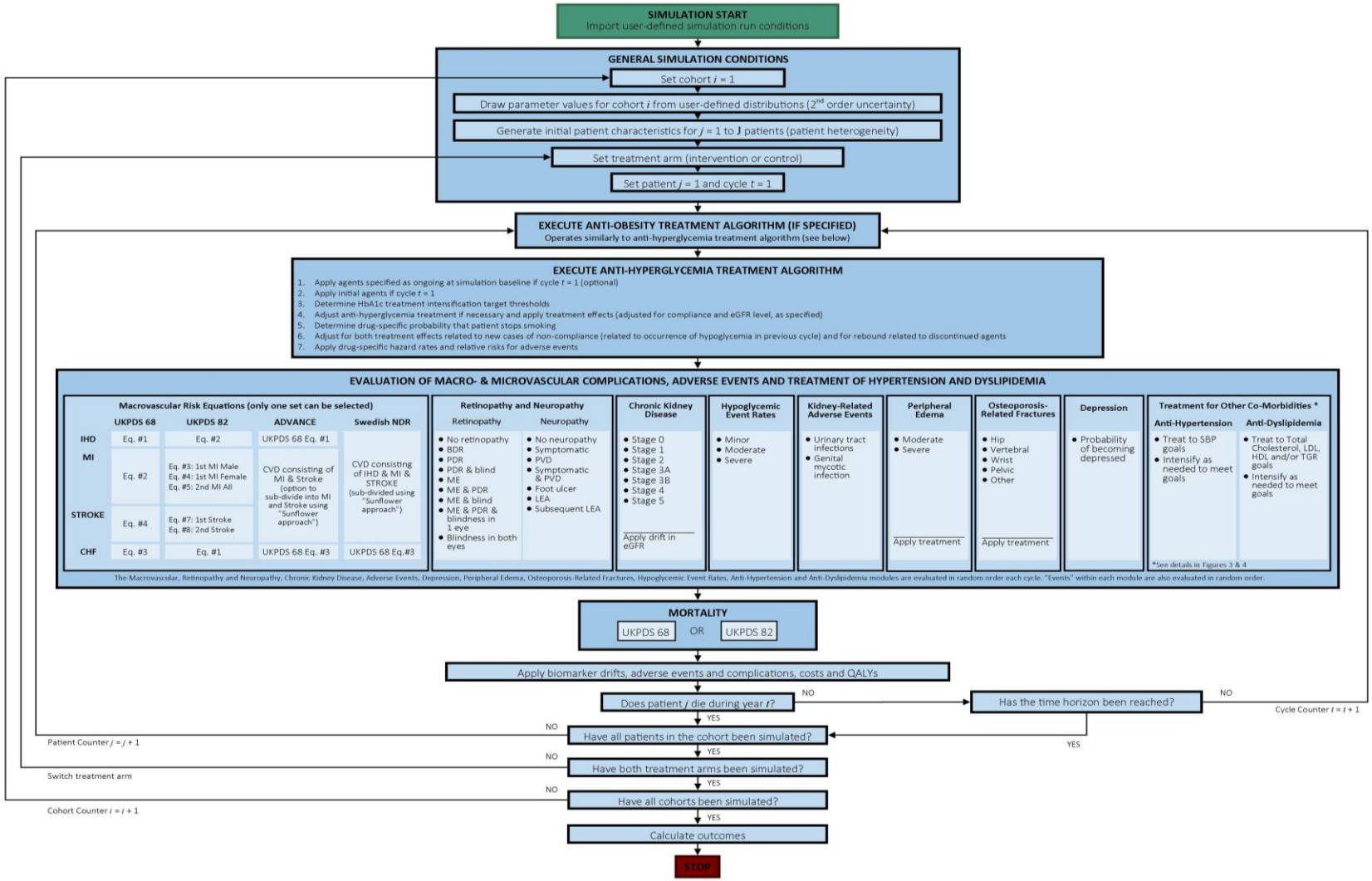
The populations considered in the economic evaluation represent those most likely to receive canagliflozin in clinical practice in England and Wales. The use of canagliflozin in the monotherapy setting is not included as part of this evaluation.

Model structure

7.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

The ECHO-T2DM was used to model all lines of therapy. (131) The general structure is shown in Figure 58. Detailed schematic diagrams of the AHA, anti-hypertension, and anti-dyslipidaemia sub-modules are contained in the technical report. (131;132) Briefly, ECHO-T2DM is a stochastic micro-simulation model in which cohorts of individual hypothetical patients are created and simulated over time using Monte Carlo (first order uncertainty) techniques. Second order (parameter) uncertainty is captured by many cohorts of patients, where each cohort is assigned unique values of the key parameters (e.g., treatment effects, risk equation coefficients, and QALY disutility weights) drawn from probability distributions; the results are aggregated.

Figure 58. Schematic structure of the ECHO-T2DM model



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Characteristics of economic evaluation models in T2DM

An economic evaluation model for T2DM should be capable of capturing a number of key disease features. Firstly, T2DM is chronic, progressive and affects multiple organ systems, thus requiring models that include a large number of inter-related health states and a long time horizon to fully capture the costs and benefits of the disease and its interventions.

Secondly, T2DM is characterised by chronic hyperglycaemia, hypertension, and disturbances of blood lipids which have been linked to elevated risks for developing micro- and macro-vascular complications and which is simulated in models of T2DM using risk equations that convert time-varying bio-marker values into the likelihood of developing complications.

Thirdly, in addition to the benefits of improved diet and lifestyle habits, treating patients to near normal blood glucose levels as well as improvements in blood pressure and lipid values has been shown to reduce the risk of developing complications.(133) Moreover, aging and disease progression typically requires treatment intensification over time and current NICE clinical guidelines (37) recommend a step-wise approach to glucose treatment, with progression to the next treatment in the algorithm being determined by loss of control of glycaemia:

- Lifestyle (diet and exercise) modifications
- Initiation of metformin monotherapy
- Dual and then triple combination therapies if adequate glucose control is not achieved with metformin therapy alone.
- Start on insulin therapy if hyperglycaemia remains particularly marked and/or oral therapeutic options are exhausted.

Models of T2DM, thus, must be capable of modelling complex treatment intensification algorithms, preferably for treating hypertension and dyslipidaemia as well as hyperglycaemia; they must be able to extrapolate the effects of interventions observed in short-term trials over long time horizons; and they should be able to model a study baseline for patients moving on to dual or triple (or later) therapies in addition to patients at diagnosis.

Fourthly, treatment with AHA is associated with short-run adverse events, including hypoglycaemia, which can require adjunctive treatment or discontinuation of particular agents. Models of T2DM must include the treatment-varying risks and consequences of hypoglycaemic events (preferably individually for different event severities) as well as other AE's relevant to the drugs under comparison, e.g., nausea and vomiting for many GLP-1s, peripheral oedema for TZD's, and GMIs for SGLT-2i's.

Finally, the treatment and disease history of T2DM has important economic and quality of life implications, which can be influenced by intervention, so the central aim of a cost-effectiveness model of T2DM is to extrapolate costs and disease outcomes

(in particular, QALY's) for two treatment alternatives for a suitable length of time (often lifetime) to support calculation of ICER's.

Choosing an adequate economic evaluation model in T2DM

A systematic literature review of the structure, capabilities, and validity of economic evaluation models of T2DM was undertaken to assess the suitability of existing models for the purposes of an evaluation of canagliflozin in support of a submission to NICE. The search strategy was similar to that outlined above for the systematic literature review of cost-effectiveness models (see Section 7.1). The details of the search are reported in the study report Twenty-one unique models of T2DM were identified (123), though only a small number are well-documented(134)

ISPOR (135;136) and the ADA (137) have issued general and diabetes-specific modelling best practice recommendations for economic modelling, both emphasising the importance of formal model validation. Eight of the models have published the results of model validation in peer-reviewed journals. (131;138-142) A number of differences were found across the models, not the least in the degree of documentation reported publically. The CORE Diabetes Model (CDM) and ARCHIMEDES have been the most widely used, with CDM and the Cardiff Mode (143)having been used in recent T2DM submissions to NICE. (59;60)

While the details of the systematic literature review are reserved for the appendix, there were important similarities and many differences between the models. Despite the complexity of the disease and need for modelling changing treatment paradigms over long time horizons, it was concluded that a sub-set of the 21 models appear to be up to the challenge of estimating the cost-effectiveness of canagliflozin in the UK treatment setting. ECHO-T2DM is one of them.(131)

ECHO-T2DM model description

ECHO-T2DM is a validated, first (Monte Carlo) and second order (parameter uncertainty) stochastic, micro-simulation model used to forecast costs and patient outcomes over a user-defined time horizon (up to lifetime) for T2DM and its treatment. (132) ECHO-T2DM is programmed in *R* with Microsoft *Excel*® front- and back-end interfaces. Model requirement are *Excel* version 2007 or newer, *R* version 2.15.3, *XLConnect*, and *Java*. Conceptually, cohorts of hypothetical patients defined by a set of characteristics including demographics (e.g., age and gender), bio-marker values (e.g., HbA1c, SBP and BMI), and disease indicators (e.g., disease duration and history of micro- and macro-vascular complications) are generated and individual patient outcomes are simulated over time through health states capturing micro- and macro-vascular complications and death using Monte Carlo techniques.

Micro-vascular health states reflect increasing severity of retinopathy, chronic kidney disease (CKD), and neuropathy (note, despite being a macro-vascular complication, PVD is located in the neuropathy sub-module). The annual probabilities of worsening are derived primarily from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based study enrolling 1,370 diabetic patients diagnosed at age 30 years or older to determine the prevalence and severity of diabetic retinopathy and associated risk variables, The Rochester Epidemiology Project (REP), a population-based registry including the medical records of all persons who ever resided in Olmsted County, Minnesota between January 1, 1966 and the present and who authorised their medical information to be used for

research, and the CDC model of CKD, and they are linked to HbA1c (and in several cases to SBP as well) via power functions. (140)

Four macro-vascular health states are modelled: IHD, MI, Stroke, and CHF. Like many other models, ECHO-T2DM uses risk equations from the original UKPDS Outcomes Model to simulate macro-vascular complications. (133) Unlike other models, however, it also includes the choice to use risk equations from the new UKPDS Outcomes Model, the ADVANCE study, and the Swedish National Diabetes Registry (NDR). (144-146)

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

ECHO-T2DM includes a wide range of treatment-related AE’s suitable for modelling many different classes of agents including SGLT-2-i’s. ECHO-T2DM allows modelling of desired AEs that can be characterised by event rates, costs, and QALY disutility weights. Hypoglycaemic events are divided into minor, moderate, and severe, and event rates, disutilities (per episode), and a probability of triggering non-compliance are included.

The SGLT-2 class of drugs are relatively new in the treatment of T2DM, and have a mechanism of action, therapeutic profile and adverse event profile that differ from products assessed by NICE. As the mode of action is primarily through inhibition of SGLT-2 in the kidney, it is important that the eGFR is taken into account in the estimation of efficacy and in the discontinuation of canagliflozin treatment when the patient eGFR falls below 60 mL/min/1.73m^2. A number of kidney-related AE’s were included for simulations of the SGLT-2 mechanism of action, including orthostatic hypotension, polyuria, upper and lower UTI’s, GMI’s, and constipation (each allow for gender-specific rates, costs, and QALYs and there are separate event rates for the first cycle on agent and subsequent cycles).

After the cohorts of patients are simulated until death or the end of the designated follow-up period, unit costs and QALYs are assigned for each patient in the two treatment arms based upon simulated health history and treatment pattern and they are summed over the simulation. Outcomes include aggregated and disaggregated costs, QALY’s, cost-effectiveness and cost-utility ICER’s, cost-effectiveness acceptability curves, net monetary benefits, and cumulative incidence curves for each of the health states.

7.2.4 Please define what the health states in the model are meant to capture.

Three parallel sets of micro-vascular complications reflecting the full range of severities and five types of macro-vascular complications (represented with Markov health states) are included in ECHO-T2DM. They capture key sources of morbidity

and elevated mortality risk in T2DM. In addition to a health state where the patient is free from complications, the included health states are defined as follows (additional detail is provided in the technical report

- Chronic Kidney Disease, including
  - Stage 1: eGFR>60, micro- or macro-albuminuria
  - Stage 2: 60<eGFR<90 and micro- or macro-albuminuria
  - Stage 3A: 45<eGFR<60 regardless of albuminuria
  - Stage 3B: 30<eGFR<45 regardless of albuminuria
  - Stage 4: 15<eGFR<30 regardless of albuminuria
  - Stage 5: eGFR<15 regardless of albuminuria
  - End stage renal disease: eGFR<15 for a period of more than one year.
- Neuropathy, including
  - Symptomatic neuropathy
  - Peripheral vascular disease
  - Diabetic foot ulcer
  - Lower extremity amputation
  - Subsequent lower extremity amputation
- Retinopathy, including
  - Background diabetic retinopathy
  - Proliferative retinopathy
  - Macular oedema
  - Blindness in one or both eyes

Patients can also experience five types of macro-vascular complications (MI and stroke can occur more than once):

- IHD (excluding MI)
- MI
- CHF
- Stroke
- PVD (because of interdependence with neuropathic outcomes, it is located in the micro-vascular neuropathy sub-module).

The health states are associated with costs, utility values, and in some cases a possible treatment contraindication (e.g., ESRD and CHF for pioglitazone) or with excess risk death (e.g., Stroke or MI).

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As described in Section 2.1, T2DM is a chronic progressive disease characterised by marked hyperglycaemia, raised blood pressure, changes in blood lipids and in patient body weight. Over time, there is growing insulin resistance, gradual loss of pancreatic β cells and some patients experience a deterioration of kidney function. The progression of T2DM is inexorable and as a result of these physiological changes, patients have an increasing risk of developing micro- and macro-vascular co-morbidities.

Intervention with the aim of improving blood glucose, SBP, and lipid values has been demonstrated to improve patient outcomes. (133) ECHO-T2DM uses well-known risk equations to translate intervention-medicated changes in these covariates into long-run differences in patient outcomes (see section 7.2.3. for more information about the risk equations use in the model).

ECHO-T2DM simulates a flexible and comprehensive AHA treatment algorithm defined by:

- treatment sequence including rescue medication(s),
- decision rules for intensification of therapy (e.g., HbA1c exceeding a threshold value, completion of a fixed duration on agent, and/or development of a contraindicating condition), and
- two types of agent-specific treatment profiles (e.g., treatment effects, durability and bio-marker evolution, stopping rules, adverse event rates, non-compliance, and contraindication), one for non-insulin agents and the other for insulin agent (which is more flexible and permits dose modification to meet HbA1c goals)

Using Monte Carlo techniques, each individual patient is assigned treatment during each cycle. ECHO-T2DM requires valid non-insulin profiles at simulation start (though one can easily simulate initiation of insulin at study baseline by inserting insulin-specific parameters into a non-insulin profile). The initial treatment effects are applied and each patient is individually evaluated for HbA1c failure, reaching a maximum duration on agent, and for contraindications and AE's that would motivate treatment discontinuation. Patients continue on this treatment as long as they survive and none of the above criteria are met. When one or more of the criteria are met, the user-defined treatment sequence will indicate which agent (if at least one is specified) will be started (and whether the original agent will be continued or discontinued). The process is then repeated. When there are no longer any available non-insulin agents or at the treatment line the analyst specifies, the initial insulin profile (e.g., basal insulin) is applied at the start dose and titrated up to the designated maximum dose as needed to maintain HbA1c control. When additional control is needed thereafter, the next insulin regimen (if one is specified) is started (e.g., prandial insulin on top of the long-acting insulin), again starting at an initial dose and titrating up to the designated maximum dose, as many additional insulin profiles can be added as desired.

As both hypertension and dyslipidaemia are major co-morbidities in T2DM patients, most patients are treated with anti-dyslipidaemia and anti-hypertension medications. The model allows for a proportion of patients to be taking these medications at baseline, and also for treatment to start if treatment thresholds of lipids or BP are exceeded, and for intensification of anti-dyslipidaemia and hypertension medication to be applied.

The model also incorporates heath states and events associated with pharmacological treatment, including:

- Patient weight change
- Hypoglycaemic events (separately by mild, moderate, and severe)
- Upper and lower UTI's
- GMI
- Gastrointestinal upset, including nausea.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 31. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (40 years)	T2DM is a chronic, progressive disease. The comorbidities resulting from hyperglycaemia make take many years to develop. T2DM and its treatments impact the patient's HRQL and incur costs over a lifetime, and a time horizon of 40 years allows the model to reflect this.	(124)
Cycle length	1 year	The comorbidities resulting from hyperglycaemia develop relatively slowly justifying an annual cycle length. Nearly all models of T2DM using an annual cycle length.	None
Half-cycle correction	No	The importance of half-cycle corrections diminished with the number of cycles simulated. In T2DM, modelling durations are typically quite long, decreasing the need for half-cycle correction.	None
Were health effects measured in QALYs; if not, what was used?	Yes	Consistent with previous T2DM economic models and NICE methods guide	(124)
Discount of 3.5% for utilities and costs	Yes	Consistent with previous T2DM economic models and NICE methods guide	(124)
Perspective (NHS/PSS)	NHS/PSS	Consistent with previous T2DM economic models and NICE methods guide	(124)
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

ECHO-T2DM applies rescue treatments when patients exceed certain biomarker thresholds for dyslipidaemia and hypertension. These treatment algorithms are consistent with NICE clinical guidelines for lipid modification and NICE guidelines for hypertension, respectively. (147;148)

Anti-hypertension treatment algorithm

Anti-hypertensive treatment and subsequent rescue is initiated within ECHO-T2DM when the simulated patient's SBP exceeds 140mmHg. The treatment sequence is to first apply an angiotensin-converting enzyme inhibitor (ACE-i) (ramipril; 5mg QD), followed by the addition of a diuretic (bendroflumethiazide, 2.5mg QD), followed by a beta blocker (atenolol, 50mg QD).

Anti-dyslipidaemia treatment algorithm (148)

Treatment for dyslipidaemia is initiated when any of the thresholds are exceeded:

- Total cholesterol exceeds: 5mmol/L

- HDL drops below: 1.4 mmol/L
- LDL exceeds: 2.0 mmol/L
- Triglycerides exceed: 4.5 mmol/L

First line treatment is with a statin (simvastatin, 40mg QD). If further treatment is required, simvastatin (80mg QD) is used, followed by the addition of ezetimibe (10mg QD) and then fenofibrate (600mg QD).

The relationship between hypoglycaemic event rate and HbA1c is described by a user-defined hazard ratio for event rates corresponding to each 1% point decrease in HbA1c, defined by the user. In an analysis based on DCCT data, the multivariate regression estimate of the RR was 1.43. (149)

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Canagliflozin and comparator therapies are implemented in the model as per their marketing authorisations. The comparisons conducted within the economic model across the lines of therapy are shown in Table 32.

Table 32. Economic modelling comparisons conducted

Comparator	Cana dose	Dual therapy	Triple therapy		Add-on to insulin
		Met	Met+SU	Met+TZD	
SU	100mg	✓	*n/a*		
	300mg	✓	*n/a*		
TZD	100mg	✓		*n/a*	
	300mg	✓		*n/a*	
DPP-4-i	100mg	✓	✓	✓	✓
	300mg	✓	✓	✓	✓
GLP-1-a	100mg	✓	✓		✓
	300mg	✓	✓		✓
Dapagliflozin	100mg	✓			✓
	300mg	✓			✓
Insulin	100mg		✓		
	300mg		✓		

Legend: DPP-4-i: Dipeptidyl peptidase-4 inhibitor; GLP-1-a: Glucagon-like peptide-1 agonist ; n/a: not applicable; SU: sulfonylurea; TZD: Thiazolidinediones

There are multiple products available in most of the comparator classes in Table 32. However, comparisons were conducted against only one member of each of the

classes. The rationale behind the choice of specific comparator is described in Table 33.

Table 33. Specific comparators selected within each pharmacological class

	Pharmacological class member selected	Justification	Reference
SU	Efficacy: glimepiride Cost: gliclazide	Glimepiride was the SU used in the trial programme Gliclazide is the SU with the highest level of UK prescribing	(150)
TZD	Pioglitazone	Rosiglitazone has no licence/ no other TZD available for prescribing in clinical practice in the UK	(151)
DPP-4-i	Sitagliptin	Most used UK DPP-4-i and comparator in two canagliflozin trials	(150)
GLP-1-a	a) Liraglutide	Market share data shows liraglutide has a wider use in UK clinical practice, and thus selected as the GLP-1-a of choice where data allow	Section 6.7.3 (150)
	b) Exenatide BID	Exenatide BID has a broader recommendation for use in T2DM; Exenatide BID is the only GLP-1 present in the Triple (MET+SU) and add on to insulin NMA networks.	Section 6.7.3 (60)
Insulin	insulin aspart	From market share data ASPART has a widest use for SA INS, in UK clinical practice	(150)
Legend: DPP-4-i: Dipeptidyl peptidase-4 inhibitor; GLP-1-a: Glucagon-like peptide-1 agonist; SU: sulfonylurea; TZD: Thiazolidinediones			

7.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**
- **Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

Current clinical guidelines suggest treatment switch for dual and triple therapy and add-on to insulin when the patient's HbA1c rises above 7.5% (59mmol/mol). (37) The

base case modelling employed an HbA1c switch threshold of 7.5% for all base case simulations. In clinical practice, the HbA1c threshold at which patients receive additional or alternative treatment may be higher. (152)

Once a threshold of 7.5% is reached, a common approach is to add an additional therapeutic option (153), for example a patient on Met+SU could switch to Met+SU+DPP-4-i. However, for the purposes of demonstrating cost-effectiveness and to stay within the bounds for which we have clinical effectiveness estimates, and consistent with other modelling approaches in T2DM, the base case modelling assumption is that the patient will discontinue the current therapy and move on to rescue therapy, as described in Section 7.2.5.

Because the final SmPC was not available at the time the modelling simulations were conducted, our base case analysis assumes that canagliflozin therapy discontinued in situations where the patient's eGFR falls below 60mL/min/1.73m^2. However, the final SmPC (see Appendix 1.10) actually states a lower threshold, advising that canagliflozin should be discontinued at an eGFR of <45 mL/min/1.73m^2.

It should be noted that within the trial there was a small proportion of patients who remained on canagliflozin at eGFR levels below 60mL/min/1.73m^2. Thus in the clinical data used for the estimation of therapeutic effect for canagliflozin within the NMA and in scenario analyses in which direct trial elicited data was used, there were a limited amount of data from treatment below 60mL/min/1.73m^2.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

ECHO-T2DM is a stochastic micro-simulation (patient-level) model. Conceptually, the model performs the following steps requiring clinical data:

1. Generates cohorts of hypothetical patients based on probability distributions for key demographic and clinical characteristics, including demographics (e.g., age and gender), disease indicators (e.g., disease duration and history of micro- and macro-vascular complications) and bio-marker values (e.g., HbA1c, SBP, BMI)

2. Assigns treatment, including treatment effects and AE rates, bio-marker evolution, and discontinuation rates

Treatment effects from RCTs are used to modify patient biomarkers, which in turn modify the risks of complications over time. Risk equations utilise these inputs and generate patient outcomes.

Initial Patient Characteristics

The source of these were the canagliflozin clinical trials

1. Dual Therapy with
    a. MET background: Pooled analysis of DIA3009 and DIA3006
2. Triple therapy
    a. MET+SU background: Pooled analysis of DIA3002 and DIA3015
    b. MET+TZD background: DIA3012
3. Add-on to Insulin: DIA3008

Further detail on the trials and study populations are described in Figure 4 of Section 6.2.6. As noted in section 7.2.2 and Section 10.9 for Appendix 9, individual patient's initial characteristics are assigned based on draws from probability distributions parameterised by the means and standard deviations observed in the clinical data.

Treatment Effects and AEs

As described in Section 6.7, where possible, NMAs were performed for HbA1c, SBP, weight/BMI and the incidence of hypoglycaemic events separately for trials of dual, triple and add-on to insulin therapy. All HbA1c treatment effect data for the base case simulations for canagliflozin and the comparators were obtained from the NMAs.

Although the canagliflozin trial programme reports data at 104 weeks in dual therapy (vs. SU) and data at 52 weeks in triple therapy (vs. sitagliptin), due to the paucity of published studies on comparators out to these time points, networks could not be constructed for the longer durations in some cases. As such, in the base cases (that primarily rely on the NMAs), 52 week data were used in dual therapy but 26 week data were used in triple therapy. In the add-on to insulin simulations, although the primary endpoint assessment in DIA3008 was at 18 weeks, post hoc analyses were performed at the 26 week time point to support the NMA.

As described in Section 7.2.3, the cycle length in the model is one year. It was assumed that no changes in treatment effects and AEs occurred during weeks 26 – 52 for the triple and add-on to insulin simulations. Treatment effects on lipids, rates of selected AEs (GMI, UTI and nausea) and first year discontinuation rates were excluded from the NMA because data were not routinely or were inconsistently reported. We sourced these effects for canagliflozin and active comparators (DPP-4-i and SU) from the clinical programme. For other comparators, placebo rates from the most relevant canagliflozin trial were generally used for these parameters. Exceptions include: lipid effects for TZD, GLP-1-a's and dapagliflozin; the selected AE rates for dapagliflozin; and rates of nausea associated with GLP-1-a. Additional details are given in the text and tables below.

As SBP data were not available in the NMA for exenatide BID in triple therapy, an estimate was based upon data obtained from the literature. (154;155) SBP was also missing from the NMA for sitagliptin in add-on to insulin therapy. In this case, the SBP value for saxagliptin in the network was used. (156)

The ECHO-T2DM model simulates changes in BMI (as opposed to weight). Where BMI was not available in the NMAs, but data on weight were, values were converted to BMI using a weighted average of male and female heights observed in the UK general population.

Treatment effects on lipids, rates of selected AEs and first year discontinuation rates for canagliflozin were obtained from the pooled datasets for dual (DIA3006 and DIA3009) and triple therapy (DIA3002 and DIA3015), except for canagliflozin 100mg in triple therapy with MET+SU (DIA3002), canagliflozin in triple therapy with MET+TZD (DIA3012) and canagliflozin added on to insulin (DIA3008). As only the 300mg dose was studied in DIA3015, it was assumed that the effects observed in DIA3002 for canagliflozin 100mg could be applied to the pooled population since the trial designs and inclusion/exclusion criteria were similar. (see Section 6.3.2)

For pioglitazone, exenatide BID and liraglutide in all lines of therapy, zero effects on lipids values were assumed. While some studies have found small positive lipid effects for these AHAs, the literature is not conclusive. (37;60) This zero assumption is conservative compared to using the placebo rates as observed in the canagliflozin programme, since placebo generally showed deterioration in lipid values. For dapagliflozin, canagliflozin 100mg lipid effects were assumed.

Published estimates for the rate of nausea associated with GLP-1-a are highly variable. (37;60) As such, it was conservatively assumed that the rate for exenatide BID was twice that observed with canagliflozin. The nausea rate for liraglutide was assumed to be one-third lower than the rate assumed for exenatide BID. (60)

The simulations included two mutually exclusive categories of hypoglycaemia events: 1) severe and 2) non-severe symptomatic. A severe hypoglycaemia event was

defined as one that required third party assistance (including medical assistance) or resulted in loss of consciousness or seizure. A non-severe symptomatic hypoglycaemia event was defined as a symptomatic episode that was biochemically confirmed (i.e., concurrent fingerstick glucose or plasma glucose ≤ 70 mg/dL [3.9 mmol/L]). Both types of events were assumed to be associated with a decrement in utility (see Table 189, in Section 10.9 for Appendix 9); costs were applied only for severe events (see Table 190, in Section 10.9 for Appendix 9).

Hypoglycaemic event rates for canagliflozin were sourced from the clinical trial programme. Where possible, event rates for the comparators were estimated by multiplying the canagliflozin rates and the odds ratios (ORs) for the proportion of patients experiencing hypoglycaemic events for the comparators as estimated in the NMA. Two assumptions are implicit. First, the OR does not vary by severity of hypoglycaemic event (i.e., non-severe symptomatic and severe). Second, the OR for event rates (as modelled in ECHO-T2DM) is the same as the OR for proportion of patients experiencing events (as estimated in the NMA).

For certain comparators NMA OR data were unavailable. As all of these comparators have MOAs that are not known to be associated with an increase in the risk of hypoglycaemia, placebo rates from the canagliflozin trial programme were used. Specifically, for liraglutide and pioglitazone in dual therapy, placebo rates from DIA3006 were assumed. In the add-on to insulin simulations for sitagliptin and exenatide BID, rates from the placebo arm of DIA3008 were used. For dapagliflozin, rates from the canagliflozin 100mg arm of DIA3008 were used.

Evolution of HbA1c and Other Biomarkers

Even with treatment, biomarkers for patients with T2DM tend to “drift” upwards over time. In long-term follow-up in the UKPDS (121), for example, HbA1c values in both treatment arms increased at about 0.15 percentage points per year (albeit at different absolute levels) in a linear fashion, despite treatment intensification. The updrift in HbA1c overtime was also observed to be linear over 5 years in the ADOPT study. (157) though there were important differences by drug (0.07 for rosiglitazone, 0.14 for metformin, and 0.24 for glyburide). In the canagliflozin modelling, linearity in drift is assumed and the metformin drift of 0.14 percentage points per year is used for: canagliflozin, dapagliflozin, sitagliptin, exenatide BID, and liraglutide; the rosiglitazone drift of 0.07 percentage points per year is used for pioglitazone; the glyburide drift of 0.24 percentage points per year is used for glimepiride; and the rate of 0.15 percentage points per year observed in the UKPDS is used for insulin therapy. Note: the non-linear HbA1c evolution equation (Equation 11 from Clarke, 2004) has been used by some analysts. (133) While this optional feature can be applied using ECHO-T2DM as well, this specification is confounded by the intermittent addition of rescue medication in the UKPDS and resultant HbA1c-lowerings. Because ECHO-T2DM applies the consequences of rescue medication explicitly, using the evolution equation would amount to double-counting of the benefits of rescue medication.

The rate of long-term drift of SBP was sourced from data on mean values over time from the UKPDS. (133) The mean SBP values over time and SBP values simulated using Equation 12 (at mean covariate values) were similar. Both sets of values overtime exhibited reasonable linearity, with an annual drift of approximately 0.3 mmHg/year.

Data on the long-term drift of lipid values (especially disaggregated into the four components) is scarce. In the UKPDS, the total to HDL to lipid ratio (used in the UKPDS macro-vascular and mortality risk equations) exhibited some fluctuation over time (rising slightly in the beginning and decreasing thereafter), but on average exhibited a slight (and mostly linear) decrease over time. The total to HDL values simulated using Equation 13 in Clarke et al. (2004) were almost constant over time. We used these relationships to generate informed assumptions about the relationship of the cholesterol components; specifically, we assumed very small (0.03 mg/dl per year) increases in each of the components, resulting in an approximately flat, but slightly downward-sloping total to HDL ratio.

For the increase in BMI over time, we applied the rate of 0.1 kg per year that was reported in the NICE review of dapagliflozin (59) and converted it to a BMI updrift using UK gender-specific standardised heights. eGFR also varies over time. The rates of drift were sourced from the CDC Model of CKD (140) where the decline varies according to whether eGFR is greater than or less than 60 mL/min/1.73 m^2 and to whether the patient has established micro- or macro-albuminuria.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities in ECHO-T2DM are individualised for each of the hypothetical patients, being determined by sets of risk equations and the patient's personal characteristics. The risk equations are taken from large outcome studies. Full detail is presented in the Technical report. (132)

For retinopathy and neuropathy complications, the base rates are generally derived from WESDR and REP, as described in Eastman and colleagues (1997) and supplemented by Bagust and colleagues (2001). (158) These complication rates vary according to race/ethnicity, disease duration, and in some cases age. (133) The base rate for an individual patient is then modified to account for current HbA1c level using power functions (higher HbA1c leads to higher risks and vice versa). (159;160) Proliferative diabetic retinopathy (PDR) and symptomatic neuropathy are additionally modified to account for differences in SBP using power functions (cite Brown et al, 2000).

The transition probabilities for CKD are taken from the CDC model of CKD (140) and consist of two parts: the development of micro- and macro-albuminuria and drift in the eGFR bio-marker passing fixed threshold values (60, 45, 30, and 15). As in the CDC model, the drift in eGFR increases when patients develop albuminuria.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities described above adjust as the covariates defining the individual patient change over time (e.g., age increases, HbA1c may drift upward or may decline as a new treatment is added, and the patient may develop disease complications that increase the risks for other complications). This is consistent with the observation that complication rates generally increase with duration of T2DM. (133)

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcome measures such as HbA1c, SBP, lipids, and BMI are linked to final clinical outcomes such as micro- and macro-vascular events, amputation, blindness and mortality through the risk equations described in Section 7.3.2. This is consistent with other diabetes models, as described in Section 7.1.2.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details2:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

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[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Although NICE clinical guidelines give recommendations on how to prescribe AHAs, there is variation in the use of medicinal products in practice. (36;37) Therefore, clinical experts were consulted to obtain details relating to the current use of treatments in UK clinical practice as well as the medical resources used for the administration of these treatments and for managing AEs. The generation of this data involved the following steps:

- Clinicians with no conflict of interest were approached to ask for their attendance at an advisory board hosted by Janssen.
- 3 advisory boards were held between December 2012 and August 2013; each with an alternative objective, namely: Health Economic model assumptions to fit clinical practice; Health Economic model assumption and input for HTA submission; and NICE strategy for a diabetic treatment submission.
- The Advisory Boards were conducted in accordance with the ABPI guidelines. (161) . The clinical experts did not declare any conflict of interest. At the consensus meeting, the panel were presented with suggested approaches of addressing uncertainties within the economic modelling to provide a foundation for discussion. This process involved individuals voicing their opinion on each value sequentially, then if there was discrepancy, a discussion followed. After discussion, the consensus panel was then asked to state their opinion. This process continued until the panel agreed.

At an advisory board hosted by Janssen (London, December 2012) (162), to determine the appropriate clinical assumptions and parameter inputs for economic modelling in the treatment of T2DM, consensus was sought for the most appropriate values for inclusion in economic modelling with the objective of providing estimates of:

- Population characteristics at each stage of therapy
- Treatment starting, stopping and discontinuation rules and rates
- Risk equations related to BP, weight, lipid change
- Parameter drift assumptions (for HbA1c, SBP, weight and lipids)

AEs with significant patient and budgetary impact were identified and the most likely management strategies for controlling BP and weight in T2DM patients were discussed and agreed upon. Lastly, the related risk of hypoglycaemia and micro-vascular complications based on HbA1c level were discussed. This information was used to define the most appropriate economic model to use in support of this submission for the use of canagliflozin in the treatment of adults with T2DM.

At an advisory board hosted by Janssen (London, May 2013) (163), to validate the appropriate clinical assumptions and parameter inputs for ECHO-T2DM, consensus was sought on the most representative values for inclusion in ECHO-T2DM with the additional objective of providing estimates of:

- Relevant modelling comparators at each line of therapy at which canagliflozin use is anticipated (i.e. dual, triple and add-on to insulin)
- Dosing, treatment cycle duration and additional resource use involved for all medicinal products used in the treatment of T2DM, including AE management
- Laboratory tests performed prior to, during and following initiation of a new treatment

- The anticipated impact of AEs on patient quality of life
- The metabolic drift of parameters after treatment discontinuation (for HbA1c, SBP, weight and lipids)

The estimates generated in this process were taken forward for inclusion in economic modelling.

At a final advisory board hosted by Janssen (London, August 2013) (67), to obtain a detailed understanding of the key treatment options (and associated health care resources) for patients with T2DM, consensus was sought for the most appropriate strategy to be taken when presenting the use of canagliflozin in the NHS. Discussions addressed:

- Current and future treatment options and the likely treatment path T2DM patients will follow; validating the key comparators for canagliflozin for three lines of therapy in the T2DM care pathway, in England and Wales;
- Treatment targets and outcomes of importance in clinical practice

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

ECHO-T2DM modelling comparisons were carried out with the specifications in Table 34.

Table 34. Model settings

Variable	Value
Number of patient cohorts per model run: base case comparisons	1000
Number of patients in each cohort: base case comparisons	1000
Number of patient cohorts per model run: scenario analyses and sensitivity analyses	500
Number of patients in each cohort: scenario analyses and sensitivity analyses	1000
Discount Rate for Costs	3.5%
Discount Rate for Health	3.5%
Modelled time horizon	40
Maximum patient age	100

A list of the key categories of inputs and corresponding sources used in the base case simulations appear in Table 35, along with the location of the information in the dossier, where applicable.

Table 35. Overview of key data sources used in the economic model

Parameter	Table number/location of submission	Source(s) of data
Baseline patient/ social demographic and clinical characteristics	Appendix 10.9 - Table 183	Pooled DIA3006 and 3009, DIA3002 and DIA3015, DIA3012 and DIA 3008
Patient medical history	Appendix 10.9 - Table 184	Pooled DIA3006 and DIA3009, DIA3002 & DIA3015, DIA3012 and DIA3008
Treatment effects	Appendix 10.9 - Tables 185 to 188	NMA and Pooled DIA3006 and DIA3009, DIA3002 and DIA3015, DIA3012 and DIA3008
Evolution of HBA1c and other clinical biomarkers	Described in Section 7.3.7 (Table 36)	(59;140;157)
Micro-vascular, macro-vascular, and mortality risk equations	Described in Section 7.3.2	(133;140;158-160)
Duration of treatment	Described in Section 7.3.1	(37)
Hypoglycaemia	Table 185 in Section 10.9 (Appendix 9) Described in Section 7.3.1	Section 6.7. (NMA) and trial data.
Selected adverse events rates and discontinuation due to AEs	Tables 185 to 188 in Section 10.9 (Appendix 9)	Pooled analysis of DIA3006 & DIA 3009, Pooled analysis of DIA3002 & DIA3015, Analysis of DIA3012 and DIA3008 (37;60)
Utility decrement values	Table 189 in Section 10.9 (Appendix 9)	(128;130;164;165)
Cost of diabetes-related complications and AEs	Table 192 in Section 10.11 (Appendix 11)	See Section 7.5.6
Drug acquisition costs, consumer costs (needles, blood glucose monitoring)	Table 190 in Section 10.9 (Appendix 9)	See Section 7.5.5

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

The estimates of the biomarker effects for each drug, HbA1c decrease and impact on SBP, lipids and body weight, were estimated from the NMA (see Section 6.7.6.) and applied to the first year (one cycle) of the economic model. Beyond this, the evolution of these four biomarkers is extrapolated as described below.

Table 36. Drift assumptions for biomarkers for all lines of therapy

	AHA	Annual Drift Value	Source
HbA1c	Canagliflozin, Dapagliflozin, DPP-4-i, GLP-1-a	0.14%	Assumed equal to value observed for the metformin arm in ADOPT (157)
	TZD	0.07%	Assumed equal to value observed for the rosiglitazone arm of ADOPT (157)
	SU	0.24%	Assumed equal to value observed for the SU arm of ADOPT (157)
	Insulin	0.15%	(133)
SBP	All AHAs	0.30 mmHg	Derived from UKPDS 68 (133)
Lipids	All AHAs	0.03 mg/dl	Derived from UKPDS 68 (133)
Weight*	All AHAs	0.1kg/year	Value from Dapagliflozin FAD (59)
eGFR	All AHAs	Varies by eGFR category and whether patient micro- or macro-albuminuria	(132;140)

* converted to BMI using UK gender-specific standardised heights

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 37 describes the assumptions used to parameterise key features of the model and perform the simulations.

Table 37. Key Assumptions for the economic modelling

Parameter	Key assumptions for Base Cases	Justification
Baseline characteristics	All values obtained from the canagliflozin clinical programme. DIA 3012 and DIA 3008 were the used for the simulations with MET+PIO and add-on to insulin background therapy, respectively. Data was pooled for the dual therapy simulations on the background of MET (DIA3009 & DIA3006) and for the triple therapy simulations on the background of MET+SU (DIA3002 & DIA3015).	Baseline characteristics from the clinical programme are generalisable to patients with T2DM in the UK The dual and triple study designs as well as inclusion/exclusion criteria were very similar. Pooling data allowed for improvement in precision in terms of identifying background characteristic parameters
Treatment effects (HbA1c, SBP, Weight, Lipids)	NMAs were the primary source of treatment effects Results observed at 26 weeks in the triple therapy and add-on to insulin trials were assumed to be equivalent to the effects that would be observed at 52 weeks. In the dual therapy base case simulations versus SU, 52 week data were used (although data were available out to 104 weeks) Treatment effects associated with an agent are immediately reversed at discontinuation (i.e., at the start of the next cycle, HbA1c, SBP, weight and lipids are returned back to baseline values)	(124) see Section 7.3.1 for details on data used when a treatment effect was not available in a NMA. The cycle length of ECHO-T2DM (as well as most other models in this therapy area) is 1 year. Although the canagliflozin programme has data at 52 weeks in all three of the triple therapy studies, due to the paucity of published studies on comparators out to this time point, networks could not be constructed. Analyses at 52 weeks support the extrapolation of treatment effects from 26 to 52 weeks. Similarly, to support the NMA in the add-on to insulin simulations, 26 week data from the DIA 3008 insulin sub-study was used to represent treatment effects expected at 1 year. Recently reported data from the extension period of this study confirms that the treatment effects observed with canagliflozin at 52 weeks were durable out to 104 weeks. (80) Data on the residual effects of drugs post-discontinuation is unavailable
AHA Treatment algorithm	In dual and triple therapy, except when long-acting insulin is the comparator, discontinue canagliflozin or comparator when HbA1c exceeds 7.5%, then switch to long-acting insulin (glargine) initiated at 40 IU/day and titrated as needed to maintain HbA1c control up to a maximum of 60IU/day at which point, post-prandial insulin (Humalog) thrice daily was added and titrated as necessary. Note that IU/day was adjusted for the weight of a patient. When insulin is the comparator in triple therapy and HbA1c exceeds 7.5%: insulin arm – add prandial insulin; canagliflozin arm: discontinue canagliflozin and start long acting insulin, then prandial as needed.	(63) As the simulations were performed prior to availability of the final label language, in the majority of the cases patients were assumed to discontinue treatment with canagliflozin when eGFR<60 ml/min/1.73m^2 or when they developed ESRD. The exception to this was in the sensitivity analyses where treatment with canagliflozin in patients with moderate renal impairment with an eGFR ≥45 was examined. In these simulations, changes in the efficacy of

Parameter	Key assumptions for Base Cases	Justification
	When insulin is added as a rescue therapy and SU is part of the background set of treatments, the SU is not discontinued When insulin is added as a rescue therapy in the third line simulations with MET and TZDs, the TZD is not discontinued. Discontinue canagliflozin and when eGFR<60 ml/min/1.73m^2 or when a patient develops ESRD; Discontinue pioglitazone when a patient develops CHF;	canagliflozin with declining eGFR, HbA1c-, SBP-, and BMI-lowering were adjusted when eGFR was simulated to fall below 60 ml/min/1.73m2. Specifically, data from the pooled moderate renal impairment analysis of subjects with eGFR ≥45 AND <60 was used to adjust the effects of canagliflozin on these biomarkers. Per SPC Per initial draft SPC Per SPC
BP and Lipid Treatment Algorithms	*Intensify BP treatment when:* SBP > 140 mmHg *Intensification sequence*: 1st ACE inhibitor (ramipril 5mg); 2nd diuretic (bendroflumethiazide 2.5mg); 3rd beta-blocker (atenolol 50mg) *Intensify dyslipidaemia treatment when:* T. Chol: ≤ 5.0 mmol/l; HDL-C: ≤ 1.4 mmol/l; LDL-C: ≤ 2 mmol/l; Triglycerides: ≤ 4.5 mmol/l *Intensification sequence*: 1st simvastatin 40mg, 2nd simvastatin 80mg, 3rd ezetimibe 10mg, 4th fenofibrate 200mg TID	(148)
Evolution of HbA1c	HbA1c drifts upwards annually at the rates displayed in Table 36	See section 7.3.1. Values in were reviewed and endorsed at the May Advisory Board Meeting on Modelling Assumptions (163)
Evolution of BP	BP drifts upwards annually at the rates displayed in Table 36	See section 7.3.1. Values were reviewed and endorsed at the May Advisory Board Meeting on Modelling Assumptions (163)
Evolution of Weight	Weight drifts upwards annually at the rates displayed in Table 36	(59)
Evolution of Lipids	Lipid parameters drifts upwards annually at the rates displayed in Table 36	See section 7.3.1. Values were reviewed and endorsed at the May Advisory Board Meeting on Modelling Assumptions (163)
AEs: GMI and UTI	Assume dapagliflozin has same AE rates as canagliflozin 100mg	Not available in NMA; these AEs are likely to be associated only with the

Parameter	Key assumptions for Base Cases	Justification
	Assume all other AHAs have rates of these events as observed in the placebo data in the canagliflozin trials	SGLT-2 MoA.
Hypoglycaemia	For all AHA, hypoglycaemic event rates are adjusted using a relative risk (RR) multiplier (for each 1 percentage point decrease in HbA1c, the relative risk of an event increases by 1.43) Rates for hypoglycaemia were higher for those on insulin if SU was part of the therapy set.	The risk of hypoglycaemia has been shown to be inversely related to the level of glucose control.] (149) Between-arm differences in the UKPDS rates of events. (121) (166)
AEs: nausea	The incidence rate of nausea for exenatide BID was conservatively assumed to be twice that observed with canagliflozin. The liraglutide rate was assumed to be one-third of this rate.	A review of the NICE Bydureon report shows higher rates than those assumed for exenatide BID and liraglutide. (167)

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 **Please outline the aspects of the condition that most affect patients' quality of life.**

The relationship between T2DM and HRQL has been well established. HRQL is worse for people with diabetes compared to the general population, for physical functioning and well-being. (168) Poorly controlled disease leads to quicker disease progression and onset of micro- and macro-vascular complications such as nephropathy, foot ulceration, neuropathy, blindness, amputation, stroke and. (52) HRQL declines as co-morbidities increase. (168;169) Researchers have estimated the impact of longer-term diabetes-related complications on measures of HRQL and utilities allowing individual assignment of specific utility estimates to each long-term complication. (130)

People with T2DM are also at increased risk for GMI – vulvovaginal candidiasis (VVC) in women and Candida balanitis in men (170), UTIs (48;49;171-173) and depression(174). Treatment of T2DM can cause variability in glucose levels which leads to hyper- and hypo-glycaemia, and effects such as increased oedema, nausea, and changes in body weight. These impacts may influence patient behaviour and subsequently affect outcomes. (175)

The opportunity to improve outcomes by recognising the important role of patients in the management of T2DM is reflected in many treatment guidelines. NICE guidelines (36) state that T2DM "is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life. Accordingly, understanding of diabetes, informed choice of management opportunities, and the acquisition of relevant skills for successful self-management play an important role in achieving optimal outcomes". The more recent guidance (37) notes that HRQL is an "important determinant of adherence to treatment." Patient-centred treatment, that is, "aligned with the perceived needs and preferences" of people with T2DM, is recommended by the NICE guidelines (37), the National Collaborating Center for Chronic Conditions and endorsed in the 2012 ADA/EASD consensus statement. (36;45)

7.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition.**

A key determinant of HRQL in T2DM is the development of long-term complications, however, due to the difficulty of collecting data over a long enough time to observe the development of complications, most researchers have analysed HRQL cross-sectionally. (176) However, a recent study that collected HRQL over 5 years was able to demonstrate a decline in HRQL over time in T2DM patients. (177)

Treatment impacts such as improved glycaemic control, low incidence of hypoglycaemia, and weight loss have been associated with an improvement in HRQL (178) and healthy behaviours (179) indicating a shorter-term feedback loop between HRQL and outcomes. Researchers have proposed that patients are more likely to adhere to treatment regimens that offer benefits from the patient perspective, such as convenience, avoidance of hypoglycaemic episodes, and weight loss, vs. those regimens that do not. (175;178)

HRQL data derived from clinical trials

7.4.3 **If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

To select measures of HRQL implemented in the clinical trials, a patient-focused framework was used that conceptualises relationships between patient characteristics (e.g., social support, mental health, personality), and outcomes (e.g., glucose control, hypoglycaemic events, complications).

A full PRO report, including a list of the concepts measured, the instruments used, the rationale for inclusion, and the trials and time points when these measurements were implemented can be found in Section 10.14 (Appendix 14). All PROs were included in the trials as exploratory endpoints; the trials were not powered to detect differences in PRO scores between study arms.

It should be noted that because of the length of the trials, it was not possible to use the clinical data to assess potential changes in HRQL for patients with T2DM who developed complications that are relevant to the economic evaluation health states. Published data sources are therefore used to populate the ECHO-T2DM model.

Mapping

7.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

Not applicable.

HRQL studies

7.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.**

A systematic review of the literature was conducted to identify all HRQL publications that might provide utility values for the health states incorporated in the economic model. Over twenty databases were searched, including MEDLINE, PubMed and EMBASE, for the time period 1st January 2002 to May 2013. Key inclusion criteria were:

- Study participants were patients with T2DM and not Type 1 diabetes (T1DM);
- The study was not of patients who had just been hospitalised unless it was for hypoglycaemia;
- Utility values had to be derived by methods underpinned by either time trade off or standard gamble techniques.

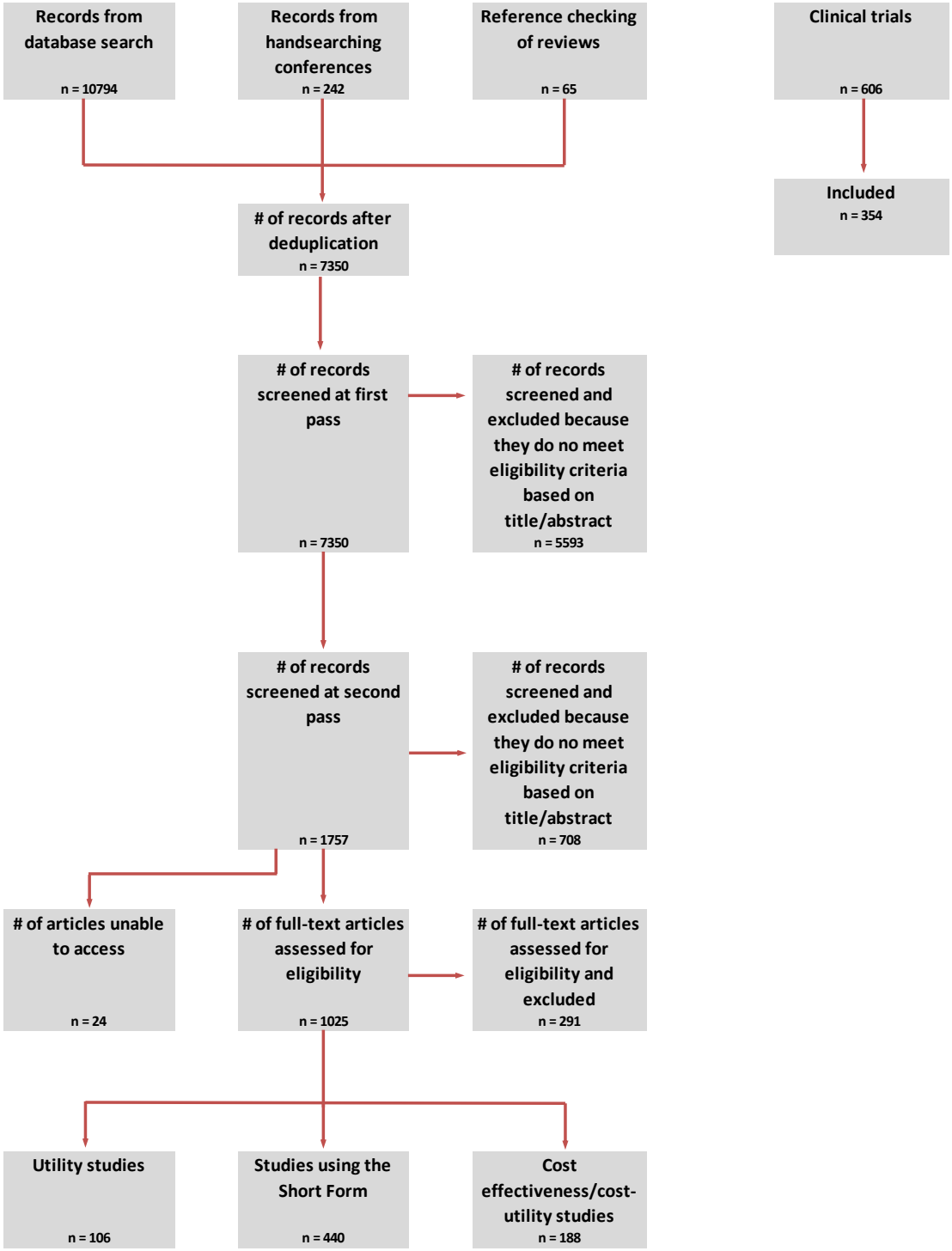
Records identified were categorised as:

- Utility studies – papers in which the abstract implies utility values are elicited using a tool such as the EQ-5D index;
- Studies using the Short Form (SF) SF-12 and SF-36 – which can be mapped onto EQ-5D;
- Cost effectiveness/cost-utility studies – papers that may utilise utility values in cost-effectiveness or cost-utility models;
- Systematic reviews of utility values.

The reference lists of the cost-effectiveness studies and systematic reviews were then checked to identify any potential utility studies that might not have been identified by the searches. Utility studies that met the inclusion criteria were extracted with key study details, methodology and specifics on the utilities provided recorded – particularly the patient characteristic or co-morbidity that the utility

represented. The full HRQL SLR, including the search strategy and the detailed extraction spreadsheet, can be found in the report. (180)

Figure 59. PRISMA diagram for the HRQL systematic literature review



Following the initial search 1757 records were identified as warranting an abstract review for assessment for inclusion. After the abstract review and full paper assessment together with papers identified from cost effectiveness studies and other systematic reviews there were 440 papers that were deemed likely to provide SF12

or SF-36 measures (identified through reference review), and 106 that provided utility estimates (identified through full text review).

Of the 106 utility studies, 80 provided utility values measured by the EQ-5D. The remainder were measured by HUI3 (7 studies), bespoke tools using time trade off techniques (10 studies), QWB-SA (4 studies), bespoke standard gamble (2 studies), SF-6D (2 studies), HU12 (1 study) and EQ-15D (1 study). Some studies used more than one tool.

Utility values were available for patients in more than 20 countries specifically with a further 13 studies providing values collected from patients in more than one country. The UK (19 studies) and USA (20 studies) were the countries with the largest number of studies on patients within their population.

As well as overall utility values for patients with T2DM, utility values or increments were also found for patient characteristics including:

- Age;
- Gender;
- Duration of diabetes;
- Number of co-morbidities;
- Treatment type.

The search also found utilities (as well as increments/ decrements) for the following broad co-morbidities:

- Diabetic foot;
- Eye diseases and vision disorders;
- Renal diseases and damage;
- Musculoskeletal disorders;
- Cardiovascular diseases;
- Mental health;
- Nerve disorders;
- Gastrointestinal symptoms;
- Lipid disorders;
- Glucose regulation;
- Respiratory diseases;
- Cancers;
- Disability;
- Neurological disorders;
- Weight status.

Utility values for specific conditions under these broad definitions, such as retinopathy or Chronic Obstructive Pulmonary Disease (COPD), were identified and recorded as part of the extraction. The availability of data for each of these broad co-morbidities varied with some co-morbidities such as cardiovascular disease having more than 20 studies reporting utility but others such as cancer only having a single study.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

A large number of relevant studies were identified in which HRQL is measured. The outlines of these study characteristics are provided in the HRQL SRL report. (180)

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Since few longer-term micro- or macro-vascular outcomes were not experienced by most subjects in Phase 3 (as expected for trials of only 1-2 years duration), the focus of the trial analyses of utility values was on the impact of weight change on PRO scores. To benchmark the canagliflozin trial populations to existing estimates of utility values associated with differences in BMI, multivariate regression analyses were performed following the approach outlined in Bagust et Al. (2005). (130) After adjustment for baseline demographic factors and the presence of co-morbidities, it was found that BMI was a significant predictor of utility values at baseline in both the dual and triple populations. The utility values were similar in magnitude to those reported in Bagust et. al. 2005 (DIA3009: estimate -0.005, DIA3002 and DIA3015 pooled: estimate -0.006, both $p < 0.0001$ vs. Bagust: -0.006, $p < 0.0001$), though it should be noted that cross-sectional differences in BMI across patients may not have the same impact as within-patient changes in BMI on HRQL. Moreover, there is currently no consensus on whether the effects of weight loss and weight gain on HRQL are equivalent in magnitude, so a linear predictor may not optimally describe the functional form. Because the clinical trials collected BMI and EQ-5D at multiple time points, it is possible to attempt to estimate the longitudinal change in HRQL associated with change in BMI. However, based on confounding factors that arise from the clinical trial setting (e.g., AHA adjustment, use of rescue therapy, withdrawals), the current data sets are unlikely to provide unbiased estimates. Future

work designed specifically to address this question in a more naturalistic setting is warranted. For more details please refer to Appendix 14 (Section 10.14).

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

A literature search was conducted to identify HRQL studies in T2DM patients and more specifically on the nine AEs considered. A large number of studies were found identifying the impact of T2DM on patients' HRQL, but a paucity of relevant literature was available for most of the side effects. (181) This was especially true, for the GI events, hypovolaemic events, and GMI in men.

As no appropriate studies were identified to provide some AE-related disutility in T2DM, a time trade off (TTO) study was conducted to capture UK societal utility values for health states associated with these events. Nine health state descriptions were developed from a literature review and supplemented with patient and clinician qualitative input to describe the burden associated the following AEs: Mild/moderate UTI; severe UTI; GMI; moderate & severe hypoglycaemic events; fear of hypoglycaemia; gastrointestinal (GI) symptoms; and hypovolaemic events.

In order to develop health states related to each AE, eight interviews with T2DM patients (who had experienced at least one of the AEs) were conducted to determine how T2DM and the AEs affected their HRQL. The HRQL dimensions considered were defined in relation to the five dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). (164;165)

Information from the literature review and eight patient interviews were used to develop draft health states, which were reviewed with four clinicians and with three members of the public to explore their interpretation and understanding of each health state. (164;165) The final health state vignettes were then used in interviews with members of the UK general public (n=100) who valued these states using the time trade-off (TTO) methodology to elicit utility values. Participants were recruited with the intent of matching UK demographic census data (182) and were interviewed across the UK by four experienced researchers. Participants completed a socio-demographic form, the EQ-5D, and a visual analogue scale (VAS) exercise with the health states before undertaking the TTO exercise. (164;165)

GMI was valued as most burdensome to HRQL (disutility from reference T2DM case, -0.25), closely followed by T2DM with GI symptoms (disutility from reference T2DM case, -0.24) when using both VAS and TTO methodology. It should be noted that, while these are surprisingly large disutilities, the vignettes did not take into account any aspect of time or duration of AE. While the vignettes captured the level of disutility compared to the reference case, once the duration of an AE such as GMI or GI symptoms were applied, the reduction in QALYs over a year with T2DM was relatively small.

The health state with the least impact on HRQL T2DM with no side effects (mean TTO value 0.92). Of the included AE states, hypovolaemic events and mild/moderate UTI were valued as being least burdensome. Detailed results can be found in the study report. (164;165)

Following a regression analysis, using a General Estimating Equations (GEE) model, all treatment-related AEs were found to have a significant effect on utility. From the T2DM baseline state (0.92), the experience of AEs was associated with the following disutility: T2DM with hypovolaemic events (0.08); T2DM with mild/ moderate UTIs (0.09); T2DM with moderate hypoglycaemic events (0.11); T2DM with severe hypoglycaemic events (0.15); T2DM with fear of hypoglycaemia (0.15); T2DM with severe UTIs (0.19); T2DM with GI symptoms (0.24); and T2DM with GMI (0.25); Males consistently scored the states with significantly lower utility values, but no significant age effects emerged. (164;165)

The study indicates the potential importance of including information regarding AEs in economic evaluations. Although some states were rated severely in terms of utility, in reality, many of these only last a few days, therefore having a minimal quality adjusted life year (QALY) impact.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.**

ECHO-T2DM utilises health-related utility values that were elicited from data from the CODE-2 study. (130) Utility values were estimated using multivariate regression techniques to attribute QALY disutility to a set of specific patient-level characteristics. In previous HTA submissions (59-61), the UKPDS (127) equation has been used to inform utility values used, however, it is more limited for micro-vascular complications, providing estimates only for the end-stage complications of LEA and blindness. In comparison, the CODE-2 utility weights match more micro-vascular health states used in the ECHO-T2DM model, for example, by providing a wider range of estimates for different severity levels of complications. Importantly, CODE-2 includes an estimate for the disutility related to BMI, thus minimising the risks that the estimates are confounded by attributing the impact of these excluded factors to correlated but included factors. Similarly, the UKPDS dataset focuses on discrete clinical events, whereas CODE-2 estimates focus on prevalent disease states. No other study has been able to control for so many potential confounding factors (patient characteristics and health complications) simultaneously, which makes it the most exhaustive set of utility weights currently available. The CODE-2 study has also been used in previous HTA submissions (60;61) and to inform utility values in the NICE clinical guidelines (37).

Although the UKPDS was a longitudinal RCT and CODE-2 a naturalistic (non-interventional) observational data collection, the patients in the UKPDS RCT are selected (relatively healthy and newly diagnosed) whereas the aim of the CODE-2 was to generate samples representative of the broader T2DM population.

Other sources were used to determine disutility weights associated with AEs, as described in Table 38 and Section 7.4.8. Where possible and appropriate, health state utilities were measured using the EQ-5D questionnaire and taken from a UK population with T2DM.

Table 38. Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Standard error	Reference in submission	Justification
Baseline	1.027	0.027	CODE 2	Values were estimated using multivariate regression techniques
Patient Characteristics				
Age (per 10 Years)	-0.0235	0.001	CODE 2	HRQL has been shown to gradually decrease over time and may change with age independent of the disease progression. (183)
Female	-0.093	0.009	CODE 2	Gender has been show to impact patient reports of HRQL, often with women reporting lower scores (130;184)
Duration of T2DM (per 10 Years)	-0.0163	0.001	CODE 2	This captures any effects of having T2DM over time, above and beyond the separate effects of aging, treatment intensification, and the effects of the development and worsening of complications. (185)
Macro-vascular Complications				
IHD	-0.028	0.01	Assumed from CHD in CODE 2	Identified in a systematic literature review, CODE-2 was deemed the most appropriate study on HRQoL related to T2DM complications, controlling for many potential confounding factors simultaneously. CODE-2 combines macro-vascular diseases together.
MI	-0.028	0.01	Assumed from CHD in CODE 2	
CHF	-0.028	0.01	Assumed from CHD in CODE 2	
Stroke	-0.115	0.017	CODE 2	
Micro-vascular Complications				
Retinopathy (BDR, ME, PDR, and combinations)	0	1E-99	CODE 2	CODE-2 controls for many potential confounding factors simultaneously.
Blindness (one or both eyes, incl. combinations)	-0.057	0.022	CODE 2	
Gross Proteinuria	-0.048	0.022	CODE 2	
ESRD	-0.175	0.028	CODE 2	
Symptomatic Neuropathy	-0.084	0.014	CODE 2	
Peripheral Vascular Disease (PVD)	-0.061	0.015	CODE 2	
Symptomatic Neuropathy & PVD	-0.085	0.018	CODE 2	
Diabetic Foot Ulcer	-0.17	0.019	CODE 2	
One lower extremity	-0.272	0.029	CODE 2	

State	Utility value	Standard error	Reference in submission	Justification
amputation				
Two lower extremity amputations	-0.272	0.029	CODE 2	
Hypoglycaemic Events				
Minor Hypoglycaemic Episode (per Episode)	0		Assumption	Advised in advisory board – (163)
Moderate Hypoglycaemic Episode (per Episode)	-0.0036		Currie et. al 2006. annualised disutility per symptomatic no help event ; not chronic	The approach taken by NICE in the evaluation of exenatide (CG-87) also used utility estimates from Currie et al. 2006. (60;128) Curie et al (2006) relates to a study that collected data from UK patients using both the hypoglycaemia fear survey and EQ-5D. The utility values were converted to annual values as follows: -0.047 x (3/12) year = -0.0118 per year.
Severe Hypoglycaemic Episode (per Episode)	-0.0118		Currie et. al 2006. annualized disutility per severe event; not chronic	
Obesity				
Excessive weight (disutility weight for each 1 kg/m^2 above a threshold of 25 kg/m^2. No disutility is applied to lower values)	-0.0061	0.001	CODE 2	Values used to inform utility values in the NICE CG-87
Adverse Events				
Lower urinary tract infections (male) (per Episode)	-0.0012		Janssen UK Study (regression analysis corrected for state duration)	No utility values related to urinary tract infections were identified in the systematic literature review. Therefore, a TTO utility study was conducted. (164;165)
Lower urinary tract infections (female) (per Episode)	-0.0012			
Upper urinary tract infections (male) (per Episode)	-0.0073			
Upper urinary tract infections (female) (per Episode)	-0.0073			
Balanoposthitis (male) (per Episode)	-0.0046			No utility values related to genital mycotic infections were identified in the systematic literature review. Therefore, a TTO utility study was conducted. (164;165)
Candidal vulvovaginitis (female) (per Episode)	-0.0046			

7.4.10 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details3:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The advisory board hosted by Janssen (London, May 2013) (163), agreed that:

- no disutility value should be applied if a patient experiences a hypovolaemic event
- the EQ-5D derived disutility value of 0.0061 is most appropriate for calculating the impact on HRQL of increased BMI. (130)
- disutility values should be associated with moderate and severe, but not minor, hypoglycaemic events

All the above determined values were later validated at another advisory board hosted by Janssen (London, August 2013) (see Section 7.3.5 for full details). (67)

7.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

ECHO-T2DM calculates over each modelling cycle the probability of the occurrence of a co-morbidity, complications and AEs, and the disutility of each is applied to the baseline utility for that year and, if relevant, for subsequent years. When multiple co-morbidities and complications are experienced, the disutilities are additive. Thus, the HRQL of simulated patients varies in the model, according to the accrual of co-morbidities and complications.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Some co-morbidities were identified through SLR although they were not included in the economic analysis. For instance, fear of hypoglycaemia was identified in the literature and also researched in the TTO study. (164;165) Omission underestimates the disutility associated with a high rate of hypoglycaemia, such as SU and insulin. Disutility associated with patient aversion to injections was also omitted, which can be argued to underestimate disutility from injectable products such as GLP-1-a and insulin. As described in 7.4.10, disutility associated with hypovolaemic events was excluded (as this was considered a minor event of short duration with very small impact on utility and NHS costs), as was minor hypoglycaemic events which is expected to have a limited impact on both utility and NHS costs.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

ECHO-T2DM uses as a baseline quality of life value from the CODE-2 regression analysis. (130)

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Patient HRQL changes over time due to incidence of co-morbidities, AEs, change in BMI and age (see Section 7.2.3 to 7.2.5).

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

Secondary care admissions in diabetes are classified by diagnosis codes (ICD 10), procedure codes (OPCS 4), and by Healthcare Resource Group (HRG version 4). (186) HRGs and NHS reference costs (187)stipulate the treatment of complications associated with diabetes, such as hypoglycaemia, ketoacidosis, coma and lower limb complications.

Other sources of cost data, drawn from a variety of departmental and academic publications were also utilised to estimate the total cost of treating diabetes to the NHS. The following data sources were used to calculate and corroborate existing cost estimates:

- NICE Clinical Guidelines CG66 (36)
- NICE Clinical Guidelines CG87 (37)
- Diabetic Retinopathy Guidelines (188)
- NICE CKD Clinical Guidelines 73 (38)
- BASHH - National Guideline on the Management of Vulvovaginal Candidiasis (189)
- National Diabetes Audit 2010/11 (40;50)
- National Diabetic Retinal Screening Programme data (190)
- British National Formulary 65 (191)
- PSSRU Report 2012 (192)

7.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

The available NHS reference costs and PbR tariffs have been used for cost estimates where appropriate. NHS reference costs are often for broader health states and are not specific enough for modelling purposes, often representing average costs for all diabetes patients and not those with T2DM. Therefore other sources have also been assessed to inform the management of AEs, complications and co-morbid conditions including UK clinical guidelines that outline best practice for treatment, such as NICE clinical guidelines 66 and 87 for the management of T2DM and NICE clinical guideline 73, early identification and management of chronic kidney disease in adults in primary and secondary care. (36-38) Reference costs, such as PbR tariffs, PSSRU, BNF65 and National Diabetic Retinal Screening Programme data were then used to cost the different health states associated with AEs, complications and co-morbid conditions. (190-193) More details about the costs used in ECHO-T2DM model can be found in the SRL report related to cost of complications. (194)

Resource identification, measurement and valuation studies

7.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A comprehensive literature search was conducted to identify published peer-reviewed studies that evaluated costs associated with common diabetes-related complications or co-morbidities that were relevant for the ECHO-T2DM model. Articles that report the resource or service use or costs associated with the treatment of T2DM complications in the UK were included. Further details of the comprehensive search strategy (databases searched, search strategies, additional screening criteria and data extraction strategy) are provided in the SRL report related to the costs of complications and AEs. (194) A summary of the coverage, methods and results from these studies are presented in Table 191, Appendix 10.10.

In total, 11 articles were identified that reported resource use or cost information in T2DM considered of most relevance and selected for review. Cost data presented in this review were reported from a variety of sources using different methods of

inflation and elicitation from original source documents to derive unit costs. Regional variations in the standard of care and usual reporting in different practices make comparisons and synthesis of these data quite challenging. However, the majority of costs reported in the cost-effectiveness analyses retrieved are inflated costs derived as part of the UKPDS trial. Most of the economic models currently available use risk equations also from the UKPDS trial to estimate transition probabilities to different health states and thus it is reasonable to assume that the UKPDS-based costs correspond well with the definition of these health states. Few other studies have derived their complication-management costs using National data sources, such as hospital care costs published by PSSRU and the latest set of Department of Health NHS National Reference Costs. (187;192) Other variances in costs may be due to the definition of specific complications such as mild or acute CHF or when patients are actually diagnosed with a complication such as blindness, the definition can vary between centres.

Although the review found some complication specific and broad diabetes economic studies that considered the resource use and costs associated with complications/ co-morbidities relative to UK clinical practice, none of the studies reported up-to-date/ recently derived costs.

In conclusion, only three studies were identified which provide costs that were used in the economic evaluations presented in this submission:

- Leese et al. 2003 (120)
- Clarke et al. 2003 (126)
- Ghatnekar et al. 2002 (195)

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

At an advisory board hosted by Janssen (London, May 2013(163), clinicians agreed with a suggested approach to use data from a Scottish publication by Leese et al. (2003) to estimate an annual cost of treating moderate to severe hypoglycaemia. Costs were inflated to 2013 values using rates reported within the PSSRU report (2012). (120;192)

At this same advisory board the approach taken to cost GMIs and UTIs was validated with clinicians. It was agreed that female patients will most commonly self-treat non-recurring GMIs with over the counter (OTC) medicines, such as Canesten (clotrimazole cream); whereas a male patient who experienced a balanitis will most likely require a GP appointment and prescription. Mild to moderate UTIs will most likely require a GP visit for both sexes and a prescription of antibiotics, such as trimethoprim.

Spend on self-monitoring blood glucose (SMBG) testing strips in England in primary care in 2010 was about £150 million. This compares to approximately £300 million on insulin and £250 million on anti-diabetic drugs. (196) However, the amount spent on blood glucose testing strips varies widely across England. (197) There appears to be little standardisation of usage within PCTs/CCGs and no apparent consensus on which products provide best value for the NHS [ref] along with little data that highlight which patients are being prescribed SMBG strips (T1DM or T2DM patients, treated with insulin or treated with AHAs such as SU). Therefore, these costs are not included in the economic evaluation presented in this submission. This decision is conservative as it minimises the costs associated with the monitoring of some comparators such as SUs and insulin.

Finally, within the advisory board it was agreed that the costs associated with managing hypovolaemic events, pollakuria, nocturia and mild hypoglycaemic events will be negligible to the NHS and thus these have not been assigned a cost in the economic modelling.

Intervention and comparators' costs

7.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Drug acquisition costs

Drug acquisition costs used within ECHO-T2DM were sourced from the BNF (July 2013) and are presented in Table 39 below.

For simplicity, within the base case a single comparator within each class of AHAs has been chosen based on frequency of prescribing within England and Wales (57): gliclazide is the most frequently prescribed generic SU; sitagliptin is the most frequently prescribed DPP-4-i; and liraglutide is the most frequently prescribed GLP-1-a; therefore, these were applied within the modelling to represent the entire respective classes. However, due to wider recommendations of use, some drugs such as exenatide are also considered as relevant comparators, especially when data on liraglutide are scarce and does not allow for an indirect comparison to be conducted.

Pioglitazone is the only TZD currently available in UK clinical practice. Insulin costs have been applied as a cost per kg body weight per day within ECHO-T2DM.

Therefore, cost of insulin will change for patients as their weight changes throughout a model comparison.

Background therapies have not been modelled within ECHO-T2DM as they are assumed equal between comparisons. Thus, no cost has been assigned to metformin.

Table 39. Drug acquisition costs applied in the model for all lines of therapy

Therapy	Daily dose¥ (mg)	Annual cost/pt	Description*
Anti-hyperglycaemic agents			
Canagliflozin	100	£ 477.26	100mg, 30-tab pack at £39.20
Canagliflozin	300	£608.63	300mg, 30-tab pack at £49.99
Glimepiride	6	£30.44	2mg, 30-tab pack at £1.24; 4mg, 30-tab pack at £1.39
Gliclazide	160	£19.60	80mg, 60-tab pack at £1.16
Pioglitazone	30	£36.13	30mg, 28 tab-pack at £2.77
Sitagliptin	100	£433.86	100mg, 28-tab pack at £33.26
Liraglutide	1.2	£955.49	6mg/mL, 2 x 3-mL prefilled pens at £78.48
Exenatide	0.2	£830.82	10µg/dose prefilled pen (60 doses) at £68.24
Dapagliflozin	10mg	£477.30	10mg, 28-tab pack at £36.59
Insulin therapy	**Daily dose**	**Cost/IU/year**	**Description**
NPH insulin	See insulin glargine and insulin aspart as applicable	£4.26	100 units/mL, 5 × 3-mL cartridge (ClikSTAR® and Autopen® 24) at £17.50: Price per unit is £0.01
Insulin glargine	10-60 IU/day	£10.11	5 × 3-mL Lantus® SoloStar® at £41.50
Insulin aspart	5-200 IU/day	£6.89	100 units/mL NovoRapid®, 10-mL vial at £14.08

** All medicinal costs have been sourced from the BNF65. (191) Annual costs were calculated using pack prices and have been rounded.*
¥As per recommended use (191)

Drug administration and monitoring costs

No administration costs have been assumed for canagliflozin and comparators. Oral AHAs do not require supervised administration whilst GLP-1-a and insulin are self-administered.

As canagliflozin is to be discontinued when eGFR is persistently below 45mL/min/1.73 m^2 or CrCl persistently below 45mL/min (see SmPC in Appendix 1), monitoring of renal function is recommended prior to initiation of canagliflozin as well as prior to initiation of concomitant medicinal products that may reduce renal function. However, diabetic patient monitoring generally includes renal monitoring and is part of routine clinical management of T2DM: prior to initiation of a new therapy and annually thereafter. (38) Thus, the cost of renal monitoring has not been accounted for as an additional cost when treating T2DM patients with a canagliflozin-based regimen.

Health-state costs

7.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the**

choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Complications and co-morbidity costs

Some costs were derived by consultation of current clinical guidelines (37;38)and assignment of relevant costs obtained from multiple sources (see Section 7.5.2.). Other costs were retrieved from the literature (see Section 7.5.3.), and were inflated to 2011/2012 values using the Community Health Service inflator. (192)

The annual costs of complications and co-morbidities used in ECHO-T2DM along with how cost estimates for health states have been derived are detailed in full in Section 10.11 for Appendix 11 for follow up costs, treatments costs and events costs.

Adverse-event costs

7.5.7 **Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

The AEs considered in ECHO-T2DM economic evaluation presented in this submission are presented in Table 40.

As described in section 7.5.4., the costs associated with UTIs and GMIs were determined by consulting clinical guidelines and using national published costs from Hospital & Community Health Services index and the British national formulary. (36;37;191;192) The derivation of UTI and GMI AE costs were validated by diabetologists and general practitioners with a special interest in diabetes at an advisory board hosted by Janssen in May 2012. (163)

The other key AE considered in ECHO-T2DM is minor, moderate and severe hypoglycaemia. Only the cost to treat severe hypoglycaemia events is included in ECHO-T2DM economic simulations. The decision to not cost minor and moderate hypoglycaemic events has been validated with clinicians who believed that most of these events will not generate any use of NHS resources. (67)

The Leese et al study (2003) was used to cost severe hypoglycaemic events, as it represents the most recent assessment of health care costs associated with hypoglycaemia, conducted in the UK. It covers many important direct healthcare costs, including primary care visits, hospital costs, ambulance services and medicinal costs, associated with the treatment of severe hypoglycaemic events. (120)

Table 40. Adverse events and summary of costs included in the economic model

Health state	First year cost (£)	Description and Reference
Minor hypoglycaemic event	0.00	Assumption
Moderate hypoglycaemic event	0.00	Assumption
Severe hypoglycaemic event	621.41	Estimating the burden of managing severe hypoglycaemic events: 86% requiring ambulance services, 59% A&E, and 20% hospitalisation [. (120) Value inflated from 1997-98 to 2011-12 using the Hospital & Community Health Services index. (192)
lower UTIs (male)	86.82	It is assumed that all male lower UTIs are uncomplicated requiring 2 GP visits, one for treatment (recommended treatment with trimethoprin for 7 days (70) and one follow-up appointment. GP visits 11.7minutes@£221/hour. (192) Trimethoprin 200mg twice daily, 200mg, 14-tab pack = 82p(191).
lower UTIs (female)	43.35	It is assumed that all female lower UTIs are uncomplicated requiring one GP visit treatment (recommended treatment with trimethoprin for 3 days (70).GP visit 11.7minutes@£221/hour. (192) Trimethoprin 200mg twice daily, 200mg, 14-tab pack = 82p (191).
upper UTIs (male)	87.64	It is assumed that all male upper UTIs are uncomplicated requiring 2 GP visits, one for treatment (recommended treatment with trimethoprin for 14 days (70) and one follow-up appointment. GP visit 11.7minutes@£221/hour (192), Trimethoprin 200mg twice daily, 200mg, 14-tab pack = 82p (191).
upper UTIs (female)	87.64	It is assumed that all female upper UTIs are uncomplicated requiring 2 GP visits, one for treatment (recommended treatment with trimethoprin for 14 days (70) and one follow-up appointment. GP visit 11.7minutes@£221/hour. (192), Trimethoprin 200mg twice daily, 200mg, 14-tab pack = 82p (191).
balanoposthitis	53.60	It is assumed that all balanoposthitis events are uncomplicated requiring 1 GP visit, 11.7minutes@£221/hour (192) , and a course of fluconazole for 7 days, 200mg , 7-cap pack = £10.60 (191).
Vulvovaginitis	45.00	It is assumed that all vulvovaginal candidiasis is uncomplicated requiring 1 GP visit, 11.7minutes@£221/hour(192), and one 500mg clotrimazole pessary, 500mg, 1 pessary with applicator = £2.00

Table 41 presents the medicinal product costs associated with treatment of complications and co-morbidities of T2DM patients. The majority of these costs have been accounted for within the costs assigned to complication health states, presented in Table 40 above.

Table 41. Pharmacological treatment costs for managing co-morbidities

Therapy	Price per unit (£)	Dose per unit	Daily treatment dose	Cost per year (£)
Anti-hypertensive treatments				
Ramipril	0.04	5mg	5mg	15.78
Bendroflumethiazide	0.03	2.5mg	2.5mg	11.48
Atenolol	0.03	50mg	50mg	11.74
Anti-dyslipidaemia treatments				
Simvastatin	0.08	80mg	80mg	29.35
Ezetimibe	0.94	10mg	10mg	343.20
Fenofibrate	0.08	200mg	600mg	91.18

Miscellaneous costs

7.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

Although ECHO-T2DM has the capability to account for indirect costs, such as annual productivity of patients, these have not been assigned costs for economic comparison. ECHO-T2DM can also account for annual service use costs that are fixed, for example administration costs that do not vary with dose (pumps or syringes), which have also not been assigned costs.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.**

Due to the number of comparators to the two doses of canagliflozin in the four lines of therapy investigated, and the number of inputs to the ECHO-T2DM model, a very large number of theoretical sensitivity analyses are possible. The complexity of the ECHO-T2DM model means that a single comparison with a reasonable cohort size can take many hours to run. Given the finite computing resources available and limited space in which to present and discuss results, as well as a recognition that there is a finite number of comparisons that are relevant to usual UK clinical practice,

a pragmatic decision was made to focus the sensitivity analyses on a number that was feasible to process and present, based on what are proposed as the key comparators to canagliflozin in each line of therapy, and the key drivers of cost-effectiveness in the modelling of T2DM.

Three levels of rigour were defined for the sensitivity analyses for each comparison in each line of therapy (Table 42). In addition to a base case analysis, 'systematic' comparisons would generate up to 95 simulations, 'thorough' 11 simulations, and 'focussed' 3 simulations. It should be noted that some scenarios were only conducted for one dose or for one line of therapy and thus not all 21 scenarios were conducted for all 8 systematic comparisons.

Table 42. Definition of levels of sensitivity analysis rigour

Level of rigour	Scenario analyses conducted	DSAs conducted	Justification
'Systematic'	21 (all)	70	Applied to the key comparisons in each line of therapy, to thoroughly explore the key drivers of the ICER
'Thorough'	9	0	Applied to comparisons considered supportive to the key comparisons
'Focussed'	3	0	Applied to the comparisons that are included in the scope but not considered from a clinical perspective to be a key comparator to canagliflozin

The three levels of rigour were applied to the modelling comparisons as shown in Table 43. As the comparisons against SU in dual therapy, and against DPP-4-i in dual, triple (Met+SU) and add on to insulin therapy are seen as most relevant, these were analyses with the highest level of rigour.

Table 43. Level of detail conducted for sensitivity analysis across the comparisons.

Comparator	Cana dose	Dual therapy +Met	Triple therapy +Met+SU	Triple therapy +Met+TZD	Add-on to insulin
SU	100mg	Systematic			
	300mg	Systematic			
TZD	100mg	Thorough			
	300mg	Thorough			
DPP-4-i	100mg	Systematic	Systematic	Thorough	Systematic
	300mg	Systematic	Systematic	Thorough	Systematic
GLP-1-a	100mg	Focussed	Thorough		Thorough
	300mg	Focussed	Thorough		Thorough
Dapagliflozin	100mg	Thorough			Thorough
	300mg	Thorough			Thorough
Insulin	100mg		Thorough		
	300mg		Thorough		

An exploratory analysis was conducted to identify the key drivers of cost-effectiveness and from this and consideration of the T2DM economic literature, the 22 scenario analyses were developed (Table 44). (198) Greater detail on the scenarios is provided in Section 10.12 for Appendix 12.

Table 44. Scenario analyses conducted

Number	Scenario	Base case	Alternative value	Level of rigour for which scenarios conducted
1	Time horizon	40 years	20 years	S
2	Discount rate	3.5% for costs and outcomes	0% for both	S
3			6% for both	S
4	Dose modification from 100mg to 300m	No dose modification applied	Increase of dose from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	S, T Only applied to 100mg simulations
5	Treatment discontinuation rate	Taken from RCT data, as described in Section 7.3.6	Comparator discontinuation rate set at that of the canagliflozin arm	S
6	HbA1c threshold for treatment switch	7.5% (59mmol/mol)	Treatment switch once HbA1c >8%	S, T
7			Treatment switch once HbA1c >9%	S; only for Add-on to insulin
8	HbA1c metabolic drift assumption	Canagliflozin drift 0.14, as described in Section 7.3.7.	Canagliflozin drift set at that of the comparator arm	S, T Conducted where comparators have different HbA1c drifts from canagliflozin
9	Patient baseline characteristics	Taken from RCT data, as described in Section 7.3.6	UK T2DM patient baseline characteristics, as described in (57)	S, T
10	Risk equations	UKPDS 68 (133)	UKPDS82 (144)	S, T
12	BMI rebound on treatment discontinuation	Full weight rebound occurs on discontinuation of treatment	No rebound occurs; divergence of weight continues for full modelling duration	S, T
13			Weight rebound occurs two years following treatment discontinuation	S
14	Therapy treatment effect	Base case NMA data, as detailed in Section 7.3.6.	Dual therapy: 26 week NMA data (only the NMA data varied)	S, T; only Dual therapy
16			Direct comparative data from RCTs	S; only for comparisons where RCTs data available
17	Disutility associated with weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	S, T
18			-0.014 (128)	S
19	Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	S
21	Rescue therapy applied following failure of first therapy	Upon discontinuation of initial therapy, Insulin rescue therapy is applied, with intensification of insulin as required	Additional rescue step of Met+SU+GLP-1 applied following discontinuation of initial therapy	Triple therapy comparisons

Number	Scenario	Base case	Alternative value	Level of rigour for which scenarios conducted
22	Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus)	S
24	Renal threshold for canagliflozin discontinuation	eGFR<60mL/min/1.73m^2	eGFR<45mL/min/1.73m^2	S, T; only for canagliflozin 100mg comparisons
25	Management of dyslipidaemia	Management according to NICE clinical guidelines (36)	All patients treated with simvastatin 80mg at baseline; no rescue treatment for dyslipidaemia applied	Only applied to Dual therapy vs. DPP-4-i for both canagliflozin doses

Dose modification Scenario analysis (Scenario 4)

As stated in Section 1.10, the canagliflozin posology is for patients to commence treatment on the 100mg dose. In patients tolerating the 100mg dose and needing tighter glycaemic control, the dose can be increased to 300mg. The RCTs did not study the increase in dose of canagliflozin and so modelling techniques were employed to explore how dose modification is likely to impact the cost-effectiveness of canagliflozin against its comparators.

In line with discussions with external UK experts, it has been agreed that dose modification would be considered for patients who are tolerating the 100mg dose and who after 6 months had not attained an HbA1c of less than 7.5%. (5) The 6 month criterion corresponds with treatment review for many T2DM products in NICE guidelines (including DPP-4-i's, pioglitazone, and GLP-1-a's as does the target HbA1c of 7.5%. (37)

ECHO-T2DM has a one-year modelling cycle length so the 6-month review is handled implicitly in the simulations. Specifically in the model, patients are started on 100mg canagliflozin. During the course of the first cycle, achievement of glycaemic control (HbA1c < 7.5%) and the occurrence of AEs sufficient to cause discontinuation are evaluated. Patients not discontinuing canagliflozin due to AEs but not achieving glycaemic control are switched to canagliflozin 300mg in cycle 2. Patients not discontinuing due to AEs and achieving glycaemic control remain on the 100mg dose for as long as the patients maintain glycaemic control and then switch to standard rescue therapy (i.e., insulin).

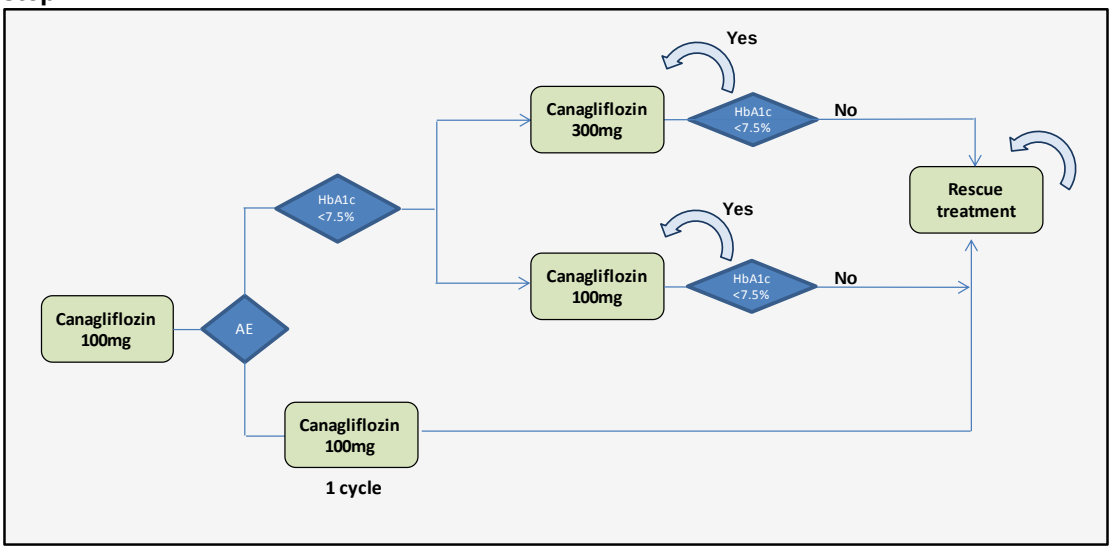
ECHO-T2DM model allows for dose modification of agents over time. However, it is hard-coded to perform dose increase in each cycle rather than limiting dose increase to the initial cycle on agent, so an accommodation was required to match the dose increase algorithm proposed by the expert panel with the mechanics of the model. Specifically, canagliflozin 100mg was sub-divided into two modelling profiles, the first for cycle 1 (in which dose increase is permitted) and the other for subsequent cycles (in which dose increase is *not* permitted). Operationally, the algorithm works as follows:

- In cycle 1, patients are assigned a profile for canagliflozin 100mg profile that is limited to one year in duration. If HbA1c control is unsatisfactory, the patient is switched to canagliflozin 300mg. If HbA1c control is satisfactory, patients complete the cycle with the first canagliflozin 100mg profile and are "switched" in the next cycle to the long-term canagliflozin 100mg profile. Because AE-related discontinuation would cause ECHO-T2DM to discontinue the first canagliflozin 100mg only to start them on the long-term canagliflozin 100mg profile (for reasons related to the workaround, the rescue medication in this simulation), AE-related discontinuation is shifted to cycle 2.

- Patients start cycle 2 on either canagliflozin 100mg if they did not require dose increase or on canagliflozin 300mg if they did. AE-related discontinuation is applied and affected patients begin rescue insulin therapy. Patients continuing on canagliflozin (either dose) do so until their HbA1c values exceed the treatment intensification threshold value (7.5% in the base case), at which time they begin the rescue insulin profile.

The impact of this modelling adaptation was limited to delaying AE-related discontinuation and it is expected to have minimal impact on the costs or benefits accrued.

Figure 60. Illustrative flow chart of how ECHO-T2DM applies the dose modification step.

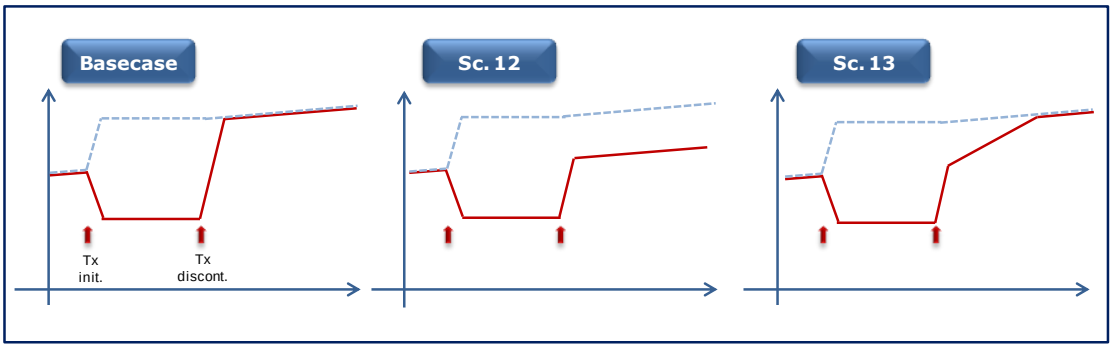


In the absence of any clinical data, it is assumed that a patient that switches to 300mg canagliflozin achieves the same peak HbA1c efficacy as patients treated with 300mg for the full 12 months. This 300mg treatment effect is also applied to SBP, BMI, change in lipid levels and the event rate of hypoglycaemia. This is a reasonable assumption, given the clear and consistent dose-dependent response observed across the clinical trials. A weighted average cost of the 100mg and 300mg doses of canagliflozin is used as the cost of therapy in Cycle 1. The actual costs are correctly applied, thereafter.

Weight loss and rebound scenarios (Scenarios 12 and 13)

The duration of weight loss and rate of regain of weight has been explored in the literature and in previous NICE STAs. (59;61;199) The impact on the ICER of increasing the time for regain (or 'rebound') of weight has been explored in these two scenarios (Figure 61). Scenario 12 assumes that weight loss from the use of canagliflozin is maintained indefinitely. Scenario 13 assumes convergence of weight between the canagliflozin and comparator arms, but at a slower rate than the base case with convergence occurring two years following treatment discontinuation. It can be argued that the base case assumption of immediate weight regain is too rapid, and that the regain of weight over a two year period following discontinuation of canagliflozin treatment is more clinically plausible.

Figure 61. Illustrative weight trajectories modelled in Scenarios 12 and 13



7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A total of 35 parameters or sets of parameters were varied by plus or minus 20%, to give a total of 70 deterministic sensitivity analyses (DSAs), conducted for each of the systematic comparisons. The parameters selected for the DSAs were based on therapeutic effects collected during the clinical trial programme and from preliminary modelling. (198) Some parameters, e.g. disutility associated with lower and upper UTIs for males and females, were grouped to reduce the number of DSAs. Tables detailing these input parameters for the eight sets of DSAs can be found in Tables 195 to 202, in Section 10.13 for Appendix 13.

Table 45. DSA conducted

DSA #	Parameter	DSA #	Parameter
Therapeutic effect		Discontinuation rates due to AEs (52 weeks)	
1	Δ Incremental HbA1c between Cana and comparator	**28**	Canagliflozin
2	Δ Incremental SBP between Cana and comparator	**29**	Comparator
3	Δ Incremental LDL between Cana and comparator	Disutility values	
4	Δ Incremental HDL between Cana and comparator	**30**	Disutility BMI
5	Δ Incremental triglycerides between Cana and comparator	**31**	Disutility hypoglycaemia:
6	Δ Incremental total cholesterol between Cana and comparator		Moderate hypoglycaemia
7	Δ Incremental BMI between Cana and comparator		Severe hypoglycaemia
Drift parameters (post-trial treatment duration)		**32**	Disutility UTI:
8	Δ HbA1c drift – Cana		Lower UTI – males
9	Δ HbA1c drift –comparator		Lower UTI – females
10	Δ SBP drift – Cana (mmHg per year)		Upper UTI – males
11	Δ SBP drift - comparator (mmHg per year)		Upper UTI – females
12	Δ Weight drift – Cana (kg/yr)	**33**	Disutility GMI:
13	Δ Weight drift - comparator (kg/yr)		Balanoposthitis
14	Δ LDL-C drift – Cana		Candidal vulvovaginitis
15	Δ LDL-C drift – comparator	Costs	
16	Δ HDL-C drift – Cana	**34**	Costs associated with management of AEs:
17	Δ HDL-C drift – comparator		Severe hypoglycaemic event
18	Δ Triglycerides drift – Cana		Lower UTI – males

DSA #	Parameter	DSA #	Parameter
19	Δ Triglycerides drift – comparator		Lower UTI – female
20	Δ Cholesterol drift – Cana		Balanoposthitis
21	Δ Cholesterol drift – comparator		Candidal vulvovaginitis
AE rates (52 weeks)		**35**	All other costs except AE management & drug costs
22	Severe+Symptomatic hypoglycaemic events – Cana		
23	Severe+Symptomatic hypoglycaemic events – comparator		
24	Lower UTIs – Cana		
25	Lower UTIs – comparator		
26	GMI (males & females) – Cana		
27	GMI (males & females) – comparator		
Abbreviations: ICER, incremental cost-effectiveness ratio; LDL, low density lipoprotein; HDL, high density lipoprotein; UTI, urinary tract infection; AE, adverse event			

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis (PSA) is a default feature of the ECHO-T2DM model and was run on all simulations conducted. The values of parameters were drawn randomly from their distributions, based on their standard deviations. Table 46 shows the stochastic variables, their distributions and limits. Further detail on PSA in ECHO-T2DM can be found in the Technical Report. (132)

Table 46. Parameter distributions for PSA in ECHO-T2DM

Parameters	Quantity	Distribution	First Column			Second Column		
			Parameter Type	Range of Permissible Values	Comment	Parameter Type	Range of Permissible Values	Comment
Baseline biomarker values, age at baseline, HbA1c at diagnosis	Mean, SD	(Multivariate) Normal	Mean	[0, ∞)	Accounts for 1st order uncertainty	SD	[0, ∞)	
Correlation coefficients for initial age and bio-marker values	Correlation coefficients	Part of above multivariate normal	ρ	(-1, 1)	Accounts for 1st order uncertainty	N/A	N/A	
Treatment effects, annual bio-marker drift, treatment target thresholds	Mean, SE	Normal	Mean	(-∞, ∞)	2nd order uncertainty	Optional SE	(-∞, ∞)	
Patient-level (1st order uncertainty) variation in treatment effects and intensification targets	SD		SD	(-∞, ∞)	Accounts for 1st order uncertainty	N/A		
# of cohorts, # of patients per cohort, modelled time horizon	Constant Integers (Positive)	N/A	Integer	[1, ∞)	N/A	N/A	N/A	
Maximum treatment duration, duration of discontinuation rebound, time until treatment effects completely depreciated	Mean	N/A	Mean	[0, ∞)	N/A	N/A	N/A	
Baseline T2DM duration, logical bounds on initial bio-marker values	Minimum, Maximum	Uniform	Minimum	[0, maximum]	Accounts for 1st order uncertainty	Maximum	[Minimum, ∞)	Sometimes optional
Proportions with co-morbidities, ethnicity, gender, proportion non-responders	Proportion	Bernoulli or categorical	Proportion	[0, 1]	Accounts for 1st order uncertainty	N/A	N/A	
Probabilities (e.g., AE's, non-compliance, dose-reduction, discontinuation, smoking cessation, contraindications)	Probability, SE	Bernoulli/Beta	Probability	[0, 1]	1st order/2nd order uncertainty	Optional SE	[0, ∞)	SE restricted by distribution assumption
Hypoglycaemic event rates	Mean, SE	Poisson/ Lognormal	Mean	[0, ∞)	1st order/2nd order uncertainty	Optional SE	[0, ∞)	
Hazard Ratio (HR) for AE's, rates associated with declining eGFR	Mean, SE	Lognormal	Mean	[0, ∞)	2nd order uncertainty	Optional SE	[0, ∞)	
Relative Risks (RR) for AE's and complications	Mean, SE	Lognormal	Mean	[0, ∞)	2nd order uncertainty	Optional SE	[0, ∞)	
Multipliers for eGFR drift, eGFR-related treatment effect multipliers	Mean, SE	Normal	Mean	(-∞, ∞)	2nd order uncertainty	Optional SE	[0, ∞)	
Unit costs	Mean, SE	Normal	Mean	(-∞, ∞)	2nd order	Optional SE	[0, ∞)	

Parameters	Quantity	Distribution	First Column			Second Column		
			Paramete r Type	Range of Permissible Values	Comment	Parameter Type	Range of Permissible Values	Comment
					uncertainty			
QALY disutility weights	Mean, SE	Normal	Mean	(-∞, ∞)	2nd order uncertainty	Optional SE	[0, ∞)	
Bio-marker logical limits	Minimum, Maximum	N/A	Optional Minimum	(-∞, maximum]	N/A	Optional Maximum	[Minimum, ∞)	Must be larger than minimum

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- **Link between clinical- and cost-effectiveness results.**
- **Costs, QALYs and incremental cost per QALY.**
- **Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.**
- **A statement as to whether the results are based on a PSA.**
- **Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.**
- **Scatter plots on cost-effectiveness quadrants.**
- **A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.**

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Comparative clinical data from DIA3002, DIA3006, DIA3008, DIA3009, DIA3015, and from the NMA were extrapolated to long-run economic outcomes using ECHO-T2DM. NICE recommends a 40-year simulation, which was chosen as the base case.

Biomarker evolution

As described in Section 7.3.7, the impact of canagliflozin and the comparator on key biomarkers is modelled, with an initial effect followed by subsequent annual drift. The figures below show the initial impact, drift and convergence of the HbA1c (Figure 62), SBP (Figure 63) and BMI (Figure 64) over the 40 year time horizon. Because of differences in the timing of requirements for rescue medication, HbA1c, SBP, and lipid curves tend to converge as patients with higher values receive treatment-related improvements sooner. BMI tends to converge as well, even without explicit anti-obesity medication, because the initial anti-hyperglycaemic agents are discontinued, their effects on BMI are reversed, and weight gain associated with insulin is applied. Biomarker plots are available for each of the analyses conducted for the biomarkers above, but for the sake of brevity only the results from canagliflozin 300mg vs. SU in dual therapy have been presented. Biomarker plots for other comparisons are very similar in form.

Figure 62. Mean HbA1c across cohorts for canagliflozin 300mg (in red) vs. SU (in blue) in dual therapy

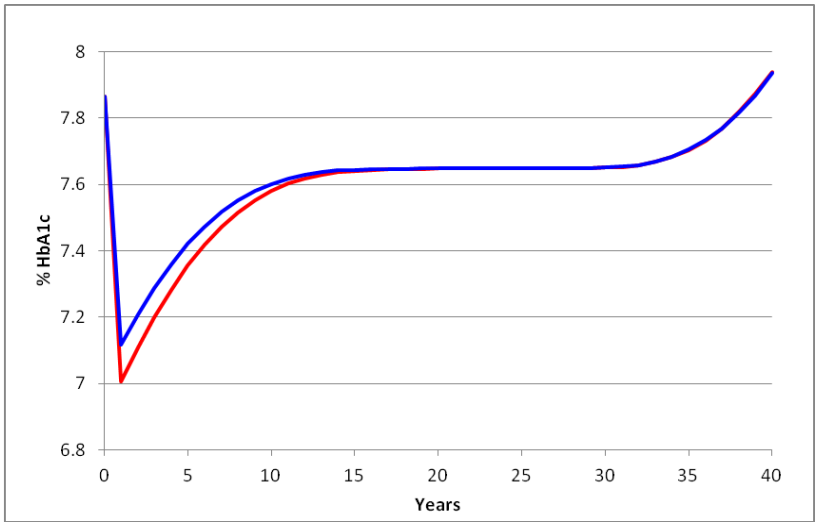


Figure 63. Mean SBP across cohorts for canagliflozin 300mg (in red) vs. SU (in blue) in dual therapy

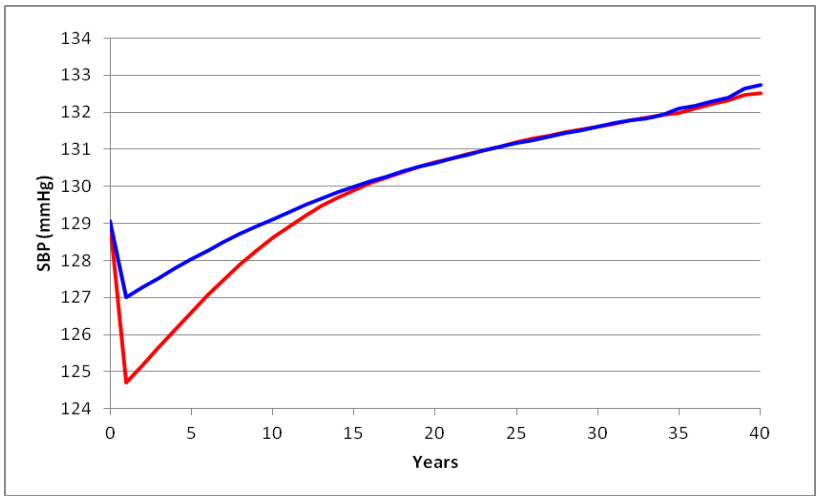
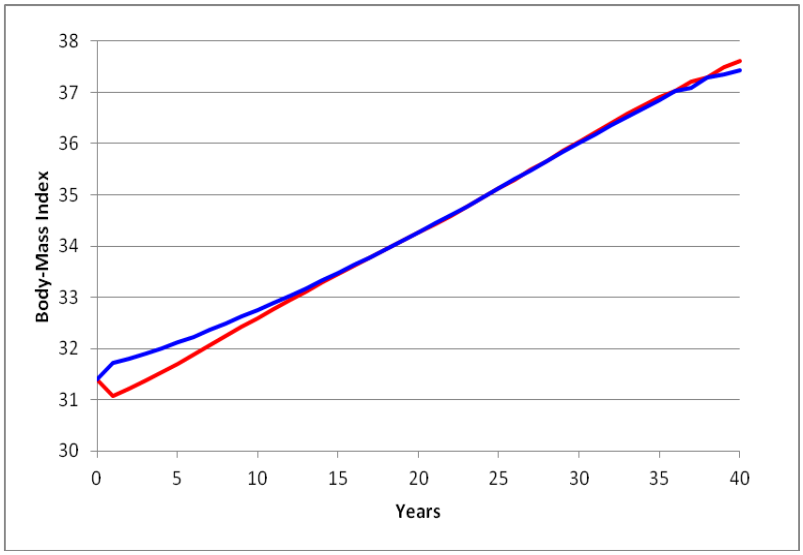


Figure 64. Mean BMI across cohorts for canagliflozin 300mg (in red) vs. SU (in blue) in dual therapy



It should be noted that the mean BMI trace above does not exactly match the BMI trajectory illustrated in Figure 61, as Figure 64 is the mean BMI across simulated patient cohorts and the duration of canagliflozin therapy and initiation of rescue medication occurs at different time points for patients.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable.

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

As described in Section 7.2.3, the model calculates the event rate each year of micro and macro-vascular events, adverse events and change in BMI. The QALY decrements are then accrued from these events, and summed over the modelled period.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The ECHO-T2DM model does not calculate disaggregated life years. The disaggregated QALYs are described in Section 7.7.5 below.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Dual therapy (+Met) base case key comparisons

As described in Section 7.2.3, ECHO-T2DM calculates the incidence of events and subtracts the disutility associated with these from a baseline HRQL state. The results therefore are therefore expressed in QALY loss rather than QALY gain over the period modelled.

The summaries of QALYs lost by health state are shown below for canagliflozin 100mg vs. SU and vs. DPP-4-i (Table 47), and for canagliflozin 300mg vs. SU and DPP-4-i (Table 50). The summary of costs by health state are shown for canagliflozin 100mg vs. SU and vs. DPP-4 (Table 48) and for canagliflozin 300mg vs. SU and DPP-4-i (Table 51) , and cost for predicted resource for 100mg vs. SU and vs. DPP-4-i (Table 49) and for canagliflozin 300mg vs. SU and DPP-4-i (Table 52).

Table 47. Summary of QALY loss by health state for canagliflozin 100mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 100mg vs. SU					Canagliflozin 100mg vs. DPP-4-i				
	QALY Cana 100mg	QALY SU	Increment	Absolute increment	% absolute increment	QALY Cana 100mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment
Survival	-	0.002	-0.002	0.002	1.0%	-	0.003	-0.003	0.003	15.2%
Macro-vascular health states										
MI	0.015	0.015	-0.000	0.000	0.1%	0.015	0.015	-0.000	0.000	0.9%
IHD	0.017	0.017	-0.000	0.000	0.1%	0.017	0.017	-0.000	0.000	0.7%
Stroke	0.025	0.026	-0.001	0.001	0.4%	0.025	0.026	-0.000	0.000	1.4%
CHF	0.011	0.012	-0.001	0.001	0.3%	0.011	0.011	-0.000	0.000	0.6%
Retinopathy	0.021	0.022	-0.001	0.001	0.3%	0.021	0.021	-0.000	0.000	1.2%
Nephropathy	0.047	0.047	0.000	0.000	0.1%	0.047	0.047	0.000	0.000	0.4%
Neuropathy	0.419	0.419	-0.001	0.001	0.5%	0.418	0.420	-0.002	0.002	10.7%
Hypoglycaemia	0.795	0.943	-0.147	0.147	78.2%	0.797	0.795	0.002	0.002	7.6%
Other AEs	0.007	0.007	0.000	0.000	0.1%	0.005	0.003	0.002	0.002	7.9%
Obesity	0.657	0.693	-0.0356	0.036	19.0%	0.657	0.668	-0.010	0.010	53.5%
Total	2.014	2.201	-0.188	0.189	100%	2.013	2.026	-0.013	0.019	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 48. Summary of costs incurred by health state for canagliflozin 100mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 100mg vs. SU					Canagliflozin 100mg vs. DPP-4-i				
	Costs Cana 100mg (£)	Costs SU (£)	Increment (£)	Absolute increment (£)	% absolute increment	Costs Cana 100mg (£)	Costs DPP-4-i (£)	Increment (£)	Absolute increment	% absolute increment
Macro-vascular health states										
MI	885	902	-17	17	4.0%	885	894	-9	9	6.3%
IHD	768	776	-8	8	2.0%	766	772	-6	6	4.1%
Stroke	280	289	-10	10	2.3%	284	288	-4	4	2.6%
CHF	660	684	-24	24	5.8%	658	665	-7	7	4.8%
Retinopathy	1,160	1,172	-12	12	2.9%	1162	1,166	-3	3	2.2%
Nephropathy	2,679	2,664	15	15	3.7%	2677	2,674	4	4	2.4%
Neuropathy	6,677	6,694	-17	17	4.0%	6662	6,695	-33	33	22.3%
Hypoglycaemia	162	347	-184	184	44.0%	154	152	3	3	1.7%
Other AEs	135	132	3	3	0.8%	108	89	19	19	12.9%
Hypertension	64	69	-5	5	1.2%	64	68	-4	4	2.6%
Dyslipidaemia	4,815	4,938	-123	123	29.4%	4,780	4,836	-56	56	38.1%
Total	18,285	18,667	-382	419	100%	18,201	18,298	-97	147	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 49. Summary of predicted resource use by category of cost for canagliflozin 100mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 100mg vs. SU					Canagliflozin 100mg vs. DPP-4-i				
	Cost Cana 100mg (£)	Cost SU (£)	Increment (£)	Absolute increment (£)	% absolute increment	Cost Cana 100mg (£)	Cost DPP-4-i (£)	Increment (£)	Absolute increment (£)	% absolute increment
Technology cost	1,568	48	1519	1,519	64.2%	1,538	1,444	95	95	96.9%
Insulin costs	6,330	7,179	-849	849	35.8%	6,362	6,359	3	3	3.1%
Total	7,897	7,227	671	2,368	100%	7,901	7,803	98	98	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4, dipeptidyl peptidase 4 inhibitor

Table 50. Summary of QALY loss by health state for canagliflozin 300mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 300mg vs. SU					Canagliflozin 300mg vs. DPP-4-i				
	QALY Cana 300mg	QALY SU	Increment	Absolute increment	% absolute increment	QALY Cana 300mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment
Survival	-	0.015	-0.015	0.015	7.2%	-	0.009	-0.009	0.009	27.6%
Macro-vascular health states										
MI	0.015	0.015	-0.000	0.000	0.2%	0.015	0.015	-0.000	0.000	0.7%
IHD	0.017	0.017	-0.000	0.000	0.1%	0.017	0.017	-0.000	0.000	0.7%
Stroke	0.025	0.026	-0.001	0.001	0.5%	0.025	0.025	-0.000	0.000	0.8%
CHF	0.011	0.011	-0.000	0.000	0.2%	0.011	0.011	-0.000	0.000	0.5%
Retinopathy	0.021	0.022	-0.000	0.000	0.2%	0.021	0.021	-0.001	0.001	1.9%
Nephropathy	0.047	0.047	-0.000	0.000	0.1%	0.047	0.047	0.000	0.000	1.0%
Neuropathy	0.419	0.421	-0.002	0.002	0.9%	0.416	0.417	-0.001	0.001	2.3%
Hypoglycaemia	0.790	0.932	-0.142	0.142	70.7%	0.785	0.788	-0.003	0.003	9.7%
Other AEs	0.008	0.007	0.001	0.001	0.4%	0.004	0.003	0.001	0.001	2.9%
Obesity	0.652	0.691	-0.039	0.039	19.4%	0.653	0.670	-0.018	0.018	51.9%
Total	2.004	2.203	-0.199	0.201	100%	1.993	2.025	-0.031	0.034	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 51. Summary of predicted resource use by category of cost for canagliflozin 300mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 300mg vs. SU					Canagliflozin 300mg vs. DPP-4-i				
	Cost Cana 300mg	Cost SU	Increment	Absolute increment	% absolute increment	Cost Cana 300mg	Cost DPP-4-i	Increment	Absolute increment	% absolute increment
Technology cost	2,206	48	2,159	2,159	70.0%	2,275	1,410	865	865	86.4%
Insulin costs	6,246	7,172	-926	926	30.0%	6,195	6,330	-136	136	13.6%
Total		7,220	-7,220	3,085	100%	8,469	7,741	729	1,000	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor;

Table 52. Summary of costs incurred by health state for canagliflozin 300mg vs. SU and DPP-4-i in dual therapy

Health state	Canagliflozin 300mg vs. SU					Canagliflozin 300mg vs. DPP-4-i				
	Costs Cana 300mg	Costs SU	Increment	Absolute increment	% absolute increment	Costs Cana 300mg	Costs DPP-4-i	Increment	Absolute increment	% absolute increment
Macro-vascular health states										
MI	872	901	-29	29	10.7%	880	897	-18	18	8.2%
IHD	760	775	-15	15	5.5%	756	767	-11	11	5.2%
Stroke	279	291	-12	12	4.3%	279	282	-4	4	1.7%
CHF	653	682	-28	28	10.3%	655	665	-10	10	4.6%
Retinopathy	1,159	1,173	-14	14	5.1%	1,148	1,161	-13	13	6.1%
Nephropathy	2,646	2,657	-10	10	3.7%	2,668	2,646	22	22	10.3%
Neuropathy	6,667	6,692	-24	24	8.8%	6,646	6,650	-4	4	2.0%
Hypoglycaemia	145	214	-69	69	25.1%	137	140	-3	3	1.2%
Other AEs	141	132	9	9	3.3%	97	88	9	9	4.1%
Hypertension	62	69	-7	7	2.6%	61	68	-6	6	2.8%
Dyslipidaemia	4,891	4,947	-56	56	20.5%	4,704	4,820	-116	116	53.8%
Total	18,277	18,533	-256	275	100%	18,032	18,185	-153	215	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Triple therapy (Met+SU) base case key comparisons

The summary of QALYs lost by health state is shown below for canagliflozin 100mg and 300mg vs. DPP-4-i (Table 53) in triple therapy (combination with metformin and SU). The summary of costs by health state are shown for canagliflozin 100mg and 300mg vs. DPP-4 (Table 54), and cost for predicted resource for 100mg and 300mg vs. DPP-4-i (Table 55).

Table 53. Summary of QALY loss by health state for canagliflozin 100mg and 300mg vs. DPP-4 in triple therapy (Met+SU)

Health state	Canagliflozin 100mg vs. DPP-4					Canagliflozin 300mg vs. DPP-4-i				
	QALY Cana 100mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment	QALY Cana 300mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment
Survival	-	0.003	-0.003	0.003	11.6%	-	0.007	-0.007	0.007	17.1%
Macro-vascular health states										
MI	0.017	0.017	-0.000	0.000	0.5%	0.017	0.017	-0.000	0.000	0.5%
IHD	0.012	0.012	-0.000	0.000	0.3%	0.012	0.012	-0.000	0.000	0.7%
Stroke	0.034	0.035	-0.000	0.000	1.1%	0.034	0.034	-0.001	0.001	1.6%
CHF	0.013	0.013	-0.000	0.000	0.6%	0.013	0.013	-0.000	0.000	0.7%
Retinopathy	0.016	0.016	0.000	0.000	0.2%	0.016	0.016	-0.000	0.000	0.8%
Nephropathy	0.048	0.048	0.000	0.000	0.2%	0.048	0.0478	-0.000	0.000	0.3%
Neuropathy	0.359	0.357	0.002	0.002	7.3%	0.356	0.359	-0.004	0.004	8.4%
Hypoglycaemia	2.067	2.073	-0.006	0.006	26.5%	2.095	2.101	-0.007	0.007	15.3%
Other AEs	0.008	0.006	0.002	0.002	7.5%	0.010	0.006	0.004	0.004	9.3%
Obesity	0.717	0.727	-0.010	0.010	44.2%	0.701	0.721	-0.019	0.019	45.4%
Total	3.291	3.307	-0.016	0.023	100%	3.300	3.335	-0.035	0.043	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 54. Summary of costs incurred by health state for canagliflozin 100mg and 300mg vs. DPP-4-i in triple therapy (Met+SU)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Costs Cana 100mg	Costs DPP-4	Increment	Absolute increment	% absolute increment	Costs Cana 300mg	Costs DPP-4	Increment	Absolute increment	% absolute increment
Macro-vascular health states										
MI	934	943	-9	9	4.4%	926	941	-16	16	4.8%
IHD	553	558	-6	6	2.9%	544	559	-15	15	4.6%
Stroke	339	343	-3	3	1.8%	335	343	-8	8	2.5%
CHF	743	751	-8	8	4.1%	738	754	-16	16	4.9%
Retinopathy	1,044	1,043	1	1	0.7%	1,031	1,041	-10	10	3.2%
Nephropathy	2,597	2,602	-5	5	2.7%	2,579	2,589	-10	10	3.1%
Neuropathy	5,994	5,974	19	19	10.0%	5,955	5,996	-41	41	12.8%
Hypoglycaemia	479	485	-6	6	2.9%	914	884	31	31	9.5%
Other AEs	192	161	32	32	16.2%	190	161	29	29	8.9%
Hypertension	76	92	-17	17	8.5%	76	92	-16	16	5.0%
Dyslipidaemia	4,635	4,725	-90	90	46.1%	4,595	4,726	-131	131	40.6%
Total	17,586	17,677	-91	195	100%	17,882	18,086	-204	324	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 55. Summary of predicted resource use by category of cost for canagliflozin 100mg and 300mg vs. DPP-4 in triple therapy (Met+SU)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Cost Cana 100mg	Cost DPP-4	Increment	Absolute increment	% absolute increment	Cost Cana 300mg	Cost DPP-4	Incremen t	Absolute increment	% absolute increment
Technology cost	1,428	1,468	-40	40	31.2%	2277	1,468	809	809	84.8%
Insulin costs	6,720	6,631	89	89	68.8%	6498	6,642	-145	145	15.2%
Total	8,148	8,099	49	130	100%	8775	8,110	665	954	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Triple therapy (Met+TZD) basecase key comparisons

The summary of QALYs lost by health state are shown below for canagliflozin 100mg and 300mg vs. DPP-4-i (Table 56) in triple therapy (combination with metformin and pioglitazone). The summary of costs by health state are shown for canagliflozin 100mg and 300mg vs. DPP-4 (Table 57), and cost for predicted resource for 100mg and 300mg vs. DPP-4-i (Table 58).

Table 56. Summary of QALY loss by health state for canagliflozin 100mg and 300mg vs. DPP-4-i in triple therapy (Met+TZD)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	QALY Cana 100mg	QALY DPP-4	Increment	Absolute increment	% absolute increment	QALY Cana 300mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment
Survival	-	0.002	-0.002	0.002	7.2%	-	0.013	-0.013	0.013	30.2%
Macro-vascular health states										
MI	0.016	0.016	-0.000	0.000	0.8%	0.016	0.016	-0.000	0.000	0.6%
IHD	0.009	0.009	-0.000	0.000	0.8%	0.009	0.009	-0.000	0.000	0.4%
Stroke	0.031	0.031	-0.000	0.000	0.7%	0.031	0.031	-0.001	0.001	1.6%
CHF	0.013	0.013	-0.000	0.000	0.3%	0.013	0.013	-0.000	0.000	0.4%
Retinopathy	0.014	0.014	0.000	0.000	1.4%	0.013	0.014	-0.000	0.000	0.5%
Nephropathy	0.040	0.040	-0.000	0.000	0.2%	0.041	0.041	0.000	0.000	0.2%
Neuropathy	0.332	0.329	0.003	0.003	11.0%	0.330	0.329	0.001	0.001	3.2%
Hypoglycaemia	0.721	0.717	0.003	0.003	14.5%	0.720	0.719	0.001	0.001	1.5%
Other AEs	0.006	0.004	0.002	0.002	8.4%	0.008	0.004	0.004	0.004	8.8%
Obesity	0.692	0.705	-0.013	0.013	54.8%	0.689	0.712	-0.023	0.023	52.7%
Total	1.873	1.880	-0.007	0.023	100%	1.869	1.901	-0.032	0.044	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 57. Summary of costs incurred by health state for canagliflozin 100mg and 300mg vs. DPP-4-i in triple therapy (Met+TZD)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Costs Cana 100mg	Costs DPP-4-i	Increment	Absolute increment	% absolute increment	Costs Cana 300mg	Costs DPP-4-i	Increment	Absolute increment	% absolute increment
Macro-vascular health states										
MI	887	902	-15	15	11.4%	875	899	-24	24	16.2%
IHD	423	431	-8	8	6.1%	414	425	-11	11	7.5%
Stroke	310	313	-3	3	2.1%	306	314	-8	8	5.7%
CHF	747	753	-6	6	4.4%	736	748	-12	12	7.7%
Retinopathy	967	959	8	8	6.2%	957	961	-4	4	2.9%
Nephropathy	2,340	2,341	-1	1	0.9%	2,362	2,360	2	2	1.5%
Neuropathy	5,584	5,553	31	31	24.0%	5,585	5,558	26	26	17.7%
Hypoglycaemia	122	121	2	2	1.2%	118	118	0	0	0.1%
Other AEs	183	176	7	7	5.4%	216	176	40	40	27.1%
Hypertension	36	39	-3	3	2.7%	35	39	-4	4	2.6%
Dyslipidaemia	3,501	3,547	-46	46	35.5%	3,558	3542	16	16	10.8%
Total	15,100	15,134	-34	130	100%	15,161	15,140	21	148	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 58. Summary of predicted resource use by category of cost for canagliflozin 100mg and 300mg vs. DPP-4-i in triple therapy (Met+TZD)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Cost Cana 100mg	Cost DPP-4-i	Increment	Absolute increment	% absolute increment	Cost Cana 300mg	Cost DPP-4-i	Increment	Absolute increment	% absolute increment
Technology cost	1,474	1,522	-48	48	34.9%	2,228	1,520	708	708	94.8%
Insulin costs	5,991	5,901	90	90	65.1%	5,888	5,927	-39	39	5.2%
Total	7,465	7,423	42	138	100%	8,116	7,446	669	747	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Add on to insulin therapy base case key comparisons

The summary of QALYs lost by health state are shown below for canagliflozin 100mg and 300mg vs. DPP-4-i (Table 59) in add on to insulin therapy. The summary of costs by health state are shown for canagliflozin 100mg and 300mg vs. DPP-4-i (Table 60), and cost for predicted resource for 100mg and 300mg vs. DPP-4 (Table 61).

Table 59. Summary of QALY loss by health state for canagliflozin 100mg and 300mg vs. DPP-4-i in add on to insulin therapy)

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	QALY Cana 100mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment	QALY Cana 300mg	QALY DPP-4-i	Increment	Absolute increment	% absolute increment
Survival	-	0.001	-0.001	0.001	4.8%	-	0.007	-0.007	0.007	14.6%
Macro-vascular health states										
MI	0.073	0.073	0.000	0.000	0.6%	0.074	0.074	0.000	0.000	0.5%
IHD	0.037	0.037	0.000	0.000	0.1%	0.037	0.037	0.000	0.000	0.1%
Stroke	0.131	0.131	0.000	0.000	0.0%	0.133	0.133	0.000	0.000	0.1%
CHF	0.017	0.018	0.000	0.000	0.6%	0.017	0.018	0.000	0.000	0.4%
Retinopathy	0.027	0.027	0.000	0.000	0.8%	0.028	0.028	0.000	0.000	0.1%
Nephropathy	0.051	0.051	0.000	0.000	0.3%	0.051	0.051	0.000	0.000	0.6%
Neuropathy	0.392	0.391	0.001	0.001	2.8%	0.396	0.395	0.001	0.001	1.8%
Hypoglycaemia	1.720	1.705	0.015	0.015	57.0%	1.688	1.712	-0.025	0.025	52.2%
Other AEs	0.004	0.002	0.002	0.002	6.7%	0.005	0.002	0.003	0.003	5.8%
Obesity	0.694	0.701	-0.007	0.007	26.4%	0.691	0.702	-0.011	0.011	23.8%
Total	3.147	3.138	0.009	0.027	100%	3.120	3.159	-0.039	0.047	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 60. Summary of costs incurred by health state for canagliflozin 100mg and 300mg vs. DPP-4-i in add on to insulin therapy

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Costs Cana 100mg	Costs DPP-4-i	Increment	Absolute increment	% absolute increment	Costs Cana 300mg	Costs DPP-4	Increment	Absolute increment	% absolute increment
Macro-vascular health states										
MI	3,318	3,325	-7	7	8.4%	3,328	3,345	-17	17	8.9%
IHD	1,562	1,564	-1	1	1.4%	1,560	1,562	-2	2	1.2%
Stroke	1,083	1,084	0	0	0.5%	1,090	1,091	-2	2	0.9%
CHF	1,047	1,057	-10	10	12.0%	1,052	1,063	-12	12	6.1%
Retinopathy	1,263	1,259	4	4	4.6%	1,261	1,263	-2	2	0.9%
Nephropathy	2,640	2,644	-4	4	4.4%	2,657	2,641	16	16	8.3%
Neuropathy	6,248	6,242	6	6	7.0%	6,288	6,271	17	17	8.7%
Hypoglycaemia	398	403	-5	5	6.0%	527	501	26	26	13.4%
Other AEs	74	50	24	24	27.8%	88	50	38	38	19.4%
Hypertension	137	142	-5	5	5.9%	134	143	-8	8	4.2%
Dyslipidaemia	3,654	3,673	-19	19	22.1%	3,624	3,678	-55	55	28.1%
Total	21,424	21,442	-18	87	100%	21,608	21,609	-1	194	100%

Abbreviations: QALY, quality-adjusted life year; DPP-4-i, dipeptidyl peptidase 4 inhibitor; MI, myocardial infarction; IHD, ischaemic heart disease; CHF, congestive heart failure

Table 61. Summary of predicted resource use by category of cost for canagliflozin 100mg and 300mg vs. DPP-4-i in add on to insulin therapy

Health state	Canagliflozin 100mg vs. DPP-4-i					Canagliflozin 300mg vs. DPP-4-i				
	Cost Cana 100mg	Cost DPP-4-i	Increment	Absolute increment	% absolute increment	Cost Cana 300mg	Cost DPP-4	Increment	Absolute increment	% absolute increment
Technology cost	827	791	37	37	71.7%	1210	784	426	426	84.9%
Insulin costs	7,183	7,169	14	14	28.3%	7127	7203	-76	76	15.1%
Total	8,010	7,959	51	51	100%	8337	7987	350	502	100%

Abbreviations: QALY, quality-adjusted life year; SU, sulfonylurea; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Base-case analysis

7.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

ECHO-T2DM generates pairwise comparisons, using cohorts of simulated patients that are specific for each comparison from the probability distribution of patient characteristics. Since each simulation run will generate slightly different cohorts of patients (with the expected differences decreasing with number of patients), there can arise differences in the absolute magnitudes of the outcomes from run to run for identical scenarios. For example, a greater proportion of patients with a stroke history at baseline will generally lead to fewer estimated life-years and QALYs, but this is the same for both treatment arms and has at most a second order impact on the incremental results. It should be cautioned, however, that for this reason it would be inappropriate to mix and match simulation results from different runs for supplementary analysis (e.g., constructing the comparison of SU vs. DPP-4-i from the comparisons of canagliflozin 100mg vs. SU and canagliflozin 100mg vs. DPP-4-i in dual therapy). The results are, thus, presented pairwise in the tables below, and calculations of extended cost-effectiveness have not been carried out.

Dual therapy

Canagliflozin 100mg shows QALY gains and a slight increase in costs when compared with SU, DPP-4-i and dapagliflozin, and the resulting ICER's are £1,537, £97, and £8,674 per QALY gained, respectively, considered well within the bounds of cost-effectiveness (Table 62). Against GLP-1-a, canagliflozin 100mg treatment is less costly but also slightly less effective (with an incremental loss of 0.048 QALYs) resulting in a cost saving per QALY lost of £50,005. Looking at it the other way, this implies that the ICER for GLP-1-a vs. canagliflozin 100mg is quite high (above £50,000). If the assumption is made that the NHS is willing to forego 1 QALY as long as savings of at least £20,000 are made, using canagliflozin 100mg instead of GLP-1-a would be considered cost-effective.

Canagliflozin 300mg generates both higher costs and higher QALY gains than canagliflozin 100mg, and is cost-effective when compared to SU and DPP-4-i, with ICERs of £4,899 and £18,349, respectively (Table 63). The ICER when compared against dapagliflozin is £27,419, so cost-effective at a willingness to pay (WTP) of £30,000 per QALY. As in the case of the 100mg dose, canagliflozin 300mg is less costly but also less effective than GLP-1-a; the incremental cost saved per QALY lost is £76,214. Thus canagliflozin 300mg can be considered cost-effective against GLP-1-a.

The assumption of greater pioglitazone durability (i.e., based on the rate of metabolic drift observed for rosiglitazone in ADOPT combined with low annual cost of therapy leads to pioglitazone dominating both canagliflozin 100mg and 300mg (i.e. is cheaper and more effective). (157) It is noted, however, that there are increasing concerns about the AEs associated with pioglitazone and its use is therefore decreasing, and thus is not considered a key comparator. (59)

Table 62. Base case incremental cost-effectiveness results for canagliflozin 100mg in dual therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
TZD	£23,236	13.667	9.119				
Cana 100mg*	£26,069	13.669	8.960	£2,833	0.001	-0.159	Dominated
SU	£25,894	13.664	8.751				
Cana 100mg*	£26,182	13.666	8.938	£288	0.003	0.188	£1,537
Dapagliflozin	£26,086	13.673	8.923				
Cana 100mg*	£26,149	13.678	8.930	£63	0.005	0.007	£8,674
DPP-4-i	£26,100	13.688	8.928				
Cana 100mg*	£26,102	13.692	8.941	1	0.003	0.013	£97
GLP-1-a	£28,390	13.650	8.970				
Cana 100mg*	£25,966	13.644	8.921	-£2,424	-0.006	-0.048	£50,005 #

 # Canagliflozin 100mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a ***to replace*** *canagliflozin 100mg*
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor; Dapa, dapagliflozin

Table 63. Base case incremental cost-effectiveness results for canagliflozin 300mg in dual therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
TZD	£23,204	13.665	9.092				
Cana 300mg*	£26,556	13.663	8.951	£3,353	-0.003	-0.141	Dominates
SU	£25,753	13.671	8.761				
Cana 300mg*	£26,729	13.690	8.961	£976	0.019	0.199	£4,899
DPP-4-i	£25,926	13.644	8.902				
Cana 300mg*	£26,501	13.655	8.933	£576	0.011	0.031	£18,349
Dapagliflozin	£26,044	13.670	8.910				
Cana 300mg*	£26,668	13.679	8.932	£625	0.009	0.023	£27,419
GLP-1-a	£28,515	13.652	8.972				
Cana 300mg*	£26,624	13.657	8.947	-£1,892	0.005	-0.025	£76,214 #

 # Canagliflozin 300mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a ***to replace*** *canagliflozin 300mg*
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Triple therapy (Met+SU and Met+TZD)

Canagliflozin 100mg is both cost-saving and more effective than DPP-4-i and GLP-1-a, and thus is dominant in triple therapy combination with Met+SU, though it should be noted that as in most scenarios, the cost increments vs. DPP-4-i, and the QALY gains vs. GLP-1-a is very small (Table 64). Both canagliflozin 100mg and 300mg are cost-effective vs. Insulin LA, with ICERs of £263 and £607, respectively. Canagliflozin 300mg is cost effective when compared to DPP-4-i, with an ICER of £13,287 per QALY (Table 65). Canagliflozin 300mg dominates GLP-1-a, with incremental cost-saving and greater efficacy.

In combination with Met+TZD, the cost increment is greater for canagliflozin vs. DPP-4i, thus the ICER is £1,095 for canagliflozin 100mg vs. DPP-4-i, and £21,430 for canagliflozin 300mg vs. DPP-4-i (Table 66and Table 67).

Table 64 Base case incremental cost-effectiveness results for canagliflozin 100mg in triple therapy (Met+SU)

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£25,776	12.964	7.060				
Cana 100mg	£25,734	12.967	7.076	£-42	0.004	0.016	Dominates
Insulin LA	£25,577	12.972	5.193				
Cana 100mg	£25,712	12.982	5.707	£135	0.010	0.514	£263
GLP-1-a	£27,119	12.978	7.101				
Cana 100mg	£25,822	12.980	7.102	-£1,297	0.002	0.001	Dominates

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Table 65 Base case incremental cost-effectiveness results for canagliflozin 300mg in triple therapy (Met+SU)

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£26,196	12.967	7.047				
Cana 300mg	£26,657	12.976	7.082	£461	0.009	0.035	£13,287
Insulin LA	£26,326	12.992	5.139				
Cana 300mg	£26,705	12.993	5.763	£379	0.002	0.624	£607
GLP-1-a	£27,153	12.936	7.068				
Cana 300mg	£26,468	12.944	7.072	-£685	0.008	0.004	Dominates

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Table 66 Base case incremental cost-effectiveness results for canagliflozin 100mg in triple therapy (Met+TZD)

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£22,557	8.294	8.287				
Cana 100mg	£22,565	12.597	12.595	£7	0.002	0.007	£1,095

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Table 67 Base case incremental cost-effectiveness results for canagliflozin 300mg in triple therapy (Met+TZD)

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£22,586	12.606	8.274				
Cana 300mg	£23,277	12.623	8.306	£691	0.017	0.032	£21,430

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Add-on to insulin

In combination with insulin, canagliflozin 100mg dominates dapagliflozin, although it should be noted that incremental gains in costs and QALYs are small (Table 68). When compared with DPP-4-i and GLP-1-a, although cost-saving, canagliflozin is not cost-effective as the cost per QALY lost is £1,340 and £12,915, respectively (maintaining the assumption that cost-effectiveness in this comparison would require savings of at least £20,000 per QALY lost). The incremental QALY losses that drive this result are small.

Canagliflozin 300mg generates a greater number of QALYs in combination with insulin, and is thus cost-effective when compared to DPP-4-i and dapagliflozin, with ICERs of £7,975 and £5,992, respectively (Table 69). In comparison with GLP-1-a, canagliflozin 300mg is less effective but cost-saving, and thus can be considered cost-effective with £35,575 saved per QALY lost.

Table 68 Base case incremental cost-effectiveness results for canagliflozin 100mg in add-on to insulin therapy

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

 # Canagliflozin 100mg is both cheaper and less effective than the other therapies, therefore the ICER is for canagliflozin 100mg to be replaced
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Table 69 Base case incremental cost-effectiveness results for canagliflozin 300mg in add-on to insulin therapy

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£29,328	10.829	5.585				
Cana 300mg	£29,650	10.838	5.625	£322	0.009	0.040	£7,975
Dapagliflozin	£29,618	10.853	5.572				
Cana 300mg	£29,946	10.863	5.627	£327	0.009	0.055	£5,992
GLP-1-a	£30,333	10.851	5.636				
Cana 300mg	£29,807	10.859	5.621	-£526	0.007	-0.015	£35,575 #

 # Canagliflozin 300mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin 300mg
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

Summary of base case cost-effectiveness

In dual therapy, both canagliflozin doses in combination with metformin are cost effective compared to the key comparators, SU and DDP-4-i (with all ICERs less than £18,500/QALY). Canagliflozin is also cost-effective compared to dapagliflozin at the 100mg dose (£8,674/QALY). Although the ICER is higher at the 300mg dose (£27,419/QALY), this is still within the threshold of other NICE approved treatments. Compared to GLP-1-a, canagliflozin is a cheaper option but generates fewer QALYs, resulting in GLP-1a not being cost-effective against either dose. Both doses of canagliflozin are dominated by TZD, although the relevance of this comparison to usual UK practice is limited by safety concerns with this class, and its use is declining.

Both doses of canagliflozin when used in triple therapy regimens are more cost-effective than triple therapy with DPP-4-i, insulin LA or GLP-1a. Triple therapy with canagliflozin dominates triple therapy with GLP-1-a and generates ICERs below £21,500/QALY when compared with DPP-4-i.

It is anticipated that canagliflozin would be used most commonly as add-on therapy to metformin in dual therapy, or when combined with two other AHAs in triple therapy. In current UK clinical practice, clinicians would typically either select an SU or DDP-4-i (dual therapy) or a DDP-4-i added to two other agents (typically metformin and an SU) in triple therapy. From this perspective, it is important to emphasise that the base case results support the cost-effectiveness of canagliflozin 100mg and 300mg doses compared to the most relevant currently used agents at this stage of the treatment pathway.

The model demonstrated that it is more cost-effective to add a 300mg canagliflozin dose to an insulin regimen than to add on DPP-4-i or dapagliflozin (<£7.975/QALY). Compared to GLP-1-a in combination with insulin, canagliflozin 300mg+insulin is cost-effective, as it costs less and generates slightly fewer QALYs (the ICER for GLP-1a to replace canagliflozin 300mg is £35,575/QALY). Canagliflozin 100mg +insulin was cost-effective to dapagliflozin, but not when compared to GLP-1-a or DPP-4-i in combination with insulin.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis.

Consider the use of tornado diagrams.

DSAs were performed for the eight ‘systematic’ analyses: comparison against SU and DPP-4-i in dual therapy and against DPP-4-i in triple therapy and add-on to insulin therapy. The details were presented in Section 7.6.2. For the sake of brevity, the full tabulated results are presented in Tables 195 to 202, in Section 10.13 for Appendix 13, and the tornado diagrams of the key comparisons are presented below.

In dual therapy comparisons against SU, the ICERs of both doses of canagliflozin varied little under the variation of the 35 DSA parameters (Figure 65 and Figure 67). The most influential parameter on the ICER was the metabolic drift of HbA1c (both for SU and for canagliflozin).

As show in Table 62, for canagliflozin 100mg vs. DPP-4-i the change in costs and QALYs (i.e., the numerator and denominator of the ICER) were small so that small changes in either (both) could potentially cause large swings in the ICER under DSA. In fact, however, the ICER is relatively stable across the DSAs; only the changes in HbA1c drift and non-AE costs changed the result from cost-effective to not cost-effective (Figure 66). In a number of instances, the base case ICER does not lie within the range created by the ICER's of the Upper and Lower parameter estimates for the DSA because of stochastic variability and the small changes observed in the incremental costs and QALYs. In none of these cases, was a qualitative result reversed.

For canagliflozin 300mg vs. DPP-4-i in dual therapy (Figure 68), the base case ICER is higher and there are a greater number of DSAs that change the results and bring them closer to conventional acceptability thresholds of £20 -30K. The greatest impact on the base case ICER is metabolic drift, cholesterol and SBP therapeutic effects and discontinuation rate of DPP-4-i.

In triple therapy (Met+SU), canagliflozin 100mg is consistently dominant when compared to DPP-4-i across the majority of the parameters, and thus a tornado diagram is not presented. The key drivers are HbA1c and the rate of severe hypoglycaemic events for DPP-4-i. For the canagliflozin 300mg vs. DPP-4-i in triple therapy, only varying the HbA1c drift changed the result significantly (Figure 69).

In add-on to insulin, canagliflozin 100mg was dominated by DPP-4-i in most DSAs as in the base case, therefore a tornado diagram was not prepared. Only increasing the DPP-4-i HbA1c drift, or decreasing the canagliflozin HbA1c drift switched the result from not cost-effective to cost-effective (and in those scenarios, canagliflozin dominated DPP-4-i illustrating the similarity of the drug profiles simulated and the small incremental differences). For canagliflozin 300mg vs. DPP-4-i in combination with insulin, as with all the other DSAs, HbA1c drift was a major factor, and was the only factor that changed the result from cost-effective to not cost-effective (Figure 70). Other than this, rates of severe hypoglycaemic event impacted the ICER to a moderate extent. It should be remembered that the evidence base for add-on to insulin was less robust than for earlier lines of therapy, being based on a sub-study of the CANVAS trial out to only 18 weeks.

Figure 65. Tornado diagram of the DSA for canagliflozin 100mg vs. SU in dual therapy, with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.

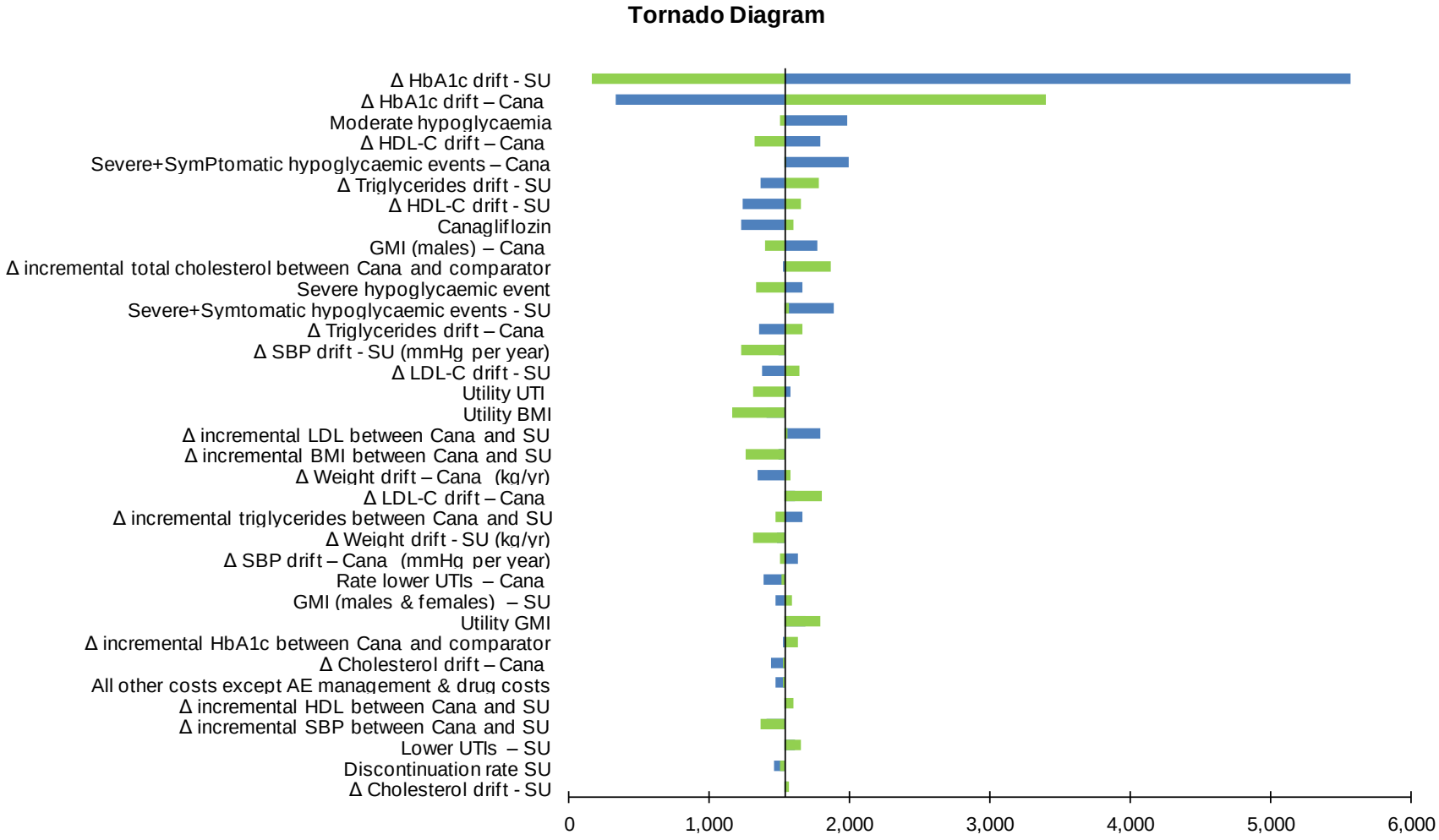


Figure 66. Tornado diagram of the DSA for canagliflozin 100mg vs. DPP-4-i in dual therapy, with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.

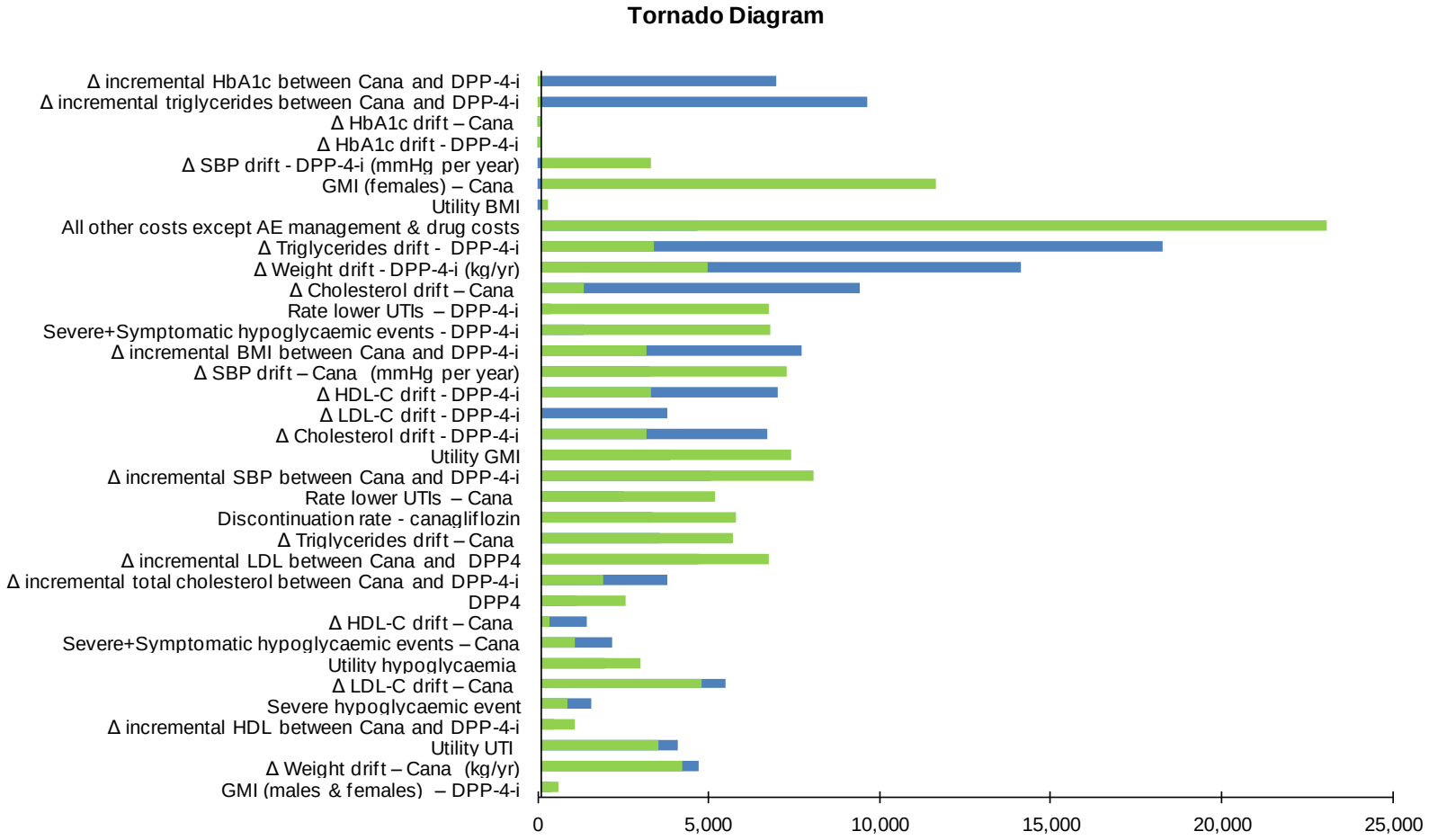


Figure 67. Tornado diagram of the DSA for canagliflozin 300mg vs. SU in dual therapy, with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.

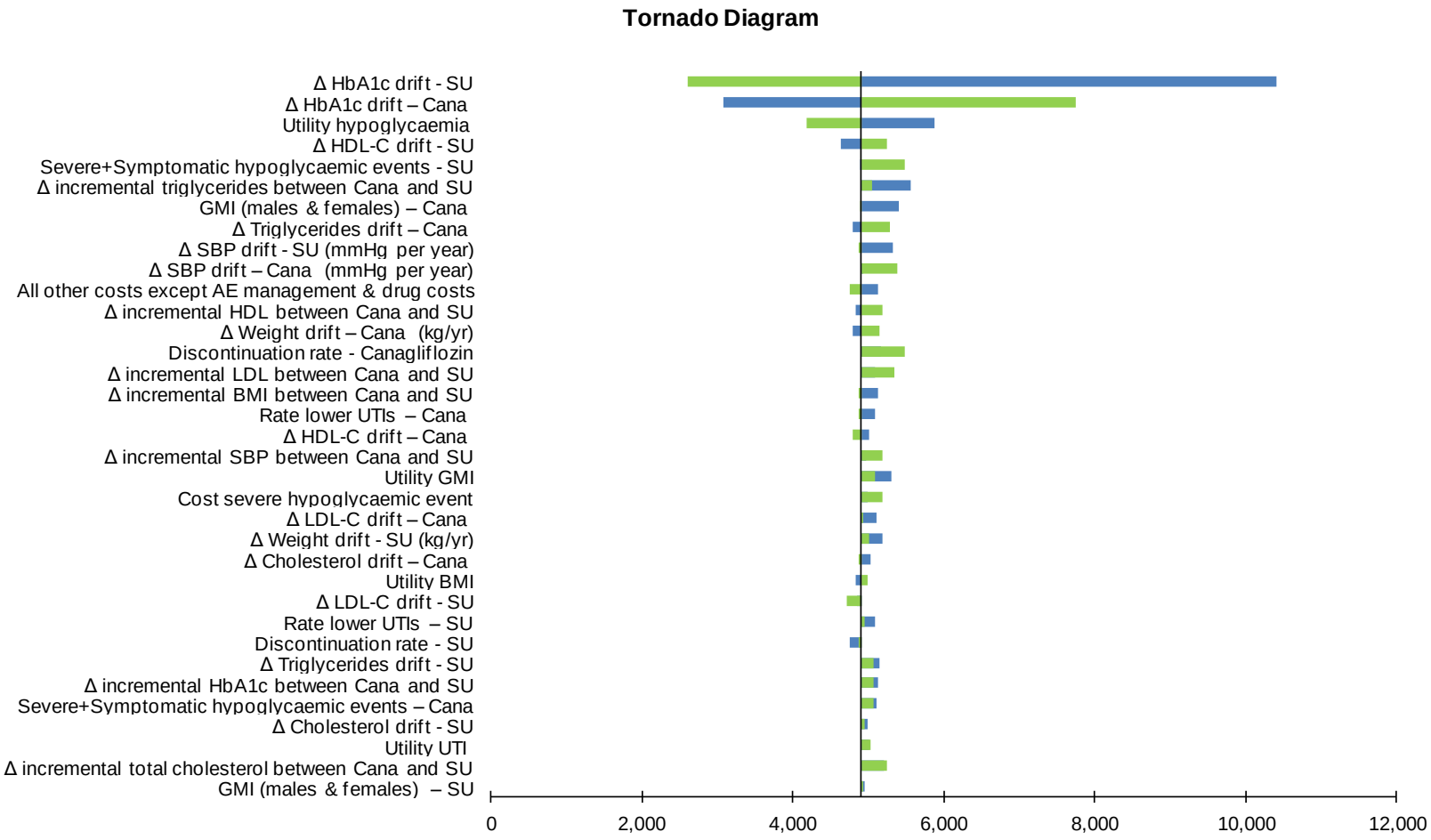


Figure 68. Tornado diagram of the DSA for canagliflozin 300mg vs. DPP-4-i in dual therapy, with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.

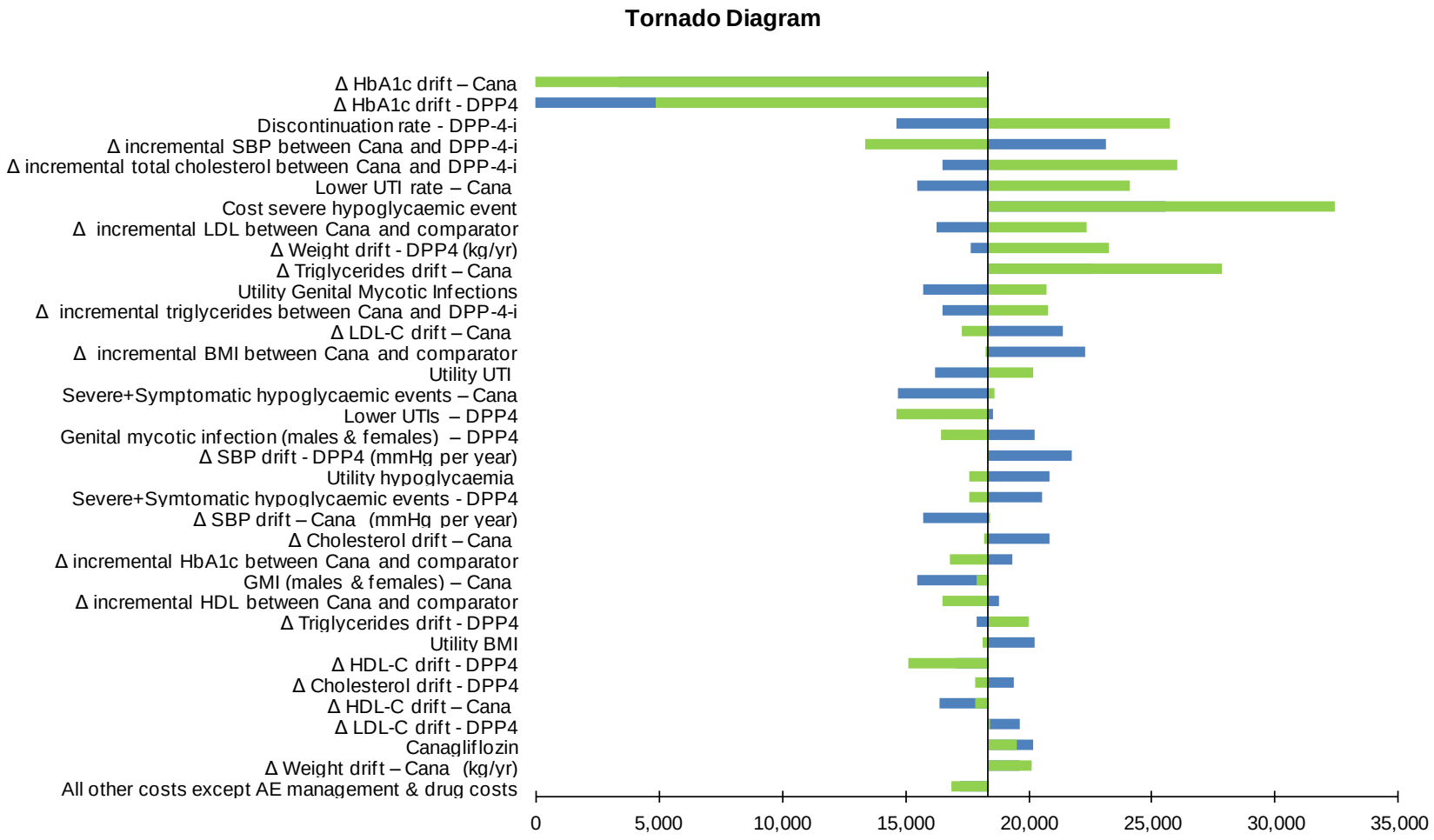


Figure 69. Tornado diagram of the DSA for canagliflozin 300mg vs. DPP-4-i in triple therapy (Met+SU), with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.

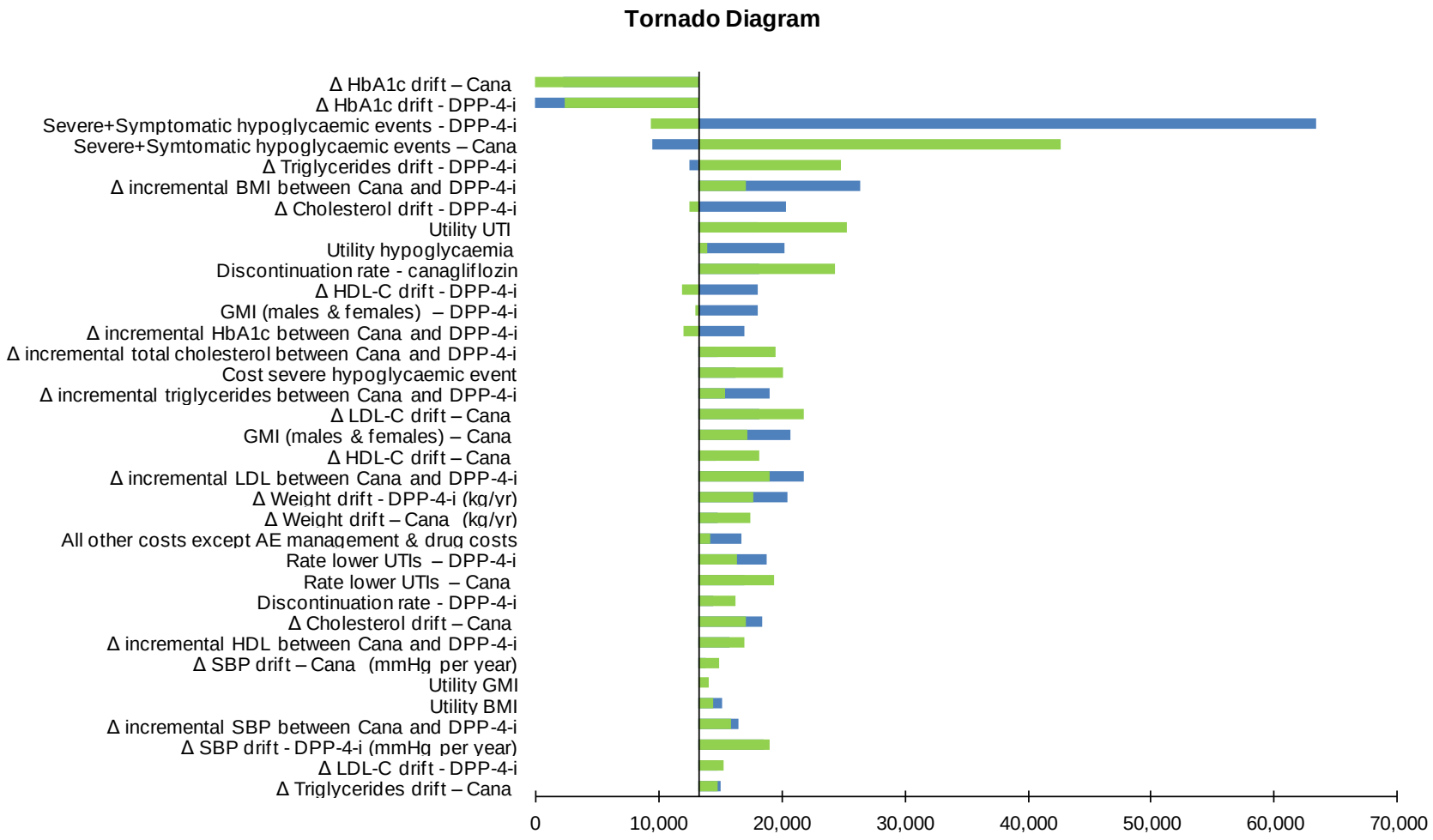
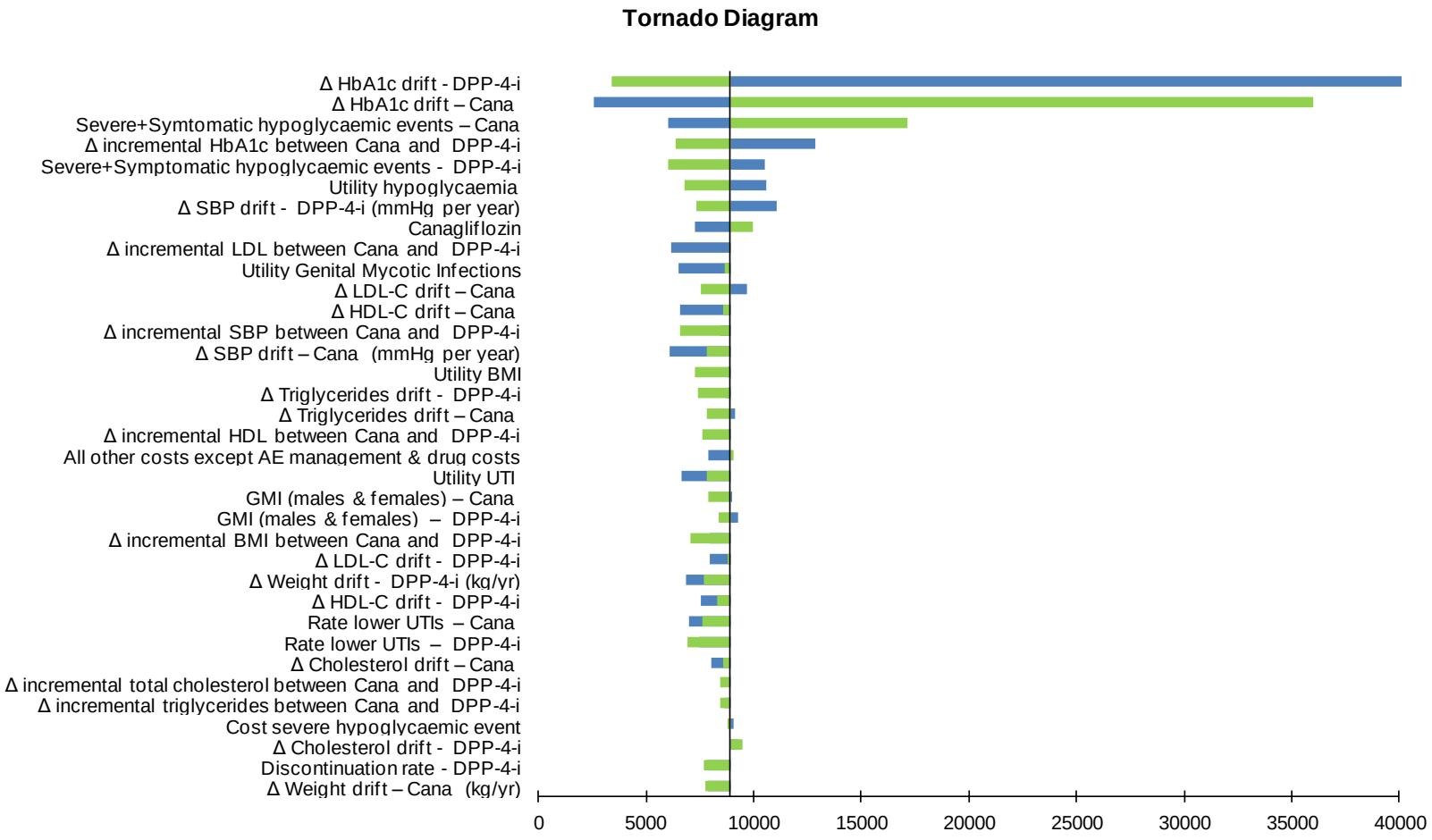


Figure 70. Tornado diagram of the DSA for canagliflozin 300mg vs. DPP-4-i in add-on to insulin therapy, with upper end analyses in blue and lower in green. Dominant and dominated results have been removed from the tornado diagram.



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Dual therapy (+Met) base case key comparisons

Met+canagliflozin 100mg vs. Met+SU

Figure 71 shows the cost-effectiveness plane for canagliflozin 100mg vs. SU in dual therapy (combination with metformin). The 95% CI for the upper and lower 95% CIs are shown in Table 70. Figure 72 shows the cost-effectiveness acceptability curve. Canagliflozin 100mg has a 92.9% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 93.6% probability of being cost effective at a WTP of £30,000/QALY.

Figure 71. Dual therapy - cost effectiveness plane for Met+canagliflozin 100mg vs. Met+SU

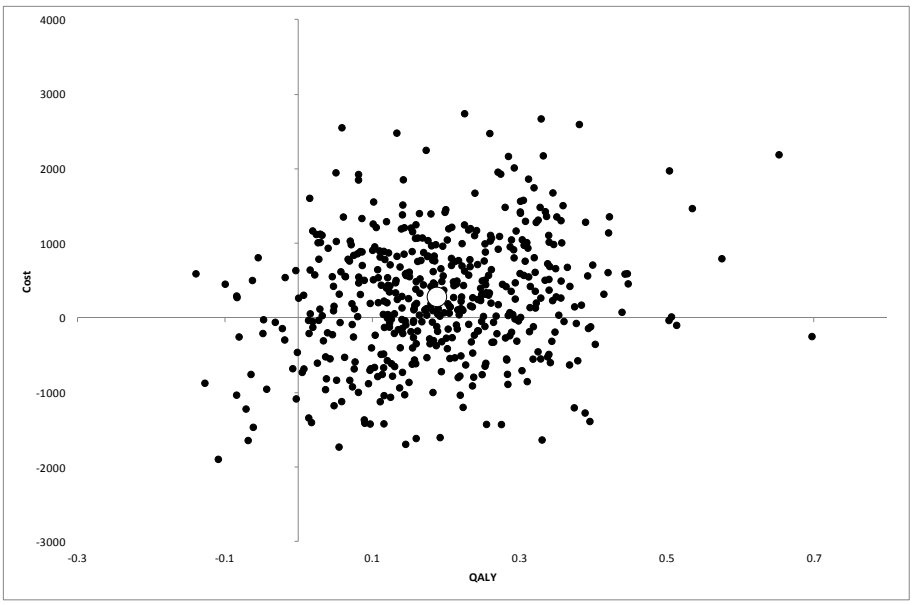
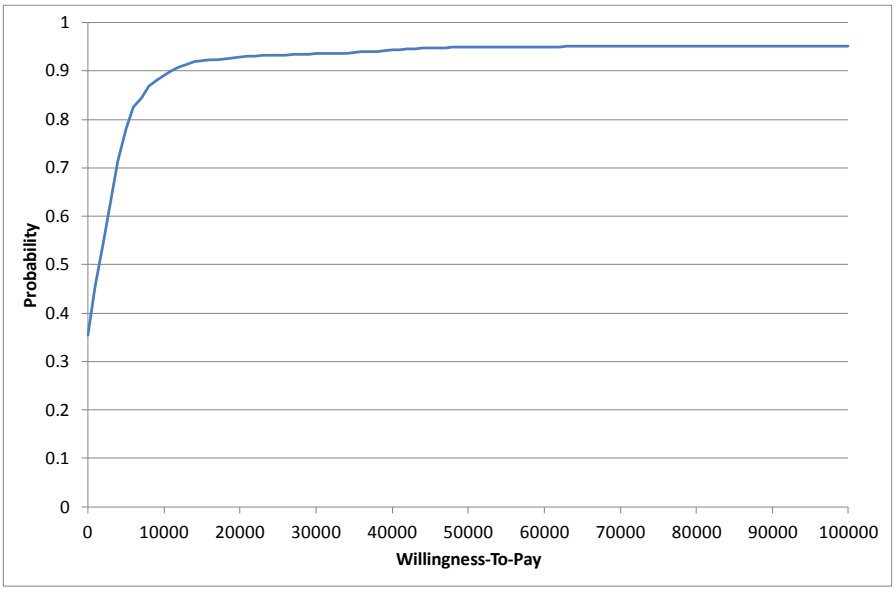


Table 70. Results of the PSA: 95% CI around incremental QALYs and costs; Met+canagliflozin 100mg vs. Met+SU

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.188	-0.049	0.421
Δ Costs	288	-1383	1858

Figure 72. Dual therapy - acceptability curve for Met+canagliflozin 100mg vs. Met+SU



Met+canagliflozin 300mg vs. Met+SU

Figure 73 shows the cost-effectiveness plane for canagliflozin 300mg vs. SU in dual therapy (combination with metformin). The 95% CI for the upper and lower 95% CIs are shown in Table 71. Figure 74 shows the cost-effectiveness acceptability curve. Canagliflozin 300mg has an 89.5% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 92.1% probability of being cost effective at a WTP of £30,000/QALY.

Figure 73. Dual therapy - cost effectiveness plane for Met+canagliflozin 300mg vs. Met+SU

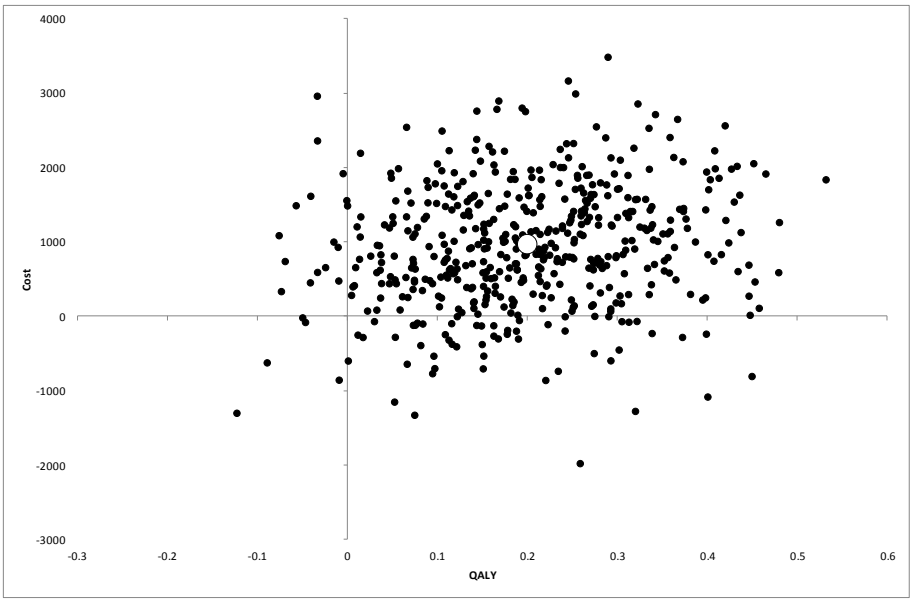
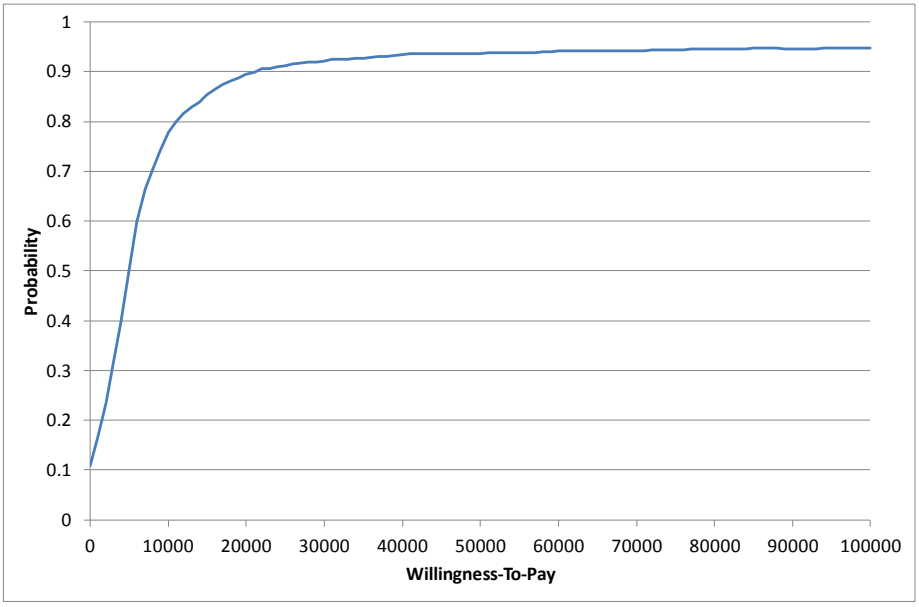


Table 71. Results of the PSA: 95% CI around incremental QALYs and costs; Met+canagliflozin 300mg vs. Met+SU

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.199	-0.034	0.444

Δ Costs	976	-620	2604

Figure 74. Dual therapy - acceptability curve for Met+canagliflozin 300mg vs. Met+SU



Met+canagliflozin 100mg vs. Met+DPP-4-i

Figure 75 shows the cost-effectiveness plane for canagliflozin 100mg vs. DPP-4-i in dual therapy (combination with metformin). The 95% CI for the upper and lower 95% CIs are shown in Table 72. Figure 76 shows the cost-effectiveness acceptability curve. Canagliflozin 100mg has a 54.5% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 54.9% probability of being cost effective at a WTP of £30,000/QALY.

Figure 75. Dual therapy - cost effectiveness plane for Met+canagliflozin 100mg vs. Met+DPP-4-i

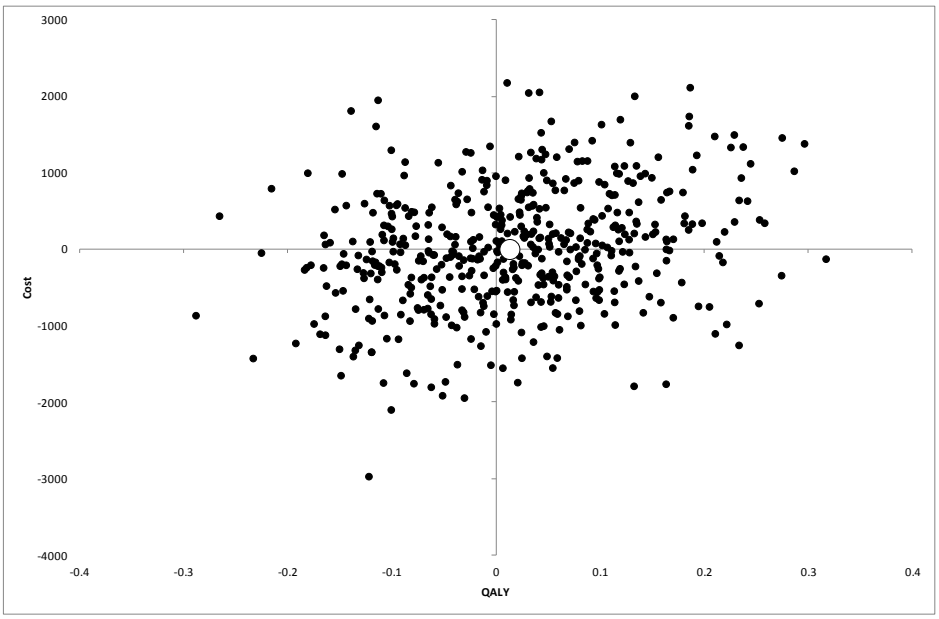
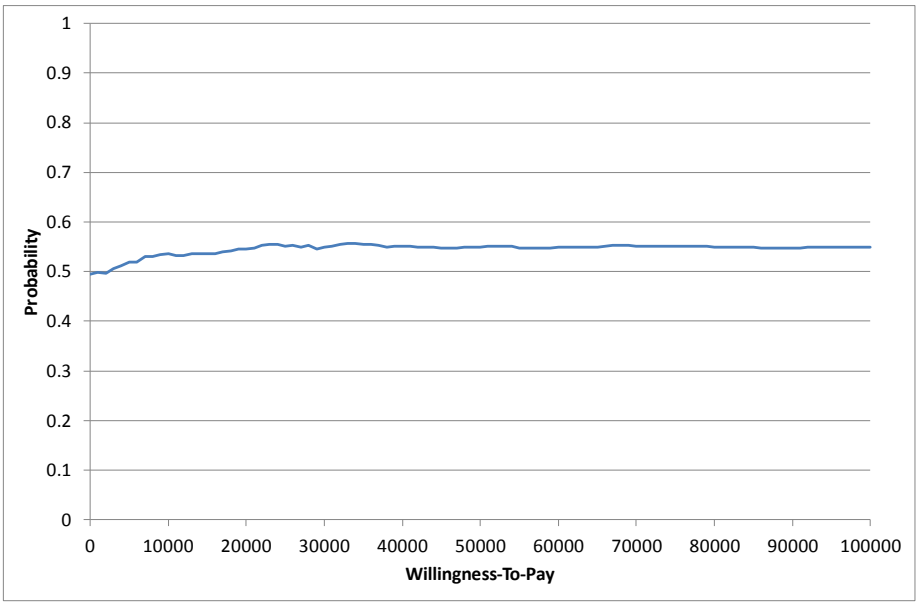


Table 72. Results of the PSA: 95% CI around incremental QALYs and costs; Met+canagliflozin 100mg vs. Met+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.013	-0.185	0.233
Δ Costs	1	-1618	1500

Figure 76. Dual therapy - acceptability curve for Met+canagliflozin 100mg vs. Met+DPP-4-i



Met+canagliflozin 300mg vs. Met+DPP-4-i

Figure 77 shows the cost-effectiveness plane for canagliflozin 300mg vs. DPP-4-i in dual therapy (combination with metformin). The 95% CI for the upper and lower 95% CIs are shown in Table 73. Figure 78 shows the cost-effectiveness acceptability curve. Canagliflozin 300mg has a 51.6% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 54.9% probability of being cost effective at a WTP of £30,000/QALY.

Figure 77. Dual therapy - cost effectiveness plane for Met+canagliflozin 300mg vs. Met+DPP-4-i

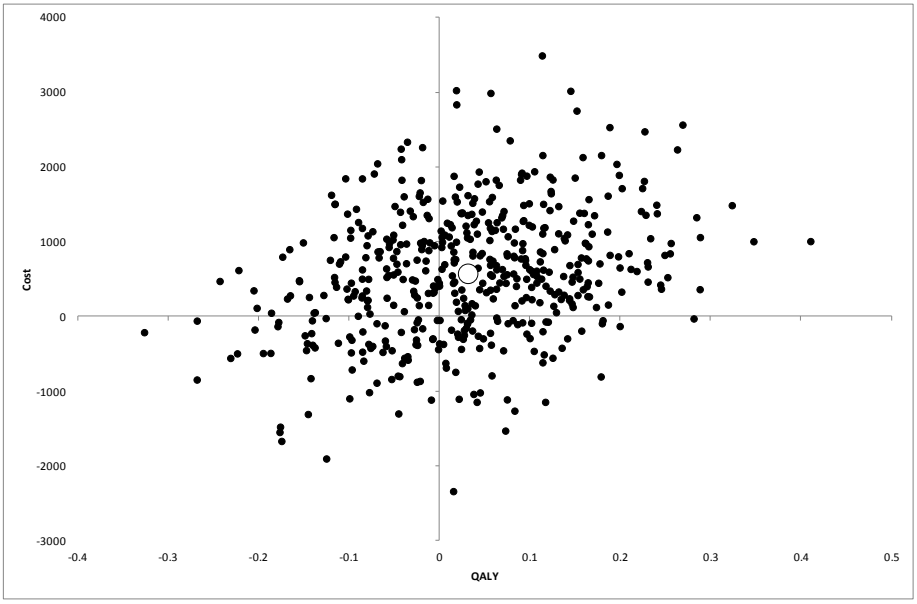
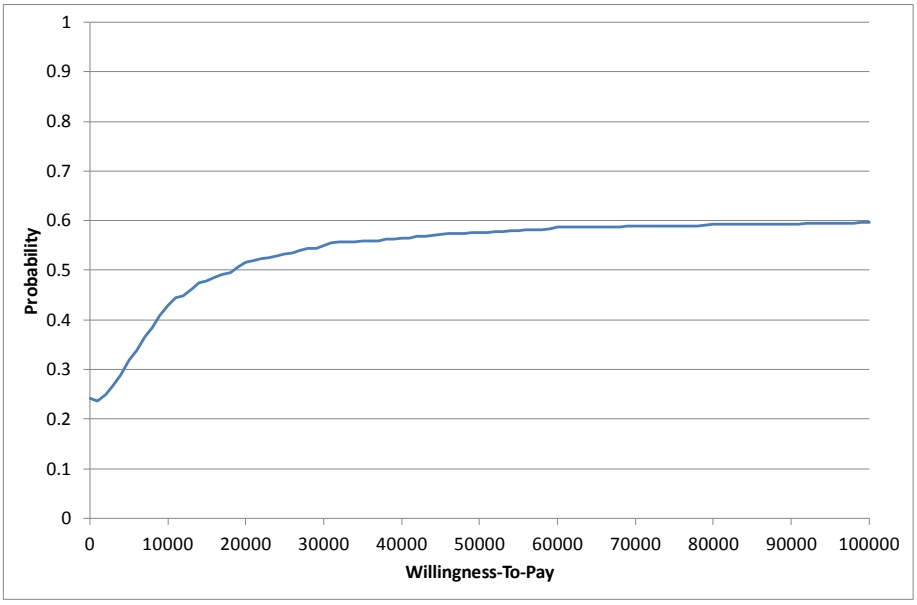


Table 73. Results of the PSA: 95% CI around incremental QALYs and costs; Met+canagliflozin 300mg vs. Met+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.031	-0.197	0.249
Δ Costs	576	-1087	2233

Figure 78. Dual therapy - acceptability curve for Met+canagliflozin 300mg vs. Met+DPP-4-i



Triple therapy (Met+SU) - base case key comparisons

Met+SU+canagliflozin 100mg vs. Met+SU+DPP-4-i

Figure 79 shows the cost-effectiveness plane for canagliflozin 100mg vs. DPP-4-i in triple therapy (combination with metformin and SU). The 95% CI for the upper and lower 95% CIs are shown in Table 74. Figure 80 shows the cost-effectiveness

acceptability curve. Canagliflozin 100mg has a 55.7% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 55.6% probability of being cost effective at a WTP of £30,000/QALY.

Figure 79. Triple therapy cost effectiveness plane for Met+SU+canagliflozin 100mg vs. Met+SU+DPP-4-i

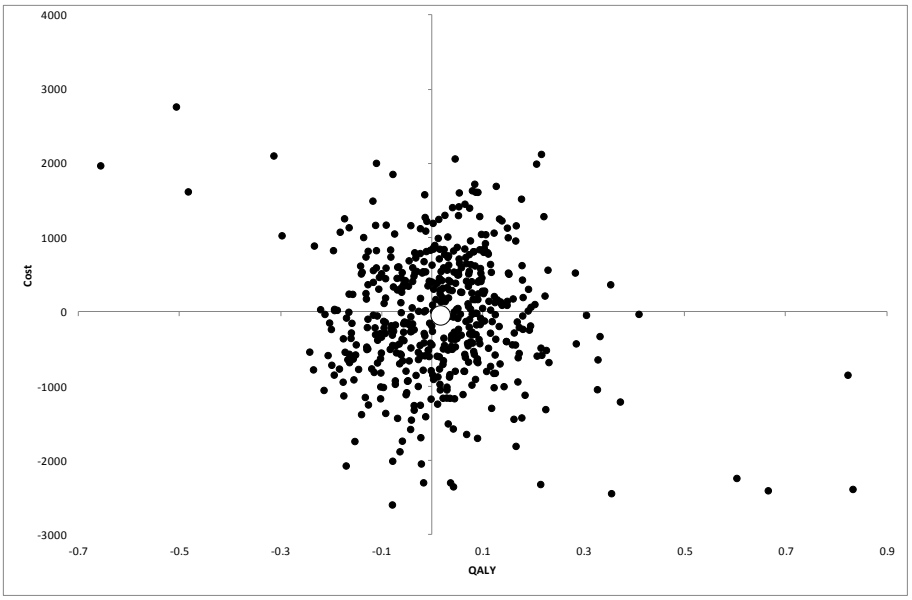
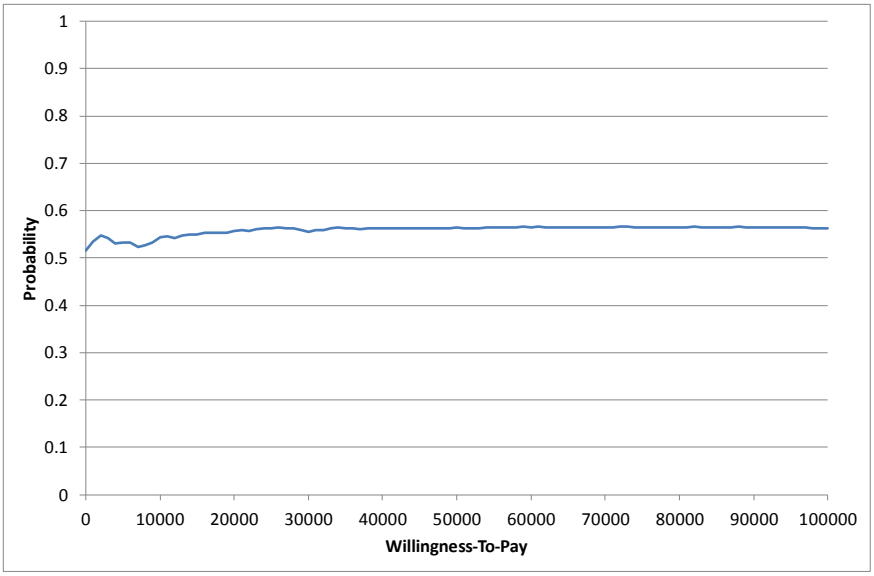


Table 74. Results of the PSA: 95% CI around incremental QALYs and costs; Met+SU+Cana100mg vs. Met+SU+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.016	-0.200	0.283
Δ Costs	-42	-1842	1616

Figure 80. Triple therapy - acceptability curve for Met+SU+canagliflozin 100mg vs. Met+SU+DPP-4-i



Met+SU+canagliflozin 300mg vs. Met+SU+DPP-4-i

Figure 81 shows the cost-effectiveness plane for canagliflozin 300mg vs. DPP-4-i in triple therapy (combination with metformin and SU). The 95% CI for the upper and lower 95% CIs are shown in Table 75. Figure 82 shows the cost-effectiveness acceptability curve. Canagliflozin 300mg has a 55.1% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 58.2% probability of being cost effective at a WTP of £30,000/QALY.

Figure 81. Triple therapy - cost effectiveness plane for Met+SU+canagliflozin 300mg vs. Met+SU+DPP-4-i

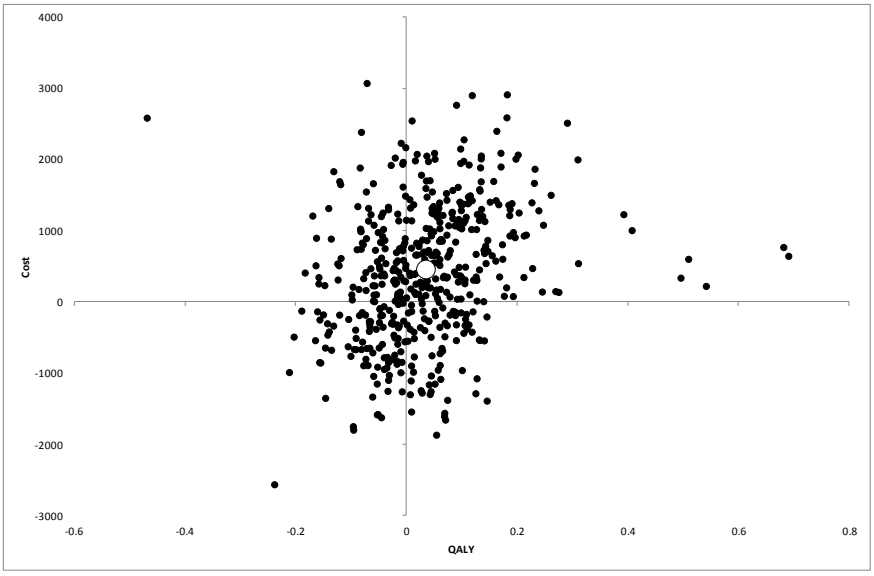
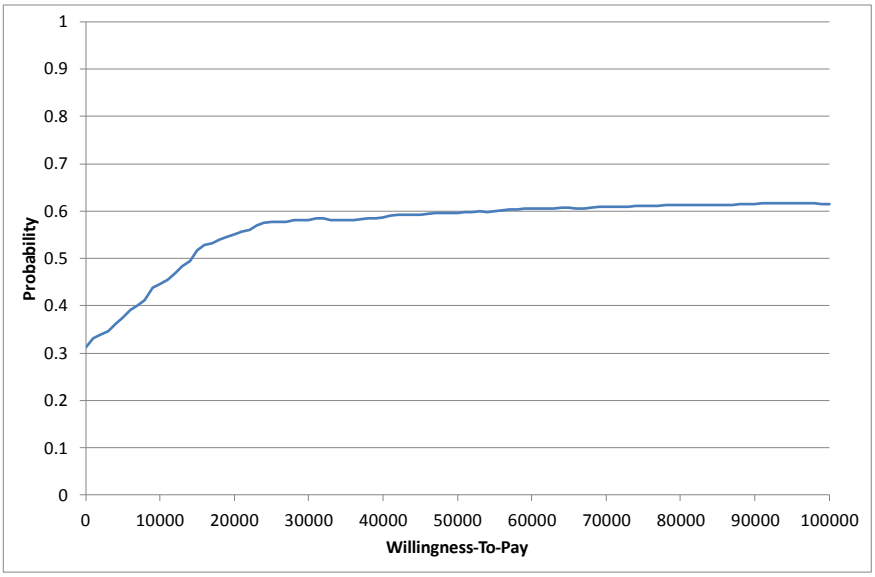


Table 75. Results of the PSA: 95% CI around incremental QALYs and costs; met+SU+canagliflozin 300mg vs. Met+SU+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.035	-0.159	0.237
Δ Costs	461	-1332	2233

Figure 82. Triple therapy - acceptability curve for Met+SU+canagliflozin 300mg vs. Met+SU+DPP-4-i



Add-on to insulin - key comparison base case

Insulin+SoC+canagliflozin 100mg vs. Insulin+SoC+DPP-4-i

Figure 83 shows the cost-effectiveness plane for canagliflozin vs. DPP-4-i as an add-on to insulin therapy. The 95% CI for the upper and lower 95% CIs are shown in Table 76. Figure 84 shows the cost-effectiveness acceptability curve. Canagliflozin 100mg has a 44.7% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 45.2% probability of being cost effective at a WTP of £30,000/QALY.

Figure 83. Add-on to insulin therapy - cost effectiveness plane for Ins+SoC +Cana100mg vs. Ins+SoC+DPP-4-i

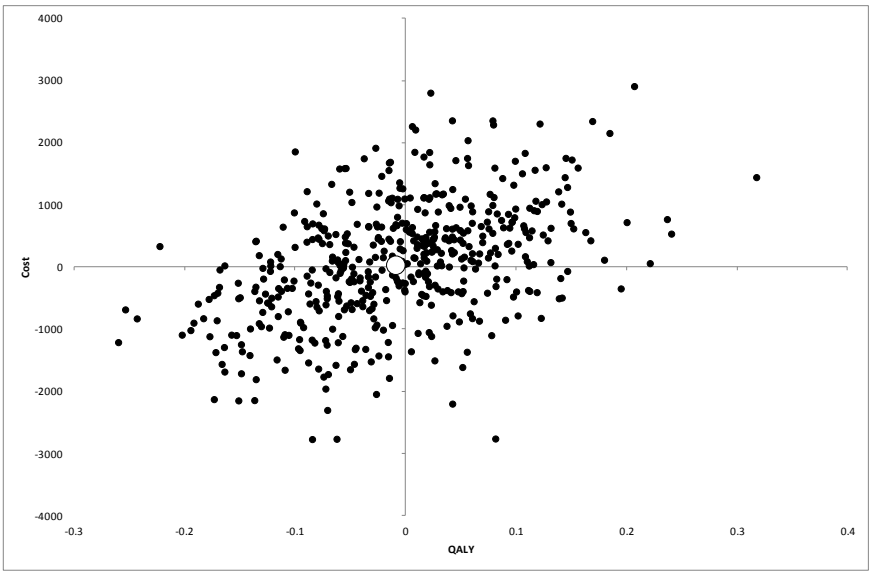
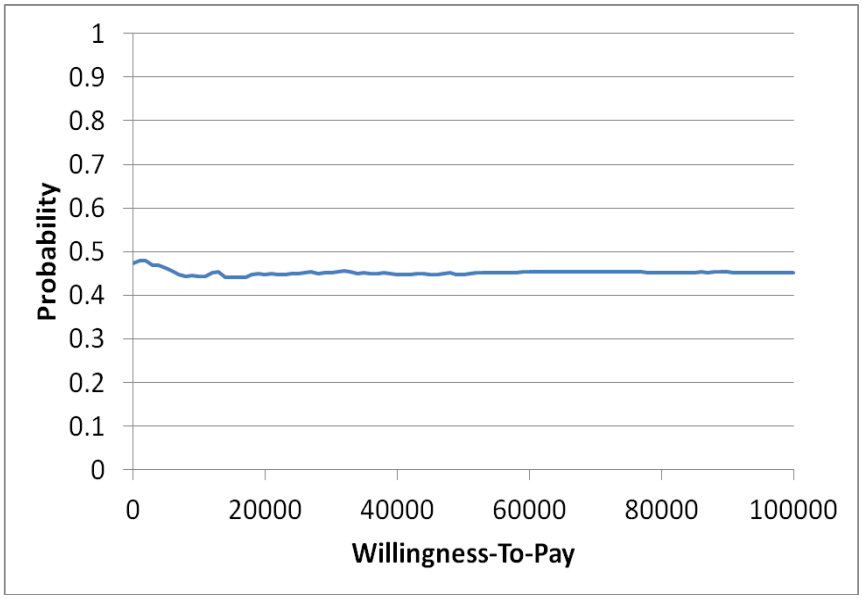


Table 76. Results of the PSA: 95% CI around incremental QALYs and costs; Ins+SoC+Cana100mg vs. Ins+SoC+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	-0.009	-0.187	0.169
Δ Costs	33	-1715	1808

Figure 84. Add-on to insulin therapy - acceptability curve for Ins+SoC+Cana100mg vs. Inst+SoC+DPP-4-i



Insulin+SoC+canagliflozin 300mg vs. Insulin+SoC+DPP-4-i

Figure 85shows the cost-effectiveness plane for canagliflozin vs. DPP-4-i as an add-on to insulin therapy. The 95% CI for the upper and lower 95% CIs are shown in Table 77. Figure 86 shows the cost-effectiveness acceptability curve. Canagliflozin 100mg has a 60.7% probability of being cost-effective at a WTP threshold of £20,000/QALY, and a 63.7% probability of being cost effective at a WTP of £30,000/QALY.

Figure 85. Add-on to insulin therapy - cost effectiveness plane for Ins+SoC+Cana300mg vs. Ins+SoC+DPP-4-i

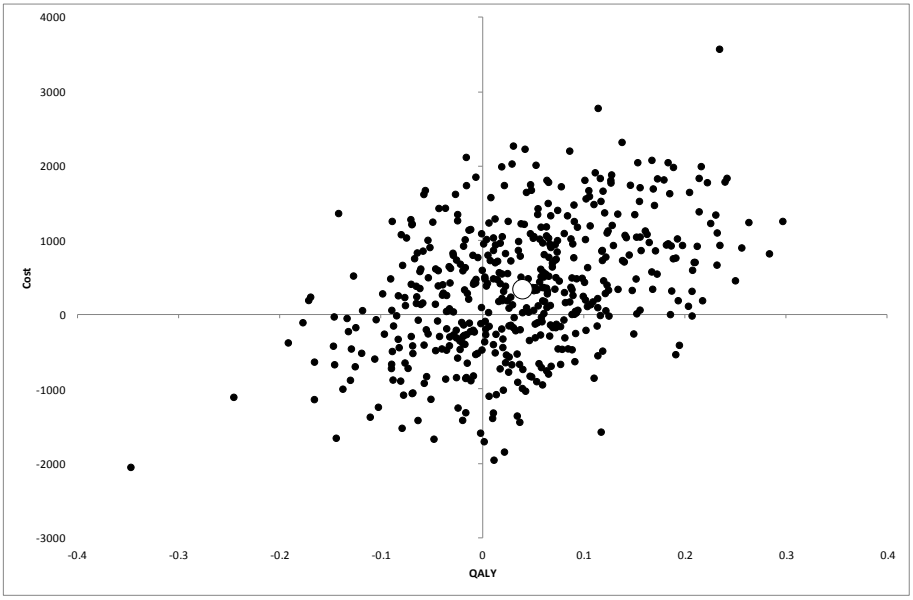
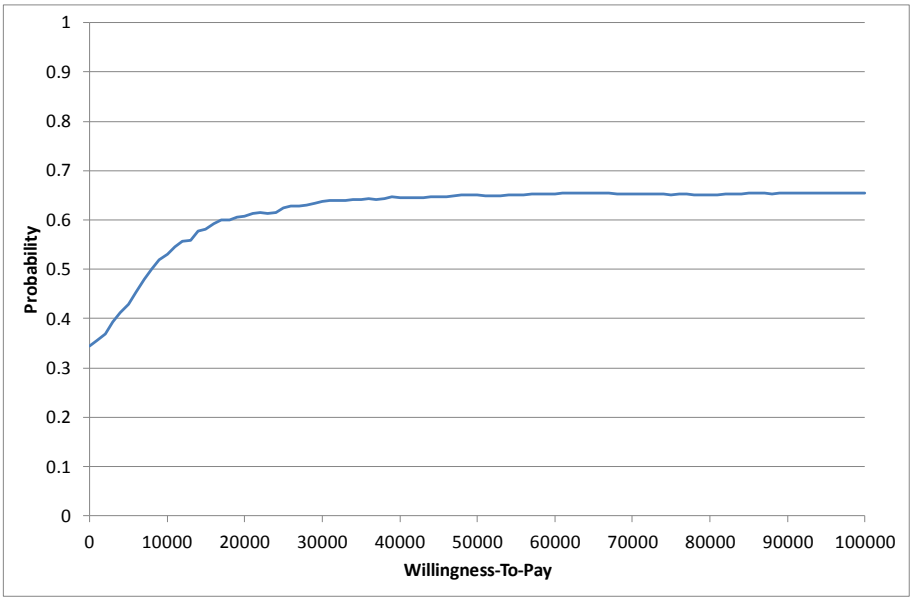


Table 77. Results of the PSA: 95% CI around incremental QALYs and costs; Ins+SoC+Cana300mg vs. Ins+SoC+DPP-4-i

Outcome	Point estimate	LL 95% CI	UL 95% CI
Δ QALYs	0.039	-0.146	0.225
Δ Costs	349	-1431	2082

Figure 86. Add-on to insulin therapy - acceptability curve for Ins+SoC+Cana300mg vs. Ins+SoC+DPP-4-i



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

As described in Section 7.6.1, scenario analyses were carried out on a select set of comparisons. Full scenario analyses were performed for the key comparisons, vs. SU in dual therapy, and vs. DPP-4-i in dual therapy, triple therapy (Met+SU) and in add-on to insulin therapy. Selected sets of scenario analysis were conducted on the remaining comparisons.

Table 78. Results of the scenario analysis for canagliflozin 100mg vs. SU in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£288	0.188	£1,537
Time horizon	40 years	20 years	£424	0.178	£2,380
Discount rate	3.5% for costs and outcomes	0% for both	-£85	0.308	Dominating
		6% for both	£437	0.142	£3,069
Dose modification	No Dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	£399	0.232	£1,721
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£282	0.196	£1,440
HbA1c switch threshold	7.5% (59mmol/mol)	8%	£609	0.237	£2,567
HbA1c metabolic drift	0.14% for canagliflozin (157)	Canagliflozin set at 0.24%, as for SU	£819	0.027	£30,358
Patient baseline characteristics	RCT data	THIN data	£160	0.106	£2,159
Risk equations	UKPDS 68 (133)	UKPDS82 (144)	£217	0.187	£1,515
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£108	0.244	£442
		Weight rebound occurs two years following treatment discontinuation	£80	0.248	£321
Therapy treatment effect	52 week NMA	26 week NMA	£283	0.219	£1,288
		RCT data	£267	0.295	£905
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£318	0.178	£1,786
		-0.014 (128)	£263	0.227	£1,158
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£226	0.188	£1,201
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus	£806	0.195	£4,125
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	£346	0.187	£1,846
Dyslipidaemia	Management of dyslipidaemia according to NICE CG67	All patients on simvastatin 80mg at baseline; no rescue medication implemented	£445	0.195	£2,286

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 79. Results of the scenario analysis for canagliflozin 100mg vs. DPP-4-i in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£1	0.013	£97
Time horizon	40 years	20 years	£25	0.007	£3,528
Discount rate	3.5% for costs and outcomes	0% for both	£268	0.015	£18,180
		6% for both	£39	0.014	£2,727
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£14	0.054	Dominating
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£55	0.016	£3,480
HbA1c switch threshold	7.50%	8%	£41	0.011	£3,696
Patient baseline characteristics	RCT data	THIN data	£28	0.008	£3,663
Risk equations	UKPDS68	UKPDS82	£55	0.019	£2,928
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£44	0.038	Dominating
		Weight rebound occurs two years following treatment discontinuation	£1	0.030	£47
Therapy treatment effect	52 week NMA	26 week NMA	£36	0.012	£3,082
		RCT data	£41	0.006	£6,886
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£67	0.005	£12,884
		-0.014 (128)	£64	0.032	£1,995
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£39	0.012	£3,172
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus	£112	0.021	£5,295
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	£37	0.009	£4,178
Dyslipidaemia	Management of dyslipidaemia according to NICE CG67	All patients on simvastatin 80mg at baseline; no rescue medication implemented	£83	0.009	£8,809

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 80. Results of the scenario analysis for canagliflozin 300mg vs. SU in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£976	0.199	£4,899
Time horizon	40 years	20 years	£1,143	0.188	£6,097
Discount rate	3.5% for costs and outcomes	0% for both	£704	0.328	£2,143
		6% for both	£1,061	0.146	£7,274
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£955	0.194	£4,916
HbA1c switch threshold	7.50%	8%	£1,518	0.245	£6,204
HbA1c metabolic drift	0.14% for canagliflozin	Canagliflozin set at 0.24%, as for SU	£1,470	0.021	£69,464
Patient baseline characteristics	RCT data	THIN data	£770	0.111	£6,915
Risk equations	UKPDS68	UKPDS82	£1,008	0.214	£4,715
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£764	0.264	£2,895
		Weight rebound occurs two years following treatment discontinuation	£762	0.262	£2,912
Therapy treatment effect	52 week NMA	26 week NMA	£934	0.206	£4,534
		RCT data	£944	0.316	£2,990
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£941	0.186	£5,064
		-0.014 (128)	£1,039	0.247	£4,197
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£950	0.194	£4,906
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus	£1,520	0.202	£7,529
Dyslipidaemia	Management of dyslipidaemia according to NICE CG67	All patients on simvastatin 80mg at baseline; no rescue medication implemented	£1,077	0.202	£5,342

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 81. Results of the scenario analysis for canagliflozin 300mg vs. DPP-4-i in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£576	0.031	£18,349
Time horizon	40 years	20 years	£534	0.032	£16,765
Discount rate	3.5% for costs and outcomes	0% for both	£615	0.040	£15,410
		6% for both	£485	0.026	£18,556
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£537	0.025	£21,351
HbA1c switch threshold	7.50%	8%	£785	0.050	£15,745
Patient baseline characteristics	RCT data	THIN data	£320	0.020	£16,031
Risk equations	UKPDS68	UKPDS82	£531	0.032	£16,573
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£495	0.054	£9,228
		Weight rebound occurs two years following treatment discontinuation	£488	0.049	£9,868
Therapy treatment effect	52 week NMA	26 week NMA	£568	0.032	£17,479
		RCT data	£552	0.045	£12,223
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£554	0.026	£21,359
		-0.014 (128)	£540	0.047	£11,580
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£535	0.040	£13,359
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus)	£565	0.027	£21,047
Dyslipidaemia	Management of dyslipidaemia according to NICE CG67	All patients on simvastatin 80mg at baseline; no rescue medication implemented	£667	0.034	£19,509

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 82. Results of the scenario analysis for canagliflozin 100mg vs. TZD in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£2,839	-0.003	Dominated
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	£2,802	-0.108	Dominated
HbA1c switch threshold	7.50%	8%	£3,950	-0.157	Dominated
HbA1c metabolic drift	0.14% for canagliflozin	Canagliflozin set to 0.07%, as for TZD	£2,354	0.003	£698,330
Patient baseline characteristics	RCT data	THIN data	£1,543	-0.051	Dominated
Risk equations	UKPDS68	UKPDS82	£2,856	-0.190	Dominated
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£2,730	-0.096	Dominated
Therapy treatment effect	52 week NMA	26 week NMA	£2,834	-0.166	Dominated
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£2,838	-0.171	Dominated
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	£2,751	-0.154	Dominated

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 83. Results of the scenario analysis for canagliflozin 300mg vs. TZD in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£3,356	-0.142	Dominated
HbA1c switch threshold	7.50%	8%	£4,626	-0.108	Dominated
HbA1c metabolic drift	0.14% for canagliflozin	Canagliflozin set to 0.07%, as for TZD	£2,997	0.028	£106,296
Patient baseline characteristics	RCT data	THIN data	£1,913	-0.048	Dominated
Risk equations	UKPDS68	UKPDS82	£3,379	-0.154	Dominated
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£3,186	-0.072	Dominated
Therapy treatment effect	52 week NMA	26 week NMA	£3,379	-0.155	Dominated
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£3,402	-0.155	Dominated

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 84. Results of the scenario analysis for canagliflozin 100mg vs. dapagliflozin in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£63	0.005	£8,674
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£20	0.056	Dominating
HbA1c switch threshold	7.50%	8%	£110	0.005	£22,200
Patient baseline characteristics	RCT data	THIN data	£10	0.001	£8,949
Risk equations	UKPDS68	UKPDS82	£46	0.005	£8,916
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£72	0.003	£24,697
Therapy treatment effect	52 week NMA	26 week NMA	£202	0.021	£9,656
Disutility from weight gain	0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£33	0.012	£2,792
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	£112	-0.001	Dominated
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years					

Table 85. Results of the scenario analysis for canagliflozin 300mg vs. dapagliflozin in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£625	0.009	£27,419
HbA1c switch threshold	7.50%	8%	£812	0.020	£39,786
Patient baseline characteristics	RCT data	THIN data	£327	0.004	£73,992
Risk equations	UKPDS68	UKPDS82	£568	0.026	£22,191
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£644	0.019	£33,368
Therapy treatment effect	52 week NMA	26 week NMA	£658	0.038	£17,177
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£620	0.010	£60,971
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years					

Table 86. Results of the scenario analysis for canagliflozin 100mg vs. GLP-1-a in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			-£2,424	-0.006	£50,005 #
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£2,498	0.007	Dominating
Therapy treatment effect	52 week NMA	26 week NMA	-£2,308	-0.022	£106,281 #
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	-£2,341	-0.030	£77,994 #

 # Canagliflozin 100mg is cheaper but less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin 100mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 87. Results of the scenario analysis for canagliflozin 300mg vs. GLP-1-a in dual therapy

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			-£1,892	0.005	£76,214 #
Therapy treatment effect	52 week NMA	26 week NMA	-£1,797	-0.005	£393,825 #

 # Canagliflozin 300mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin 300mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 88. Results of the scenario analysis for canagliflozin 100mg vs. DPP-4-i in triple therapy (Met+SU)

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			-£42	0.004	Dominating
Time horizon	40 years	20 years	-£33	0.017	Dominating
Discount rate	3.5% for costs and outcomes	0% for both	-£56	0.024	Dominating
		6% for both	-£48	0.017	Dominating
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£84	0.083	Dominating
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£7	0.023	£308
HbA1c switch threshold	7.50%	8%	-£115	0.020	Dominating
Patient baseline characteristics	RCT data	THIN data	-£38	0.013	Dominating
Risk equations	UKPDS68	UKPDS82	-£66	0.020	Dominating
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£93	0.022	Dominating
		Weight rebound occurs two years following treatment discontinuation	-£92	0.041	Dominating
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	-£61	0.018	Dominating
		-0.014 (128)	£4	0.043	£90
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	-£18	0.022	Dominating
Rescue therapy applied following failure of first therapy	Insulin rescue therapy is applied upon discontinuation of initial therapy	Additional rescue step of Met+SU+GLP-1 applied following discontinuation of initial therapy	£180	0.026	£7,028
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus)	-£85	0.022	Dominating
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m^2	Discontinue at eGFR<45mL/min/1.73m^2	-£36	0.023	Dominating

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 89. Results of the scenario analysis for canagliflozin 300mg vs. DPP-4-i in triple therapy (Met+SU)

Scenario	Base	New value	Incremental Costs	Incremental QALYs	ICER
Base case			£461	0.009	£13,287
Time horizon	40 years	20 years	£534	0.020	£26,459
Discount rate	3.5% for costs and outcomes	0% for both	£589	0.027	£21,708
		6% for both	£439	0.022	£20,005
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£491	0.025	£19,820
HbA1c switch threshold	7.50%	8%	£714	0.040	£17,977
Patient baseline characteristics	RCT data	THIN data	£155	0.020	£7,592
Risk equations	UKPDS68	UKPDS82	£462	0.029	£16,008
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£390	0.049	£8,018
		Weight rebound occurs two years following treatment discontinuation	£479	0.061	£7,887
Therapy treatment effect		RCT data	£666	0.032	£21,117
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£483	0.016	£30,729
		-0.014 (128)	£437	0.042	£10,519
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£570	0.028	£20,408
Rescue therapy applied following failure of first therapy	Insulin rescue therapy is applied upon discontinuation of initial therapy	Additional rescue step of Met+SU+GLP-1 applied following discontinuation of initial therapy	£500	0.032	£15,774
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus	£498	0.028	£18,102

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 90. Results of the scenario analysis for canagliflozin 100mg vs. GLP-1-a in triple therapy (Met+SU)

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			£-1297	0.001	Dominating
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£1,302	0.081	Dominating
HbA1c switch threshold	7.50%	8%	-£2,000	-0.009	£217,020 #
Patient baseline characteristics	RCT data	THIN data	-£867	0.000	Dominating
Risk equations	UKPDS68	UKPDS82	-£1,282	-0.004	£330,086 #
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£1,249	-0.003	£357,581 #
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	-£1,163	-0.010	£122,336 #
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m^2	Discontinue at eGFR<45mL/min/1.73m^2	-£1,249	-0.002	£509,837 #

 # Canagliflozin 100mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin100mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 91. Results of the scenario analysis for canagliflozin 300mg vs. GLP-1-a in triple therapy (Met+SU)

Scenario	Base case	Alternative value	Incremental Costs	Incremental QALYs	ICER
Base case			-£685	0.004	Dominating
HbA1c switch threshold	7.50%	8%	-£983	0.002	Dominating
Patient baseline characteristics	RCT data	THIN data	-£561	-0.002	£271,910 #
Risk equations	UKPDS68	UKPDS82	-£488	0.017	Dominating
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£574	0.011	Dominating
Disutility from weight gain	-0.0061 (Bagust 2005)	-0.0038 (Bagust 2005)	-£617	0.000	Dominating

 # Canagliflozin 300mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin300mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 92. Results of the scenario analysis for canagliflozin 100mg vs. Insulin LA in triple therapy (Met+SU)

Scenario	Base case	Alternative value	Scenario result		
			Incremental Costs	Incremental QALYs	ICER
Base case			£135	0.514	£263
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	£48	0.557	£87
HbA1c switch threshold	7.50%	8%	£265	0.505	£525
HbA1c metabolic drift	0.14% for canagliflozin; 0.15% for Insulin LA	Canagliflozin set to 0.15%, as for Insulin LA	£198	0.367	£538
Patient baseline characteristics	RCT data	THIN data	£70	0.250	£279
Risk equations	UKPDS68	UKPDS82	£81	0.489	£165
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£138	0.499	£275
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£107	0.476	£225
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years					

Table 93. Results of the scenario analysis for canagliflozin 300mg vs. Insulin LA in triple therapy (Met+SU)

Scenario	Base case	Alternative value	Scenario result		
			Incremental Costs	Incremental QALYs	ICER
Base case			£379	0.624	£607
HbA1c switch threshold	7.50%	8%	£671	0.601	£1,116
HbA1c metabolic drift	0.14% for canagliflozin; 0.15% for Insulin LA	Canagliflozin set to 0.15%, as for Insulin LA	£456	0.499	£913
Patient baseline characteristics	RCT data	THIN data	£22	0.315	£71
Risk equations	UKPDS68	UKPDS82	£394	0.574	£687
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£354	0.598	£591
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£351	0.563	£624
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years					

Table 94. Results of the scenario analysis for canagliflozin 100mg vs. DPP-4-i in triple therapy (Met+TZD)

Scenario	Base case	Alternative value	Scenario result		
			Incremental Costs	Incremental QALYs	ICER
Base case			£7	0.007	£1,095
Time horizon	40 years	20 years	£71	0.014	£5,178
Discount rate	3.5% for costs and outcomes	6% for both	-£3	0.011	Dominating
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£44	0.045	Dominating
HbA1c switch threshold	7.50%	8%	£8	0.014	£606
Patient baseline characteristics	RCT data	THIN data	£20	0.011	£1,806
Risk equations	UKPDS 68	UKPDS82	-£68	0.008	Dominating
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£6	0.039	Dominating
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£9	0.006	£1,517
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	-£38	0.008	Dominating

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 95. Results of the scenario analysis for canagliflozin 300mg vs. DPP-4-i in triple therapy (Met+TZD)

Scenario	Base case	Alternative value	Scenario result		
			Incremental Costs	Incremental QALYs	ICER
Base case			£691	0.032	£21,430
Time horizon	40 years	20 years	£687	0.027	£25,754
Discount rate	3.5% for costs and outcomes	6% for both	£591	0.025	£23,684
HbA1c switch threshold	7.50%	8%	£913	0.045	£20,401
Patient baseline characteristics	RCT data	THIN data	£215	0.014	£15,169
Risk equations	UKPDS 68	UKPDS82	£694	0.033	£21,195
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£604	0.063	£9,640
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£661	0.014	£47,579

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 96. Results of the scenario analysis for canagliflozin 100mg vs. DPP-4-i in add on to insulin therapy

Scenario	Base case	Alternative value	Scenario result		
			Incremental Costs	Incremental QALYs	ICER
Base case			£-13	-0.010	£1,340 #
Time horizon	40 years	20 years	£28	-0.010	Dominated
Discount rate	3.5% for costs and outcomes	0% for both	-£17	-0.019	£894 #
		6% for both	£39	-0.008	Dominated
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	£19	0.037	£503
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£96	-0.004	Dominated
HbA1c switch threshold	7.50%	8%	£67	-0.018	Dominated
		Treatment switch once HbA1c >9%	-£40	-0.065	£603
Patient baseline characteristics	RCT data	THIN data	-£16	-0.064	£253 #
Risk equations	UKPDS68	UKPDS82	£66	-0.012	Dominated
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£9	0.004	£1,965
		Weight rebound occurs two years following treatment discontinuation	-£19	0.014	Dominating
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£59	-0.005	Dominated
		-0.014 (128)	-£20	-0.004	£4,575
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£83	-0.006	Dominated
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart; with insulin intensification, add 0.5 iU/kg Glargine (Lantus)	£77	-0.006	Dominated
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	-£22	0.002	Dominating

 # Canagliflozin 100mg is both cheaper and less effective than DPP-4-i, therefore the ICER is for DPP-4-i to replace canagliflozin100mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 97. Results of the scenario analysis for canagliflozin 300mg vs. DPP-4-i in add on to insulin therapy

Scenario	Base case	Alternative value	Scenario results		
			Incremental Costs	Incremental QALYs	ICER
Base case			£322	0.040	£7,975
Time horizon	40 years	20 years	£325	0.042	£7,701
Discount rate	3.5% for costs and outcomes	0% for both	£334	0.050	£6,702
		6% for both	£341	0.040	£8,626
Treatment discontinuation rate	RCT data	Comparator discontinuation rate set at that of the canagliflozin arm	£316	0.054	£5,828
HbA1c switch threshold	7.50%	8%	£471	0.023	£20,648
		Treatment switch once HbA1c >9%	£536	-0.052	Dominated
Patient baseline characteristics	RCT data	THIN data	£59	-0.045	Dominated
Risk equations	UKPDS68	UKPDS82	£298	0.037	£7,974
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£195	0.055	£3,541
		Weight rebound occurs two years following treatment discontinuation	£228	0.069	£3,316
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£374	0.039	£9,486
		-0.014 (128)	£376	0.056	£6,690
Disutility values for macro-vascular complications	Dataset from Bagust et al. 2005 (130)	Dataset from Clarke et al. 2002 (127)	£297	0.039	£7,585
Insulin choice for rescue therapy	Start on 0.5 iU/kg glargine; upon insulin intensification, add 0.5 iU/kg insulin aspart	Start on 0.5 iU/kg insulin aspart with insulin intensification, add 0.5 iU/kg Glargine (Lantus)	£402	0.047	£8,484

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 98. Results of the scenario analysis for canagliflozin 100mg vs. dapagliflozin in add on to insulin therapy

Scenario	Base case	Alternative value	Scenario results		
			Incremental Costs	Incremental QALYs	ICER
Base case			-£72	0.003	Dominating
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£21	0.063	Dominating
HbA1c switch threshold	7.50%	8%	-£55	0.005	Dominating
		Treatment switch once HbA1c >9%	£18	0.005	£3,698
Patient baseline characteristics	RCT data	THIN data	-£9	0.011	Dominating
Risk equations	UKPDS68	UKPDS82	-£31	0.004	Dominating
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£9	0.014	Dominating
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£46	0.007	£6,198
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m^2	Discontinue at eGFR<45mL/min/1.73m^2	£38	0.022	£1,776

 # Canagliflozin 100mg is both cheaper and less effective than dapagliflozin, therefore the ICER is for dapagliflozin to replace canagliflozin100mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 99. Results of the scenario analysis for canagliflozin 300mg vs. dapagliflozin in add on to insulin therapy

Scenario	Base case	Alternative value	Scenario results		
			Incremental Costs	Incremental QALYs	ICER
Base case			£327	0.055	£5,992
HbA1c switch threshold	7.50%	8%	£427	0.056	£7,577
		Treatment switch once HbA1c >9%	£647	0.028	£23,413
Patient baseline characteristics	RCT data	THIN data	£132	0.009	£14,867
Risk equations	UKPDS68	UKPDS82	£345	0.057	£6,084
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	£237	0.066	£3,582
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	£385	0.056	£6,880

ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 100. Results of the scenario analysis for canagliflozin 100mg vs. GLP-1-a in add-on to insulin therapy

Scenario	Base case	Alternative value	Scenario analysis		
			Incremental Costs	*Incremental QALYs*	*ICER*
Base case			-£836	-0.065	£12,915 #
Dose modification	No dose modification applied	Dose increase from 100mg to 300mg if HbA1c>7.5% in first year, and 100mg tolerated	-£834	-0.019	£44,237 #
HbA1c switch threshold	7.50%	8%	-£1,427	-0.089	£16,030 #
		Treatment switch once HbA1c >9%	-£2,811	-0.118	£23,898 #
Patient baseline characteristics	RCT data	THIN data	-£947	-0.081	£11,672 #
Risk equations	UKPDS68	UKPDS82	-£799	-0.067	£11,869 #
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£754	-0.067	£11,193 #
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	-£848	-0.068	£12,523 #
Renal discontinuation threshold	Discontinue at eGFR<60mL/min/1.73m2	Discontinue at eGFR<45mL/min/1.73m2	-£820	-0.059	£13,820 #

 # Canagliflozin 100mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin100mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

Table 101. Results of the scenario analysis for canagliflozin 300mg vs. GLP-1-a in add-on to insulin therapy

Scenario	Base case	Alternative value	Scenario analysis		
			Incremental Costs	Incremental QALYs	ICER
Base case			£-526	-0.015	£35,575 #
HbA1c switch threshold	7.50%	8%	-£1,151	-0.048	£23,960 #
		Treatment switch once HbA1c >9%	-£2,078	-0.108	£19,242 #
Patient baseline characteristics	RCT data	THIN data	-£756	-0.078	£9,656 #
Risk equations	UKPDS68	UKPDS82	-£482	-0.014	£35,605 #
BMI rebound on treatment discontinuation	Full weight rebound	No rebound	-£604	-0.016	£38,933 #
Disutility from weight gain	-0.0061 per BMI point gained (130)	-0.0038 per BMI point (130)	-£507	-0.016	£32,169 #

 # Canagliflozin 300mg is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a to replace canagliflozin300mg
ICER, incremental cost-effectiveness ratio; NMA, Network Meta-Analysis; QALYs, quality-adjusted life years

7.7.10 What were the main findings of each of the sensitivity analyses?

The economic modelling estimates of the changes in costs and QALYs that could be expected to result from canagliflozin treatment in the dual, triple and add-on to insulin therapy of T2DM are for the most part small in magnitude across the different comparisons made. This is consistent with previous submissions made to NICE. (59) It might be expected that the ICER, as a ratio made up of two small numbers, could be very sensitive to small changes in either the numerator or denominator. However, the ICERs in the vast majority of cases in fact remain cost-effective under the many DSAs applied and scenarios explored.

PSA confirmed that comparisons where the incremental changes in costs and QALYs were small (e.g., canagliflozin 100mg vs. DPP-4-i in dual therapy and triple therapy (metformin + SU)) naturally exhibited greater uncertainty. Estimates were spread across all four quadrants of the cost-effectiveness plane and the probabilities of cost-effectiveness were 54.5 and 55.6%, respectively, at a WTP of £20,000/QALY. In contrast, comparisons against SU in dual therapy and for the canagliflozin 300mg dose exhibited less uncertainty.

The multiple comparisons of canagliflozin 100mg and 300mg against other alternative treatments do show that canagliflozin brings incremental value to the treatment of these patients, and the DSA, scenario analyses and PSA show that this incremental gain is consistent across a broad set of conditions.

Modelling the dose increase from the 100mg to 300mg was specifically explored as a scenario rather than being incorporated into the base case modelling due to the late finalisation of the posology in the SmPC (Appendix 1 in Section 10.1). The use of canagliflozin in clinical practice in the UK will incorporate a dose increase step in those patients requiring greater glycaemic control and therefore the dose modification scenario is of particular relevance. Economic modelling for the dose modification scenario showed that this step improved the cost-effectiveness in each line of therapy and against each comparator (a total of 12 comparisons), with the exception of dual therapy vs. SU (where the ICER changed to being slightly less cost-effective (from £1,537 to £1,721). For all comparisons in which a dose increase was applied, in dual, triple and in combination with insulin therapy, canagliflozin was the more cost-effective option, with the exception of comparison against TZD, which continued to dominate canagliflozin 100mg. Crucially, in combination with insulin, where the base case ICERs vs. DPP-4-i or GLP-1-a were not cost-effective, the dose modification step sufficiently improved the ICER to the extent that canagliflozin 100mg is estimated to be cost-effective vs. DPP-4-i or GLP-1-a in combination with insulin (Table 96 and Table 100). The conclusion of this scenario analysis is therefore that dose intensification schedule from 100mg to 300mg is a cost-effective strategy. When compared to discrete analyses of the two doses, the ICERs in almost all cases did not increase and indeed tended to decrease.

There are a number of assumptions within the base case that might be considered conservative. Due to a lack of clinical data for comparators, the triple therapy modelling has used the 26 week NMA. The clinical trial (DIA3006) does, however, show that at 52 weeks, the reduction in HbA1c is greater for canagliflozin compared to sitagliptin than at 26 weeks (an incremental difference of canagliflozin 300mg over sitagliptin of -0.23 at 26 weeks compared with -0.37 at 52 weeks). Secondly, it is

assumed that patient bodyweight immediately returns to baseline upon discontinuation of canagliflozin. This immediate regain of weight is less plausible than a gradual weight gain. In both these respects, the base case assumption is more conservative than may be the reality.

7.7.11 What are the key drivers of the cost-effectiveness results?

The relative contribution of parameters to the cost-effectiveness differed across the different comparisons. Some factors were universally important (e.g., therapeutic effects on biomarkers and their change over time), whereas other factors only gained prominence in comparisons where there was a significant difference in that factor between the two therapies compared (e.g., weight assumptions had far more impact in comparisons of canagliflozin to SU than to dapagliflozin and GLP-1-a).

A consistent finding across DSA and scenario modelling was the paramount importance of HbA1c drift on cost-effectiveness, as this has a direct influence on the duration of effectiveness of a therapy (i.e. time to reach the threshold of HbA1c of 7.5%. As described in section 7.3.1, and two year data for canagliflozin shown in Section 6.5.3.1.2, this assumption is considered reasonable.

The greater HbA1c lowering associated with canagliflozin, especially the 300mg dose, and the lower metabolic drift versus SU, combined to generate QALYs and cost offsets, both due to reductions in micro- and macro-vascular co-morbidities but also a lengthening of the time to insulin rescue and associated weight gain and increases in hypoglycaemic events. As these events often occur after many years, however, their impact is greatly lessened by discounting.

In many comparisons, especially for the canagliflozin 300mg dose, cost-savings are derived from the delay to start of insulin therapy. The disutility from weight gain and hypoglycaemic events associated with insulin therapy also contributes to delay to insulin as a driver of cost-effectiveness. This is borne out by the comparisons of canagliflozin 100mg and 300mg vs. Insulin LA being robustly cost-effective in favour of canagliflozin.

In a number of comparisons, a cost difference is seen for the management of dyslipidaemia, often in favour of canagliflozin. This result is a feature of how ECHO-T2DM manages the dyslipidaemia of the hypothetical patient cohort. The relatively high cost compared for example with the management of hypertension in the model, results from the combination of the stringent thresholds for treatment from NICE clinical guidelines (148) and the high baseline lipid profile for the patients. When correcting for management of dyslipidaemia, the ICERs were not greatly affected. For canagliflozin vs. SU in dual therapy, the changes were from £1,537 to £2,286 and £4,899 to £5,342, for the 100mg and 300mg respectively (Table 78 and Table 80). For canagliflozin 300mg vs. DPP-4-i, the ICER increased from £18,349 to £19,509 (Table 81). For the 100mg dose vs. DPP-4-i in dual therapy, the ICER changed to a relatively greater extent, from £97 to £8,809 (Table 79), but this seemingly large swing is as a result of the numerator and denominator in the base case ICER being very small. In addition, scenario analysis using the macro-vascular and mortality risk equations from the revised UKPDS Outcomes Model (UKPDS82) , which uses LDL and HDL lipid values separately, rather than Total-to-HDL cholesterol ratio as included in the original UKPDS Outcomes Model (UKPDS68, has little impact on the ICER (Table 79 and Table 81). (133;144)

7.8 Validation

7.8.1 **Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.**

Naturally, the usefulness of a model depends upon its ability to predict accurately the actual health and economic outcomes of patients in a real-life treatment setting. The latest joint International Society for Pharmacoeconomics and Outcomes Research/ Society for Medical Decision Making (ISPOR/SMDM) good research guidelines describe five principal forms of validation.(135;136)

- Face validity is the extent to which a model, its assumptions, and the applications for which it is used accurately reflect current scientific evidence (as judged by experts).
- Verification examines the extent to which the model calculations are correctly implemented.
- Cross-validation (often called convergent validity) consists of simulating identical scenarios with different models and comparing the results and examining differences.
- Simulating scenarios based on actual events that have occurred and assessing concordance is termed external validation, and called ‘dependent’ if the source data were used in model construction and ‘independent’ otherwise.
- Finally, predictive validation consists of external validation in which the study has not yet been conducted, ensuring that the external validation is independent.

We followed the ISPOR/SMDM principles of good practice, with the exception of the impractical prediction in advance of the outcomes of a trial not yet conducted, and the actions are described below. (131)

Face Validity

The face validity of ECHO-T2DM has been evaluated throughout the model development process and upon completion in several ways. We obtained clinical expert feedback during the design and programming phase of the key model features, and we have presented the model at numerous conferences to experts in T2DM modelling, including the Fifth and Sixth Mount Hood. (200;201)

Verification

The model has been thoroughly tested and de-bugged, including artificial simulations designed to reveal errors in both logic and programming (i.e., so-called ‘stress tests’). Idiosyncratic results were investigated and any identified errors in programming or logic were corrected.

Cross-validation

We have assessed cross-validity by replicating the intensive vs. conventional blood glucose control analysis conducted and published by the NIH using the seminal model of T2DM and then examining the degree of concordance between the two sets of predictions. (159;160) Specifically, we loaded the model with the same distributions of baseline patient characteristics, applied identical treatment effects and assumptions about drift (annual evolution in subsequent years) in biomarker values over time, simulated for the same lifetime horizon, and then extracted the same set of predicted cumulative incidence values. The outcomes are presented in. (131) The outcomes tracked generally well, though there was a small tendency for ECHO-T2DM to generate higher estimates. But with any true cross-validation exercise, one cannot conclude which (if either) of the models accurately predicted reality.

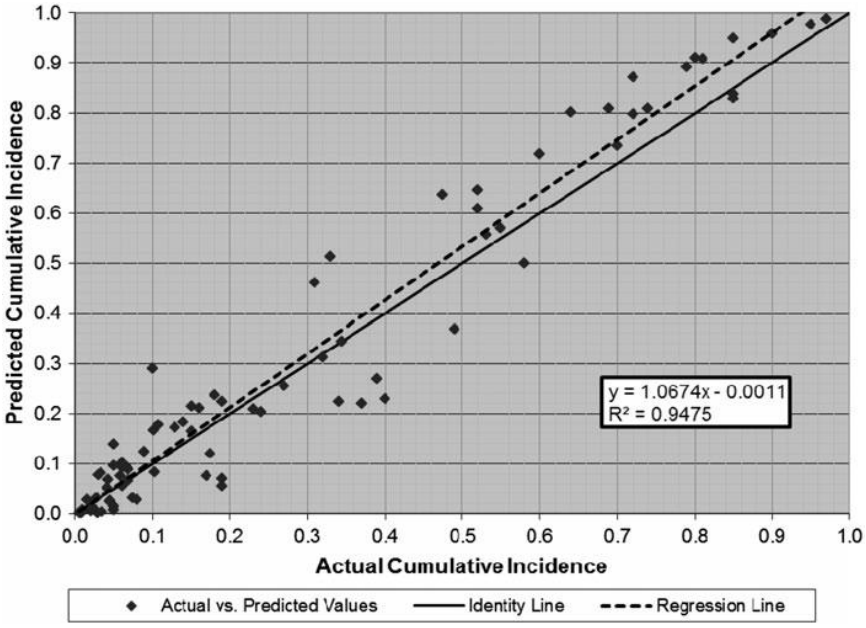
In addition, ECHO-T2DM has been subjected to cross-validation as part of the Fifth and Sixth Mount Hood Challenges, in which a large number of modelling groups predicted end-points for a number of standardised scenarios. (200;201) Like each of the other models, ECHO-T2DM predicted the results of some of the study trials closely and others less closely. Overall, regression trend lines through the scatterplot fit well.

External validation (dependent and independent)

The external validity of ECHO-T2DM was evaluated by simulating the key features of a broad set of clinical trials and then compared the model predictions with the corresponding actual observed outcomes for a variety of clinical end-points. (131) The choice of studies is important and, for a multi-application model, should include data from differing settings. Published studies were chosen for validation based on importance, relevance, and replicability (i.e., the publicly available data on baseline patient characteristics and outcomes were sufficiently comprehensive to allow modelling). With inspiration from Eddy et al (2003), Palmer et al. (2013), and The Mount Hood 4 Modelling Group (139;201;202), five published studies were selected, as was the NIH cross-validation study mentioned above.

Two of these studies were used in construction of the model and form a sub-set of dependent external validation studies; the UK Prospective Diabetes Study (UKPDS) is the source of macro-vascular and mortality risks, and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is the source of many of the micro-vascular transition probabilities.(203) The other three studies were not part of model construction, and formed the independent external validation sub-set (204;205) which investigated the role of lipid-lowering therapy in preventing CVD in a cohort of T2DM patients, was recommended by The Mount Hood 4 Modelling Group (202); MICROHOPE, a large interventional trial of ACE Inhibitors in T2DM patients with high risk of CVD, was used in validation of ARCHIMEDES; and the Osaka study of T2DM survival, an observational 15-year study of nearly 2000 patients in Japan , was used in validation of CDM. (139;142;202;206-208)

The results are summarised in the following figure, where the predicted values are represented on the vertical axis and the actual observed values on the horizontal axis. The results track well and the coefficient of determination (R^2) indicates that almost 95% of the variation in the predictions can be explained by variation in the actual values. While the slope is greater than the theoretical value of 1, the null hypothesis of concordance could not be statistically rejected with a formal F test.



ECHO-T2DM has also been validated against the recent ADVANCE, ACCORD and ASPEN trials as part of the fifth Mt. Hood Challenge, observational data from Kaiser Permanent Northwest (KPNW), and the Swedish NDR as part of the Sixth Mt Hood. Using conventional methods, ECHO-T2DM simulated the treatment, progression, and patient outcomes observed in important clinical trials with accuracy consistent with other well-accepted models. More detailed is provided in the ECHO-T2DM Technical Report. (132;142;200)

Internal validation exercise

To assess the importance of stochastic variability in the case in which small changes vs. comparators were observed, the comparison of canagliflozin 100mg vs. DPP-4-i in dual therapy (which had limited treatment effect differences) was simulated 10 times with identical input parameters. The total costs and total QALY's varied from simulation to simulation, but the degree of variation was quite small in relative terms (Table 102). The coefficients of variation, in fact, were less than 1% in each case. The incremental costs and incremental QALYs were also fairly stable, though the much lower incremental differences were associated with larger coefficients of variation, approximately 0.54 for costs and 0.21 for QALYs (which can still be considered relatively low). The coefficient of variation for the ICER was 0.57, and importantly the ICER was £6,533 or less in each of the 10 simulations. This engenders confidence that, even in cases with modest incremental benefits, stochastic variability does not override the signal generated in the model simulations.

Table 102. Absolute and incremental costs and QALYs for 10 replications of a single comparison, canagliflozin 100mg vs. DPP-4-i in dual therapy

Model run #	Absolute costs Cana 100mg	Absolute costs DPP-4-i	Absolute QALYs cana	Absolute QALYs DPP-4-i	Incremental cost change	Incremental QALY change	ICER
1	£26,102	£26,100	8.94	8.93	1	0.013	£97
2	£26,055	£26,001	8.95	8.93	54	0.013	£4,133
3	£25,871	£25,807	8.92	8.91	64	0.010	£6,533
4	£26,034	£25,996	8.94	8.93	37	0.015	£2,424
5	£26,057	£26,010	8.95	8.93	46	0.015	£3,114
6	£25,936	£25,891	8.92	8.91	46	0.013	£3,414
7	£25,917	£25,894	8.93	8.92	23	0.009	£2,538
8	£26,058	£26,025	8.94	8.92	34	0.017	£1,993
9	£25,967	£25,946	8.93	8.92	21	0.009	£2,374
10	£26,062	£25,987	8.94	8.92	75	0.014	£5,289

Modelling cross-validation exercise

The results of preliminary ECHO-T2DM simulation results were cross-validated using CDM (v 8.5; IMS Health, Danbury, CT, USA) to simulate a set of five standardised canagliflozin treatment comparisons (and 11 scenario analyses each) independently. Because aligning the input sets as closely as possible for two distinct models required some compromise and because direct trial data rather than the NMA for therapeutic effect were used, the results do differ numerically (but not directionally or qualitatively) from the ECHO-T2DM presented in this submission (Section 7.7.1). When comparing the results across the 12 versions of each of the treatment comparisons, net monetary benefit (NMB) was used to circumvent discontinuity problems that occurred in cases where canagliflozin dominated the comparator (more QALYs at lower cost). A monetary value of £20,000 per QALY gained was assumed.

The models naturally generated different quantitative results (Table 103). Estimates of total costs, LY's, and QALY's, for example, were consistently higher in the CDM simulations than in the ECHO-T2DM simulations, primarily related to differences in the dosage of rescue insulin therapy (CDM applies a fixed dose, while ECHO-T2DM titrates as needed to maintain control), in non-diabetes-related mortality risks (CDM uses a UK life table while ECHO-T2DM uses UKPDS risk equations), and in QALY's (CDM uses utilities approach while ECHO-T2DM uses disutilities).

The incremental differences between canagliflozin and the comparator followed a clear pattern. CDM generated larger gains in life expectancy and (with one exception) greater cost savings or smaller cost increases. CDM also generated larger gains in QALYs versus sitagliptin, though ECHO-T2DM estimated greater QALY gains vs. SU, largely attributable to using the ADOPT upward drift in HbA1c for SU and differences in time on agent. CDM limited time on canagliflozin and the comparator to 2 to 3 years, whereas 50%, 25%, and 2% of the patients were still taking canagliflozin at 5, 10, and 20 years, respectively, in the ECHO-T2DM simulations.

Despite these quantitative differences, the qualitative results were remarkably robust. Both doses of canagliflozin were cost-effective (indeed cost-saving in many cases) in dual therapy for both models, irrespective of comparator, for both models, which was

robust in sensitivity analysis. In triple therapy, CDM found canagliflozin was to be cost-saving, while ECHO-T2DM estimated an ICER on the border of cost-effectiveness (£20,908 per QALY gained). Sensitivity analysis suggested that the ECHO-T2DM estimate may be conservatively high and that the CDM estimate may be optimistic, an artefact of the assumptions required to achieve model alignment.

In particular, three differences were important in explaining the results. Time on agent before discontinuation was shorter in the CDM simulations, though the differences between agents may have been greater because of model alignment (magnifying the benefits). Differences in HbA1c and SBP lowering by agent were reversed immediately in the ECHO-T2DM simulations, but were eliminated gradually in the CDM simulations which prolonged two of canagliflozin's key benefits. Finally, the difference in how QALY's are applied are likely to affect the results, though it is not entirely obvious in which direction.

In summary, while there were some quantitative differences in the ICERs generated, the results of the models were qualitatively similar, indicating a high likelihood that canagliflozin is cost-effective in the comparisons modelled. A wide range of sensitivity analyses confirmed this finding.

Table 103. Summary of base case results for CDM and ECHO-T2DM modelling comparisons

Comparison	**DIA3006: canagliflozin 100mg vs. DPP-4-i in dual therapy**	
Model	CDM	ECHO
Incremental cost (£)	-£266	-£14
Incremental QALYs	0.027	0.011
ICER	Dominant	Dominant
NMB	£806	£244
	DIA3006: canagliflozin 300mg vs. DPP-4-i in dual therapy	
Incremental cost (£)	-£212	£328
Incremental QALYs	0.072	0.034
ICER	Dominant	£9,654
NMB	£1,652	£352
	DIA3009: canagliflozin 100mg vs. SU in dual therapy	
Incremental cost (£)	£381	£265
Incremental QALYs	0.078	0.257
ICER	£4,907	£1,031
NMB	£1,179	£4,874
	DIA3009: canagliflozin 300mg vs. SU in dual therapy	
Incremental cost (£)	£480	£901
Incremental QALYs	0.101	0.280
ICER	£4,740	£3,215
NMB	£1,540	£4,703
	DIA30015 - canagliflozin 300mg vs. DPP-4-i in triple therapy (Met+SU)	
Incremental cost (£)	-£886	£600
Incremental QALYs	0.265	0.029
ICER	Dominant	£20,908
NMB	£6,186	-£26
ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit		

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- **Individual utilities for health states and patient preference.**
- **Subgroups based solely on differential treatment costs for individuals according to their social characteristics.**
- **Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).**

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.**

Pre-specified sub-group analyses were undertaken to assess the differences in change in HbA1c between canagliflozin and comparators (sitagliptin and glimepiride) or placebo according to different baseline patient and disease characteristics (Table 15).

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

The patient subgroup of interest is those patients with an HbA1c exceeding 9% (75 mmol/mol) at baseline.

7.9.3 **Please describe how the statistical analysis was undertaken.**

Sub-group analyses were conducted using the same statistical methods as described in table 14 6.3.6]. Due to the paucity of data on the efficacy of other AHAs in this subgroup of patients, analysis and economic modelling was only conducted for the comparisons for which direct comparative data were generated in the canagliflozin clinical trial programme, i.e. for canagliflozin vs. DPP-4-i and SU in dual therapy, and against DPP-4-i in triple therapy combination with metformin plus SU.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

In dual therapy of patients with baseline HbA1c>9%, canagliflozin 100mg is marginally more effective and cost-saving than DPP-4-i and is thus dominant (Table 104). Canagliflozin 100mg also dominates SU, but the gain in QALYs is more substantial. Canagliflozin 300mg is cost-effective when compared to SU and to DPP-4-i in this population, with ICERs of £1,001 and £1,029 per QALY, respectively.

In comparison, the base case ICERs for canagliflozin 100mg vs. SU and DPP-4-i are £1,537 and £97, respectively (Table 62). For canagliflozin 300mg the ICERs vs. SU and DPP-4-i are £4,899 and £18,349, respectively (Table 63). This suggests that canagliflozin is more cost-effective in this subgroup than SU and DPP-4-i in dual therapy.

Table 104. Incremental cost-effectiveness results for canagliflozin 100mg and 300mg vs. DPP-4-i in dual therapy in patients with baseline HbA1c>9%

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
SU	£30,457	13.592	7.924				
Cana 100mg	£30,285	13.596	8.155	-£172	0.004	0.232	Dominating
DPP-4-i	£33,226	13.583	7.588				
Cana 100mg*	£33,169	13.586	7.624	-£56	0.003	0.037	Dominating
SU	£30,581	13.653	7.913				
Cana 300mg*	£30,816	13.661	8.147	£234	0.008	0.234	£1,001
DPP-4-i	£33,216	13.584	7.602				
Cana 300mg*	£33,326	13.597	7.709	£110	0.013	0.107	£1,029

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

In triple therapy (combination with Met+SU) of patients with baseline HbA1c>9%, canagliflozin 100mg is marginally less effective but cost-saving than DPP-4-i and is therefore not cost-effective, with the ICER for DPP-4-i to replace canagliflozin 100mg being £1,200/QALY. In contrast, canagliflozin 300mg is cost-effective when compared to DPP-4-i in this population, with an ICER of £699 (Table 105). Both base case comparisons are cost-effective, with the canagliflozin 100mg dose dominating DPP-4-i (Table 68) and canagliflozin 300mg has an ICER of £13,287 (Table 69). These results suggest that canagliflozin 300mg but not 100mg is differentially more cost-effective in this subgroup of patients with baseline HbA1c >9%..

Table 105. Incremental cost-effectiveness results for canagliflozin vs. DPP-4-i in triple therapy (Met+SU) in patients with baseline HbA1c>9%

Comparator	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
DPP-4-i	£31,502	13.348	5.070				
Cana 100mg*	£31,390	13.362	4.978	-£112	0.014	-0.092	£1,220 #
DPP-4-i	£31,604	13.458	5.300				
Cana 300mg*	£31,759	13.465	5.523	£155	0.007	0.222	£699

 # Canagliflozin 100mg is both cheaper and less effective than DPP-4-i, therefore the ICER is for DPP-4-i ***to replace*** *canagliflozin 100mg*
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DPP-4-i, dipeptidyl peptidase 4 inhibitor

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

As reported in the subgroup analyses in Section 6, the response to canagliflozin by baseline BMI was consistent, and so given the lack of differential effectiveness for canagliflozin, no further assessment of the cost-effectiveness by BMI was considered.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The systematic review of the literature described in Section 7.1.1 did not identify any previously published cost-effectiveness analysis for canagliflozin. A *de novo* economic analysis was therefore conducted, as is standard practice for economic evaluations of chronic and progressive diseases such as T2DM. The drivers of cost-effectiveness identified in the current modelling application were consistent with previous modelling exercises for other therapies, in particular the magnitude of improvements in HbA1c, SBP, BMI and hypoglycaemic events.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The canagliflozin economic analyses can be considered relevant for the patients identified in Section 5, with the exception of dual therapy in combination with SU which, as stated previously, is not expected to be commonly used. There was no subgroup of patients identified in the economic analysis where canagliflozin demonstrated differentially inferior cost-effectiveness.

In the add-on to insulin, the application of dose increase of canagliflozin 100mg to 300mg increased QALY gains so that a strategy of starting patients on 100mg canagliflozin and switching to 300mg during the first year if tighter glycaemic control was required was demonstrably cost-effective when compared to either DPP-4-i or dapagliflozin.

In patients treated with insulin in combination with other AHAs, the need for more effective treatment is higher, increasing the prominence of the canagliflozin 300mg results and canagliflozin 100mg with the dose modification scenario results. Also, these patients are likely to have a lower renal function thus making canagliflozin, with its discontinuation threshold of <45mL/min/1.73m^2 the preferential choice over dapagliflozin, which is discontinued at <60mL/min/1.73m^2. (209)

Analysis of the subgroup of patients with high baseline HbA1c (>9%; Section 7.9.4) shows that both doses of canagliflozin are differentially more cost-effective than SU and DPP-4i in dual therapy compared to the base case. In triple therapy, canagliflozin 300mg but not 100mg is differentially more cost-effective than DPP-4-i in a subgroup of patients with baseline HbA1c>9% compared to the base case.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the evaluation

- The evaluation was informed by data from the largest trial programme in T2DM to date, including three head to head RCTs, enrolling more than 10,000 patients.
- A large NMA was performed to facilitate consistent comparisons with comparators not included in the clinical trial programme (and for which head-to-head data are not available). For consistency, the NMA was used in favour of the trial data even for comparators included in the trials.
- A validated and previously published model was used for the canagliflozin modelling analysis. A large sub-set of the modelling analyses were cross-validated by running them with another model of T2DM, CDM (CORE model). (142) The additional results using CDM were directionally consistent and showed canagliflozin was cost-effective when compared to SU or DPP-4-i across all scenarios tested. The ECHO-T2DM results were more conservative across many of the scenarios.
- A comprehensive set of modelling analyses were conducted, including over 900 comparisons against six different agents in four different lines of therapy, and in the number of DSAs and scenarios conducted, allowing for a broad assessment of the cost-effectiveness of canagliflozin in T2DM.
- The unit costs, resource use and disutility weights used to load the simulations are consistent with previous models and relevant for the UK setting. Where there were data gaps, e.g. disutility for GMI and UK-specific baseline patient characteristics, research was conducted to identify input values. Sensitivity analyses were conducted where alternative data were available.

- From the perspective of canagliflozin, the analyses were intentionally conservative in a number of aspects. In particular, a number of arguably minor AE's specific to the class of SGLT-2 inhibitors were included, but most AEs tied to other drug classes (with the exception of nausea and vomiting for the GLP-1-a's) were excluded. Limitation of the NMA to 26-week data in triple therapy (in combination with metformin and SU) reduced the difference in HbA1c lowering between canagliflozin 300mg and sitagliptin 100mg by about 50% vs. the 52-week difference in the DIA3015 trial.

Collectively, these strengths speak to the high likelihood that the benefits and cost-effectiveness of canagliflozin have not been overestimated and that the modelling results for both doses are credible and robust.

Limitations of the evaluation

- As with other economic evaluations of T2DM interventions, the main limitation is the need to extrapolate short-term trial data (maximum two years) over a 40 year time horizon using economic modelling techniques. In particular, assumptions must be made about drug durability, treatment intensification, and the consequences (bio-marker rebound) of discontinuing agents.
- While direct comparative trial data are available for both doses for comparisons with SU and DPP-4-i in dual and for the canagliflozin 300mg vs. DPP-4i in triple therapy, there are no direct comparisons against GLP-1-a. There are, moreover, no direct comparative data in add-on to insulin. A NMA was performed to address these data gaps and ensure consistency across the different comparisons
- ECHO-T2DM is a stochastic micro-simulation model, capturing both first and second order uncertainty. Relatively large numbers of replications were performed to minimise the first order uncertainty and ensure convergence of the second order uncertainty. In order to complete more than 900 simulations, each requiring upwards of 12 hours to run, endlessly large sample sizes were not feasible. Some degree of first order uncertainty is noticeable in some sensitivity analyses of the same scenario, manifest as slight differences in the distribution of mean patient characteristics leading to difference in the absolute magnitudes of life-years and QALY's. However, this did not impact the incremental differences in costs or QALY's. Second order uncertainty was larger when using the base case assumption of NMA efficacy than in the sensitivity analyses based on actual trial results, an artefact of building networks.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

It has already been stated that a pragmatic decision was made to conduct a focussed rather than exhaustive set of analyses (Section 7.6.1). While additional comparisons could be selected for which to conduct the full DSAs and scenario analyses, it is not considered that these additional analyses would add to what is known about the cost-effectiveness of canagliflozin.

Analyses using data from real life treatment, and conducting analyses using treatment thresholds for HbA1c, dyslipidaemia and hypertension based on real life

databases would be interesting to compare with the modelling results based on RCT data, and using assumptions of treatment based on clinical guidelines.

Other analyses that might be conducted in the future include use of longer term data once trial data matures, e.g. 104 week RCT data in dual therapy for DIA3009. Also, further examination of cost-effectiveness of other therapies with the updated UKPDS could be conducted. (144)

To further examine the variation observed in the model, it could be possible to re-run the base case analyses with a very large number of hypothetical patients and cohort replications, in order to ensure that first order uncertainty is all but eliminated and that the second order has converged. As stated in Section 7.8.1, however, running the comparisons with larger replications is very unlikely to change the result generated.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

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

In 2011, there were 2.8 million people diagnosed with diabetes in the UK(40); however, it was estimated that roughly 850,000 of T2DM remained undiagnosed. (43) With an average prevalence of 4.57%, it is anticipated that by 2025 five million people will have diabetes in the UK. (40;43) Approximately 90% of adults currently diagnosed with diabetes have T2DM. (43) The incidence of diagnosed T2DM and prevalence has increased markedly and consistently for more than a decade in the UK.(210;211) The proportion of very early onset T2DM continues to increase as a proportion of those diagnosed and these people have a greater opportunity to develop long-term complications. (211)

Not all patients receive anti-diabetic therapy immediately after diagnosis. Initial management of T2DM typically involves lifestyle interventions, although as the condition progresses glucose-lowering agents may be required to control blood glucose levels. It is estimated that 80% of diagnosed diabetic patients receive anti-diabetic therapy. (186)

As described in Section 2.5, most T2DM patients start treatment on a monotherapy; once blood glucose control remains or becomes inadequate it is recommended to add a second AHA. (37)

The anticipated recommendation for canagliflozin is for its use after failure to control blood glucose with metformin monotherapy. Of the 1,700,000 T2DM patients estimated to receive pharmacological intervention, it is predicted that approximately 50% (212) of these patients would be eligible to be treated with canagliflozin combination therapy; a figures that account for those patients that may: be at high risk of hypoglycaemia; have weight management difficulties; or not be suitable for injection therapy. This figure of 50% is based on the number of patients estimated to be receiving dual-, triple- or add-on to insulin therapy.

National population data were taken from the Office of National Statistics Annual Mid-year Population Estimates, 2011 and 2012. (56) The estimated number of patients with T2DM eligible for treatment with canagliflozin is shown in Table 106. The prevalence data to inform these projections originate from the National Diabetes

Audit 2010-2011, Report 1 (40); 87.61% of people with diagnosed diabetes in England and over 85,000 people from almost 50 per cent of the practices in Wales are included. Diabetes prevalence in England and Wales is estimated at 4.07% and 4.70%, respectively. (40)

To calculate the proportion of patients receiving dual- (23%), triple (9%) and add-on to insulin (18%) therapy a prescribing report generated by Cegedim in May 2013 was consulted (212) Patient cohorts considered as part of the budget impact are those presented within the economic analysis. This same report was consulted to further determine the fraction of patients treated with particular combination treatment within each treatment line: 93% of patients treated at dual therapy receive metformin in combination with another anti-diabetic therapy; 96% of patients treated at triple therapy either receive metformin + SU or metformin + TZD in combination with another anti-diabetic therapy; and 52% receive intensification treatment add-on to insulin ± AHA.

Table 106. T2DM Patient population in England and Wales eligible for pharmacological intervention

	2014	2015	2016	2017	2018
Population in England and Wales	57,369,963	57,775,367	58,183,681	58,594,926	59,009,123
Diabetes population in the England and Wales	2,354,455	2,371,020	2,387,704	2,404,508	2,421,432
T2DM population in the England and Wales	2,119,009	2,133,918	2,148,934	2,164,057	2,179,289
T2DM patients receiving pharmacological intervention	1,695,207	1,707,135	1,719,147	1,731,246	1,743,431
T2DM patients receiving dual therapy	389,898	392,641	395,404	398,187	400,989
T2DM patients receiving triple therapy	169,521	170,713	171,915	173,125	174,343
T2DM patients receiving INS±AHA	305,137	307,284	309,446	311,624	313,818

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact of current treatment is based on 80% of diagnosed T2DM patients receiving anti-diabetic therapy (Table 106). (186)

The proportion of patients receiving dual, triple or add-on to insulin combination therapies was estimated for 5 years using the Cegedim prescribing Report, May 2013. (212) Patient numbers were projected forward using a constant inflation rate of 8% across all treatment combinations. (212)

Although patient treatment varies with individual response, lifestyle, and comorbidities, data of prescribing patterns suggests the use of some common approaches in managing diabetes. (213) Therefore, for simplicity, combination treatments considered within the canagliflozin NICE scope have been assumed to make up one hundred per cent of the current diabetes market.

Patient uptake of treatment has been adjusted to account for uptake of treatment throughout the year and it is assumed that patients will remain on treatment for an average of three years within this budget impact model.

8.3 What assumption(s) were made about market share (when relevant)?

Estimates are based on the assumption of canagliflozin receiving positive NICE guidance for use in combination with Met, Met+SU, Met+TZD and as add-on to insulin, at the start of Q3 2014. Market share was estimated based on existing technologies in this therapeutic area; in particular the uptake trend of sitagliptin (Januvia) was considered as a relevant model in the projection process.

The resource impact for England and Wales will differ depending upon the comparator chosen. In the case of canagliflozin, this is complicated by the range of existing therapies, which canagliflozin may displace.

For simplicity the proportion of patients on a given treatment class was assumed constant across a 5 year period in the scenario when canagliflozin is not considered. The predicted displacement by the SGLT-2 class was applied to these values, of which canagliflozin gains a percentage in the scenario considering positive canagliflozin recommendation by NICE.

At dual therapy it was anticipated that the drugs displaced by canagliflozin would primarily be those from the DPP-4i class (e.g. sitagliptin), and GLP-1-a class (e.g. liraglutide), rather than from the SU (e.g. gliclazide) and the TZD class (pioglitazone), with estimated displacement rates at year 5 of 7.04%, 4.88% 3.10% and 0.62%, respectively. The anticipated low displacement rate of the TZD class is due to the observed decline in the TZD market share. (214) Canagliflozin is expected to gain approximately 53% of the predicted SGLT-2i class displacement, at year 5.

At triple therapy it was anticipated that the drugs displaced would again primarily be those from the DPP-4i class, and GLP-1a class rather than the TZD class and insulin, with estimated displacement rates at year 5 of 18.69%, 18.06%, 6.65% and 5.85%, respectively. For insulin treatments there were no assumptions around which forms of insulin were most likely to be displaced; the expected level of displacement was applied to a weighted use and cost of the three most commonly used insulin.

Canagliflozin is anticipated to displace intensification strategies when treating patients with an insulin backbone. Therefore, it is assumed that it would be inappropriate to consider replacing metformin or SU added on to insulin as these are most commonly prescribed as part of the backbone of insulin therapy. Therefore, canagliflozin is anticipated to most likely displace medicines from the DPP-4i and GLP-1 classes, rather than from the TZD class or intensified insulin, at this line of therapy; with estimated displacement rates at year 5 of 4.21%, 3.38%, 2.28% and 1.17%, respectively. Canagliflozin is expected to gain 40% of the predicted SGLT-2i class displacement, at year 5.

Estimates of the uptake of canagliflozin are included in the table below. The displacement of existing therapies by canagliflozin was derived discussion within Janssen.

Table 107. Estimated uptake of canagliflozin across treatment lines, a 5-year projection

	2014	2015	2016	2017	2018
% uptake of canagliflozin at dual therapy, in combination with metformin	0.44%	2.16%	2.87%	3.12%	3.24%
% uptake of canagliflozin at triple therapy, in combination with MET+SU or MET+TZD	5.78%	10.00%	11.56%	11.56%	13.07%
% uptake of canagliflozin as add-on to INS±AHA	0.18%	1.10%	1.46%	1.46%	1.46%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Costs of treatment and monitoring associated with canagliflozin are outlined in section 7.5. No additional costs related to AEs are included, as canagliflozin is assumed to have no incremental impact on the cost of treating AEs in this patient population when compared to other anti-diabetic therapies.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Costs of treatments have been taken from the BNF September 2013. No other costs have been considered for incorporation into the BIM. Unit costs for treatment and monitoring can be found in Section 7.5.4.

8.6 Were there any estimates of resource savings? If so, what were they?

It was assumed that the introduction of canagliflozin for the treatment of T2DM would not be associated with any resource savings that would be suitable for inclusion into this budget impact review. All resource use and service implications have been identified throughout the economic analysis, Section 7.5.5.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Assuming NICE guidance is available in Q3 2013, and that canagliflozin achieves market shares as presented above, the net incremental budget impact would be £308,596 in 2014 until year end, increasing to £7,523,237 in 2018.

Table 108. Budget Impact by treatment line for the NHS in England and Wales, Dual Therapy

		2014	2015	2016	2017	2018
Patients receive dual therapy add-on to metformin		362,605	365,156	367,726	370,313	372,920
Current Practice without canagliflozin						
SU + Met	% of patients receiving SU	70.00%	69.05%	67.94%	67.62%	67.46%
	No. of patients receiving SU	63,456	188,665	310,548	372,990	374,726
	Annual cost	£ 1,243,819	£ 3,698,079	£ 6,087,158	£ 7,311,102	£ 7,345,134
TZD + Met	% of patients receiving TZD	10.22%	10.18%	10.12%	10.11%	10.11%
	No. of patients receiving TZD	9,265	27,815	46,258	55,767	56,159
	Annual cost	£ 331,432	£ 995,049	£ 1,654,830	£ 1,995,000	£ 2,009,040
DPP-4i + Met	% of patients receiving DPP-4i	15.00%	13.83%	13.60%	13.48%	13.42%
	No. of patients receiving DPP-4i	13,598	37,788	62,165	74,355	74,545
	Annual cost	£ 5,789,420	£ 16,088,648	£ 26,467,489	£ 31,657,922	£ 31,738,815
GLP-1a + Met	% of patients receiving GLP-1a	3.15%	2.96%	2.96%	2.96%	2.96%
	No. of patients receiving GLP-1a	2,856	8,088	13,530	16,327	16,442
	Annual cost	£ 2,614,782	£ 7,405,769	£ 12,389,295	£ 14,950,829	£ 15,056,047
DAPA + Met	% of patients receiving DAPA	1.64%	3.98%	5.38%	5.83%	6.05%
	No. of patients receiving DAPA	1,487	10,875	24,592	32,158	33,607
	Annual cost	£ 709,582	£ 5,190,335	£ 11,737,376	£ 15,348,855	£ 16,040,152
Total Annual Cost of Treatment		£ 10,689,034	£ 33,377,880	£ 58,336,149	£ 71,263,708	£ 72,189,187
Future with canagliflozin						
SU > CANA	% displacement of patients receiving SU+Met	0.51%	1.65%	2.66%	2.95%	3.10%
	No. of SU patients displaced by CANA	324	3,113	8,261	11,003	11,617
	Incremental cost	£ 152,358	£ 1,465,539	£ 3,888,958	£ 5,180,145	£ 5,468,881
TZD > CAN	% displacement of patients receiving TZD+Met	0.08%	0.17%	0.56%	0.62%	0.62%
	No. of TZD patients displaced by CANA	7	47	259	346	348
	Incremental cost	£ 3,369	£ 21,496	£ 117,764	£ 157,183	£ 158,289
DPP-4-i > CANA	% displacement of patients receiving DPP-4i+Met	1.05%	6.12%	6.37%	6.82%	7.04%
	No. of DPP-4i patients displaced by CANA	143	2,313	3,960	5,071	5,248
	Incremental cost	£ 9,226	£ 149,442	£ 255,891	£ 327,695	£ 339,130
GLP-1-a > CANA	% displacement of patients receiving GLP-1a+CANA	1.06%	5.43%	4.88%	4.88%	4.88%
	No. of GLP-1a patients displaced by CANA	30	439	660	797	802
	Incremental cost	-£ 12,873	-£ 186,777	-£ 280,815	-£ 338,875	-£ 341,260
DAPA > CANA	% displacement of patients receiving DAPA+Met	26.60%	54.43%	53.39%	53.56%	53.65%
	No. of TZD patients displaced by CANA	395	5,919	13,129	17,224	18,030
	Incremental cost	£ 5,178	£ 77,498	£ 171,904	£ 225,513	£ 236,066
Total Incremental Cost of Treatment with CANA		£ 157,258	£ 1,527,198	£ 4,153,702	£ 5,551,662	£ 5,861,107
Net Budget Impact at Dual Therapy		£ 10,846,291	£ 34,905,077	£ 62,489,851	£ 76,815,370	£ 78,050,294

Table 109. Budget Impact by treatment line for the NHS in England and Wales, Triple Therapy

		2014	2015	2016	2017	2018
Patients receive triple therapy add-on to Met+SU or Met+TZD		162,740	163,885	165,038	166,200	167,369
Current Practice without canagliflozin						
+ TZD	% of patients receiving TZD	26.11%	26.11%	26.11%	26.11%	26.11%
	No. of patients receiving TZD	10,623	32,018	53,564	64,638	65,093
	Annual cost	£ 380,023	£ 1,145,418	£ 1,916,198	£ 2,312,379	£ 2,328,652
+ DPP-4-i	% of patients receiving DPP-4i	46.68%	46.68%	46.68%	46.68%	46.68%
	No. of patients receiving DPP-4i	18,992	57,242	95,762	115,562	116,375
	Annual cost	£ 8,086,025	£ 24,371,860	£ 40,772,293	£ 49,202,120	£ 49,548,383
+ GLP-1-a	% of patients receiving GLP-1a	11.01%	11.01%	11.01%	11.01%	11.01%
	No. of patients receiving GLP-1a	4,479	13,501	22,587	27,257	27,448
	Annual cost	£ 4,101,782	£ 12,363,066	£ 20,682,482	£ 24,958,664	£ 25,134,312
+ INS	% of patients receiving INS	16.19%	16.19%	16.19%	16.19%	16.19%
	No. of patients receiving INS	6,587	19,853	33,213	40,080	40,362
	Annual cost	£ 1,554,007	£ 4,683,889	£ 7,835,795	£ 9,455,876	£ 9,522,422
Total Annual Cost of Treatment		£ 14,121,839	£ 42,564,233	£ 71,206,768	£ 85,929,038	£ 86,533,770
Future with canagliflozin						
TZD > CANA	% displacement of patients receiving TZD+SU+Met	3.12%	5.45%	6.23%	6.23%	6.65%
	No. of TZD patients displaced by CANA	331	1,745	3,337	4,027	4,329
	Incremental cost	£ 150,673	£ 793,290	£ 1,517,050	£ 1,830,706	£ 1,967,876
DPP-4-i > CANA	% displacement of patients receiving DPP-4-i+SU+Met	7.88%	13.78%	15.75%	15.75%	18.69%
	No. of DPP-4-i patients displaced by CANA	1,497	7,888	15,083	18,201	21,750
	Incremental cost	£ 96,708	£ 509,730	£ 974,649	1,176,162	£ 1,405,534
GLP-1-a > CANA	% displacement of patients receiving GLP-1-a+SU+Met	7.65%	13.38%	15.29%	15.29%	18.06%
	No. of GLP-1-a patients displaced by CANA	343	1,806	3,453	4,168	4,957
	Incremental cost	-£ 145,743	-£ 768,310	-£ 1,468,805	-£ 1,772,486	-£ 2,108,331
INS > CANA	% displacement of patients receiving INS+SU+Met	2.76%	4.14%	5.53%	5.53%	5.58%
	No. of INS patients displaced by CANA	182	822	1,837	2,216	2,252
	Incremental cost	£ 46,261	£ 209,150	£ 467,368	£ 563,998	£ 573,103
Total Incremental Cost of Treatment with CANA		£ 147,899	£ 743,860	£ 1,490,262	£ 1,798,380	£ 1,838,183
Net Budget Impact at Dual Therapy		£ 14,269,738	£ 43,308,093	£ 72,697,030	£ 87,727,418	£ 88,371,953

Table 110. Budget Impact by treatment line for the NHS in England and Wales, Add-on to Insulin Therapy

		2014	2015	2016	2017	2018
Patients receive intensification to add-on INS±AHA		158,671	159,788	160,912	162,045	163,185
Current Practice without canagliflozin						
+ TZD	% of patients receiving TZD	0.56%	0.55%	0.54%	0.54%	0.54%
	No. of patient receiving TZD	222	658	1,080	1,303	1,313
	Annual cost	£ 7,947	£ 23,525	£ 38,640	£ 46,628	£ 46,957
+ DPP-4i	% of patients receiving DPP-4i+INS±AHA	6.03%	5.88%	5.73%	5.73%	5.73%
	No. of patients receiving DPP-4i+INS±AHA	2,392	7,030	11,461	13,831	13,928
	Annual cost	£ 1,018,418	£ 2,993,228	£ 4,879,705	£ 5,888,602	£ 5,930,044
+ GLP-1a	% of patients receiving GLP-1a+INS±AHA	7.34%	7.19%	7.04%	7.04%	7.04%
	No. of patients receiving GLP-1a+INS±AHA	2,912	8,596	14,081	16,993	17,112
	Annual cost	£ 2,666,159	£ 7,871,770	£ 12,894,147	£ 15,560,061	£ 15,669,566
+ INS	% of patients receiving INT INS±AHA	84.25%	83.64%	83.03%	83.03%	83.03%
	No. of patients receiving INT INS±AHA	33,420	100,001	166,075	200,411	201,822
	Annual cost	£ 11,826,902	£ 35,389,030	£ 58,771,414	£ 70,922,627	£ 71,421,751
+ DAPA	% of patients receiving DAPA + Met	1.83%	2.74%	3.66%	3.66%	3.66%
	No. of patients receiving DAPA + Met	726	3,276	7,321	8,834	8,896
	Annual cost	£ 346,477	£ 1,563,608	£ 3,494,097	£ 4,216,514	£ 4,246,188
Total Annual Cost of Treatment		£ 15,865,903	£ 47,841,161	£ 80,078,001	£ 96,634,433	£ 97,314,505
Future with canagliflozin						
TZD > CANA	% displacement of patients receiving TZD+INS±AHA	0.28%	1.68%	2.28%	2.28%	2.28%
	No. of TZD patients displaced by CANA	1	11	25	30	30
	Incremental cost	£ 283	£ 5,022	£ 11,195	£ 13,510	£ 13,605
DPP-4i > CANA	% displacement of patients receiving DPP-4i+INS±AHA	0.50%	3.07%	4.21%	4.21%	4.21%
	No. of DPP-4i patients displaced by CANA	12	216	483	582	586
	Incremental cost	£ 773	£ 13,947	£ 31,180	£ 37,627	£ 37,892
GLP-1a > CANA	% displacement of patients receiving GLP-1a+INS±AHA	0.40%	2.48%	3.38%	3.38%	3.38%
	No. of GLP-1a patients displaced by CANA	12	213	476	574	578
	Incremental cost	-£ 4,953	-£ 90,673	-£ 202,425	-£ 244,277	-£ 245,996
INS > CANA	% displacement of patients receiving INT INS±AHA	0.14%	0.87%	1.17%	1.17%	1.17%
	No. of INS patients displaced by CANA	47	870	1,943	2,345	2,361
	Incremental cost	£ 6,387	£ 118,758	£ 265,232	£ 320,069	£ 322,322
DAPA > CANA	% displacement of patients receiving DAPA+Met	10.00%	40.00%	40.00%	40.00%	40.00%
	No. of DAPA patients displaced by CANA	73	1,310	2,928	3,534	3,559
	Incremental cost	£ 950	£ 17,157	£ 38,340	£ 46,267	£ 46,592
Total Incremental Cost of Treatment with CANA		£ 3,439	£ 64,211	£ 143,522	£ 173,196	£ 174,415
Net Budget Impact at Dual Therapy		£ 15,869,342	£ 47,905,372	£ 80,221,524	£ 96,807,629	£ 97,488,920

Table 111. Overall Budget Impact for the NHS in England and Wales

		2014	2015	2016	2017	2018
Dual	Total Annual Cost of Treatment w/o CANA	£ 10,689,034	£ 33,377,880	£ 58,336,149	£ 71,263,708	£ 72,189,187
	Total Incremental Cost of Treatment with CANA	£ 157,258	£ 1,527,198	£ 4,153,702	£ 5,551,662	£ 5,861,107
	Net Budget Impact at Dual Therapy	£ 10,846,291	£ 34,905,077	£ 62,489,851	£ 76,815,370	£ 78,050,294
Triple	Total Annual Cost of Treatment w/o CANA	£ 14,121,839	£ 42,564,233	£ 71,206,768	£ 85,929,038	£ 86,533,770
	Total Incremental Cost of Treatment with CANA	£ 147,899	£ 743,860	£ 1,490,262	£ 1,798,380	£ 1,838,183
	Net Budget Impact at Dual Therapy	£ 14,269,738	£ 43,308,093	£ 72,697,030	£ 87,727,418	£ 88,371,953
INS Add-on	Total Annual Cost of Treatment w/o CANA	£ 15,865,903	£ 47,841,161	£ 80,078,001	£ 96,634,433	£ 97,314,505
	Total Incremental Cost of Treatment with CANA	£ 3,439	£ 64,211	£ 143,522	£ 173,196	£ 174,415
	Net Budget Impact at Dual Therapy	£ 15,869,342	£ 47,905,372	£ 80,221,524	£ 96,807,629	£ 97,488,920
Across all Tx lines	Net Incremental Costs across all treatment lines	£ 308,596	£ 2,335,269	£ 5,787,487	£ 7,523,237	£ 7,873,704
	Net Budget Impact across all treatment lines	£ 40,985,371	£ 126,118,542	£ 215,408,405	£ 261,350,416	£ 263,911,167

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The below service use and associated costs have been considered for inclusion into the Budget Impact Model (BIM), however, on the grounds that there is a paucity of cost data on such services it has been assumed that they are not expected to be significant in terms of budget impact nationally and all costs have sequentially been discounted from inclusion into the BIM.

- SMBG strips for insulin, SU and GLP-1-a treated patients
- Health care professional (HCP; e.g. nurse) time taken to train patients before injection use (insulin and GLP-1)
- SGLT-2 specific AEs; i.e. less hypoglycaemia is expected, and no additional monitoring is required compared to current used treatment.

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

Reference List

(1) Abdul-Ghani MA, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011 Aug;32(4):515-31.

(2) Cefalu W, Leiter L, Yoon KH, Arias P., Niskanen L., Xie J., et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. The Lancet 2013 Jul 12;Published online.

(3) Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010 Jul;9(7):551-9.

(4) Wilding J., Blonde L., Chiasson J-L., Polidori D., Meininger G., Stein P. Canagliflozin Lowers HbA1c and Blood Pressure Through Weight Loss-Independent and Weight Loss-Associated Mechanisms - Poster presented at EASD. 2013 Sep 23; 2013.

(5) Janssen. Canagliflozin Proposed Titration Guidance - Proposal based on Discussion from Advisory Board 9 August 2013 (data on file). 2013 Sep.

(6) Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013 Sep 13.

(7) Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care 2013 Sep;36(9):2508-15.

(8) Janssen Research & Development. Integrated Summary of Safety - Canagliflozin As an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus. 2012.

(9) Neal B, Perkovic V, de ZD, Mahaffey KW, Fulcher G, Stein P, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)-A randomized placebo-controlled trial. Am Heart J 2013 Aug;166(2):217-23.

(10) DeFronzo RA, Davidson JA, Del PS. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012 Jan;14(1):5-14.

(11) Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005 Dec;54(12):3427-34.

(12) Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010 Feb;27(2):136-42.

(13) Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci 2011 Feb;32(2):63-71.

(14) Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab 2010 Jan;95(1):34-42.

(15) Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. J Am Soc Nephrol 2003 Nov;14(11):2873-82.

(16) Santer R, Calado J. Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target. Clin J Am Soc Nephrol 2010 Jan;5(1):133-41.

(17) Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. J Intern Med 2007 Jan;261(1):32-43.

(18) Stenlof K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013 Apr;15(4):372-82.

(19) Polidori D, Sha S, Mudaliar S, Ciaraldi TP, Ghosh A, Vaccaro N, et al. Canagliflozin Lowers Postprandial Glucose and Insulin by Delaying Intestinal Glucose Absorption in Addition to Increasing Urinary Glucose Excretion: Results of a randomized, placebo-controlled study. Diabetes Care 2013 Aug;36(8):2154-61.

(20) Polidori D, Zhao Y, Alba M, Ferrandinnini E. Treatment with Canagliflozin (CANA), a Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor, for 26 Weeks Improves Indices of Beta-cell Function (BCF). 2013 Sep 2; 2012.

(21) Polidori D, Vercruysse F, Ferrandinnini E. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Indices of ß-cell Function in Patients With Type 2 Diabetes on Metformin Plus Sulphonylurea. 2012.

(22) Rothenberg P, Devineni D, Ghosh A, Polidori D, Hompesch M, Arnolds S, et al. Canagliflozin, a Novel Inhibitor of Sodium Glucose Co-Transporter 2, Improved Glucose Control in Subjects with Type 2 Diabetes: Results of a Phase 1b Study. 2010 Sep; 2010.

(23) Polidori D, Zhao Y, Sha S, Canovatchel W. Canagliflozin Treatment Improves Beta Cell Function in Subjects with Type 2 Diabetes. 2010.

(24) European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) positive opinion for the medicinal product Invokana (100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 diabetes. http:, www.ema.europa.eu/ema, editors. 20-9-2013. 4-10-2013.
Ref Type: Online Source

(25) Janssen. Canagliflozin Summary of product Characteristics - Draft. 2013.
Ref Type: Unpublished Work

(26) Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012 Jun;35(6):1232-8.

(27) Fulcher G, Matthews D, Perkovic V, Mahaffey KW, Weiss R, Rosenstock J, et al. Canagliflozin in Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Sulfonylurea Monotherapy: A CANVAS Substudy - Poster presented at ADA. 2013 Jun; 2013.

(28) Wilding JP, Mathieu C, Deng L, Black S, Vercruysse F, Canovatchel W, et al. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycaemia in Subjects With Type 2 Diabetes Inadequately Controlled With Metformin Plus Sulphonylurea - Poster presented at EASD and ADA. 2012 Oct; 2012.

(29) Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G., et al. Efficacy and Safety of Canagliflozin in Subjects with Type 2 Diabetes Mellitus on Metformin and Pioglitazone Over 52 Weeks - Poster presented at ADA. 2013 Jun 23; 2013.

(30) Matthews D, Fulcher G, Perkovic V, de ZD, Mahaffey KW, Rosenstock J, et al. Efficacy and Safety of Canagliflozin, an Inhibitor of Sodium Glucose Co-Transporter 2, Added On to Insulin Therapy With or Without Oral Agents in Type 2 Diabetes - Poster presented at EASD. 2012 Oct; 2012.

(31) Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K, Meininger G. Efficacy and Safety of Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, in Older Subjects With Type 2 Diabetes Mellitus - Poster presented at EASD. 2012 Oct; 2012.

(32) Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995) 2013 Apr;41(2):72-84.

(33) Yale JF, Bakris G, Wajs E, Xi L, Figueroa K, Usiskin K, et al. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycaemic Control and Is Well Tolerated in Type 2 Diabetes Subjects With Moderate Renal Impairment - Poster presented at EASD. 2012 Oct; 2012.

(34) Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013 May;15(5):463-73.

(35) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3014 - 18-week Core Double-blind period. 2013 Jun 7.

(36) The National Collaborating Centre for Chronic Conditions. Type 2 Diabetes - National clinical guideline for management in primary and secondary care (update) - NICE Clinical Guideline 66. 2008. 2-9-2013.
Ref Type: Online Source

(37) The National Collaborating Centre for Chronic Conditions. Type 2 diabetes - The management of type 2 diabetes: NICE guideline 87. http://guidance nice org uk/CG87/NICEGuidance/pdf/English 2009 May [cited 213 Sep 2];Available from: URL: http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf

(38) The National Collaborating Centre for Chronic Conditions. Chronic Kidney Disease - National clinical guideline for early identification and management in adults in primary and secondary care – NICE Clinical Guidelines 73. NICE 2008 September [cited 2013 Sep 2];Available from: URL: http://www.nice.org.uk/nicemedia/pdf/cg073niceguideline.pdf

(39) American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care 2013 Jan;36 Suppl 1:S11-S66.

(40) Health and Social Care Information Centre. National Diabetes Audit 2010-2011 Report 1:Care Processes and Treatment Targets - Findings about the quality of care for people with diabetes in England and Wales. Healthcare Quality Improvement Partnership (http://www hqip org uk/) 2012 [cited 2013 Sep 2];Available from: URL: http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Diabetes-Audit-Report-2010-11-Care-Process-and-Treatment-Targets-published-2012.pdf

(41) Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010 Jan;87(1):4-14.

(42) Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabet Med 2012 Jul;29(7):855-62.

(43) Diabetes UK. Diabetes in the UK 2012 - Key statistics in diabetes. http://www diabetes org uk/About_us/What-we-say/Statistics/Diabetes-in-the-UK-2012/ 2012 April [cited 2013 Sep 2];Available from: URL: http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf

(44) Alvarez GF, Mavros P, Nocea G, Alemao E, Alexander CM, Yin D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008 Jun;10 Suppl 1:8-15.

(45) Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012 Jun;35(6):1364-79.

(46) Reasner CA. Reducing cardiovascular complications of type 2 diabetes by targeting multiple risk factors. J Cardiovasc Pharmacol 2008 Aug;52(2):136-44.

(47) Hammes HP. Optimal treatment of diabetic retinopathy. Ther Adv Endocrinol Metab 2013 Apr;4(2):61-71.

(48) Boyko EJ, Fihn SD, Scholes D, Abraham L, Monsey B. Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. Am J Epidemiol 2005 Mar 15;161(6):557-64.

(49) Donders GG, Prenen H, Verbeke G, Reybrouck R. Impaired tolerance for glucose in women with recurrent vaginal candidiasis. Am J Obstet Gynecol 2002 Oct;187(4):989-93.

(50) Health and Social Care Information Centre. National Diabetes Audit 2010-2011 Report 2: Complications and Mortality - Findings about the outcomes for people with diabetes in England and Wales. http://www hqip org uk 2012 [cited 2013 Sep 2];Available from: URL: http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Diabetes-Audit-Report-10-11-ComplicationsMortality-pub-2012.pdf

(51) Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet 2013 Mar 23;381(9871):997-1020.

(52) Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000 Aug 12;321(7258):405-12.

(53) Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. N Engl J Med 2012 Apr 5;366(14):1319-27.

(54) Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.

(55) Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000 Aug 12;321(7258):412-9.

(56) Office for National Statistics. Statistical Bulletin - Annual Mid-year Population Estimates, 2011 and 2012. http://www ons gov uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2011-and-mid-2012/stb---mid-2011---mid-2012-uk-population-estimates html 2013 August 8 [cited 2013 Sep 2];Available from: URL: http://www.ons.gov.uk/ons/dcp171778_320900.pdf

(57) CEGEDIM. Patient Data Report: Diabetes Treatment Combinations - Report AH [JAN2364513_ADH.DN2]. 2013.
Ref Type: Unpublished Work

(58) Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. Diabetes Res Clin Pract 2010 Jan;87(1):15-9.

(59) NICE. Technology appraisal guidance 288 - Dapagliflozin in combination therapy for treating type 2 diabetes. http://www.nice.org.uk . 2013. 2-9-2013.
Ref Type: Online Source

(60) NICE. Technology appraisal guidance 248 - Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. http://www.nice.org.uk . 2012. 2-9-2013.
Ref Type: Online Source

(61) NICE. Technology appraisal guidance 203 - Liraglutide for the treatment of type 2 diabetes mellitus. http://www.nice.org.uk . 2010. 2-9-2013.
Ref Type: Online Source

(62) NICE. Technology appraisal guidance 151 - Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. http://www.nice.org.uk/ . 2008. 2-9-2013.
Ref Type: Online Source

(63) NICE. NICE Pathways - Diabetes: Managing type 2 diabetes. http://pathways.nice.org.uk/ . 2013. 2-9-2013.
Ref Type: Online Source

(64) Nau DP. Recommendations for improving adherence to type 2 diabetes mellitus therapy--focus on optimizing oral and non-insulin therapies. Am J Manag Care 2012 Apr;18(3 Suppl):S49-S54.

(65) NICE. Final Scope - STA canagliflozin in combination therapy for treating type 2 diabetes. 27-8-2013. 10-10-2013.
Ref Type: Online Source

(66) Aurobindo Pharma - Milpharm. Summary of Product Characteristics - Metformin 500mg tablets. 15-4-2013. 10-10-2013.
Ref Type: Online Source

(67) Janssen. Advisory Board Minutes - August 2013. 2013.
Ref Type: Unpublished Work

(68) Association for Genitourinary Medidine and the Medical Society for the Study of Venereal Diseases. National Guideline on the Management of Vulvovaginal Candidiasis. http://www.bashh.org . 1999. 2-9-2013.
Ref Type: Online Source

(69) NHS Choice. Treating Balanitis. http://www.nhs.uk/ . 29-11-2012. 2-9-2013.
Ref Type: Online Source

(70) NHS Choice. Urinary Tract Infection in Adults - Treatment. http://www.nhs.uk/ . 9-4-2012. 2-9-2013.
Ref Type: Online Source

(71) Cryer PE. Preventing hypoglycaemia: what is the appropriate glucose alert value? Diabetologia 2009 Jan;52(1):35-7.

(72) Amaris. Study report - systematic literature review and meta-analysis of tretments of type 2 diabetes. 2013 Oct.

(73) Janssen Research & Development L. Clinical Study Report JNJ-28431754 DIA3009 (52-week Core Double-Blind Period) - The CANTATA-SU Trial JNJ Data on file. 2012 May 15.

(74) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3009 (104-week double-blind treatment phase). 2013 Jul 24.

(75) Niskanen L, Cefalu WT, Leiter LA, Xie J, Balis D, Canovatchel W, et al. Efficacy and Safety of Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Compared With Glimepiride in Patients With Type 2 Diabetes on Background Metformin - Poster presented at EASD. 2012 Oct 1; 2012.

(76) Toubro S, Cefalu WT, Xie J, Sullivan D, Usiskin K, Canovatchel W, et al. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Reduces Body Weight Mainly Through Loss of Fat Mass in Subjects With Type 2 Diabetes - Poster presented at EASD. 2012 Oct 1; 2012.

(77) Niskanen L, Cefalu WT, Leiter LA, Xie J, Balis DA, Canovatchel W, et al. Canagliflozin Compared To Glimepiride in Subjects With Type 2 Diabetes on Background Metformin - Poster presented at CODHy. 2012 Nov 8; 2012.

(78) Toubro S, Cefalu WT, Xie J, Sullivan D, Usiskin K, Canovatchel W, et al. Canagliflozin Reduces Body Weight Mainly Through Loss of Fat Mass in Subjects With Type 2 Diabetes - Poster presented at CODHy. 2012 Nov 8; 2012.

(79) Cefalu WT, Leiter LA, Niskanen L, Xie J, Millington D, Canovatchel W, et al. Efficacy and Safety of Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Compared With Glimepiride in Patients With Type 2 Diabetes on Background Metformin - Poster presented at ADA. 2012 Jun 8; 2012.

(80) Cefalu W.T., Leiter L.A., Yoon K-H., Arias P., Balis D.A., Millington D., et al. Canagliflozin Demonstrates Durable Glycemic Improvements Over 104 Weeks Versus Glimepiride in Subjects With Type 2 Diabetes Mellitus on Metformin - Poster presented at ADA. 2013 Jun 21; 2013.

(81) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3006 - 26-week Core double-blind period. 2012 Apr 20.

(82) Janssen Research & Development L. Clinical Study report - JNJ-28431754 DIA3006 - 52-week double-blind extension phase. 2012 Dec 18.

(83) Lavalle-Gonzalez FJ, Januszewicz A, Davidson J., Qiu R, Tong C, Meininger G. Canagliflozin Compared With Sitagliptin in Subjects With Type 2 Diabetes Mellitus on Metformin Over 52 Weeks - Poster presented at ADA. 2013 Jun 23; 2013.

(84) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3008 Insulin sub-study - 18-week double-bling core Period. 2012 May 16.

(85) Janssen Research & Development L. Clinical Study report JNJ-28431754 DIA3015 - 52-week Double-blind period. 2012 May 3.

(86) Schernthaner G, Gross J, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin Compared to Sitagliptin in Subjects With Type 2 Diabetes on Metformin and Sulphonylurea – Poster presented at CODHy. 2012 Nov 8; 2012.

(87) Gross LG, Schernthaner G, Fu M, Patel S, Kawaguchi M, Canovatchel W, et al. Efficacy and Safety of Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor,

Compared With Sitagliptin in Patients With Type 2 Diabetes on Metformin Plus Sulfonylurea - Poster presented at ADA. 2012 Jun 8; 2012.

(88) Schernthaner G, Ferrannini E, Mari A, Tong C, Meininger G, Polidori D. Effects of One-year Treatment With Canagliflozin or Sitagliptin on Glycaemic Control and ß-Cell Function Measures in Subjects With Type 2 Diabetes on Metformin Plus Sulphonylurea - Poster presented at EASD. 2013 Sep 23; 2013.

(89) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3002 - 26-week core double-blind period. 2012 Apr 30.

(90) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3002 - 52-week double-blind period. 2013 Feb 13.

(91) Wilding J, Mathieu C, Deng L, Black S, Vercruysse F, Canovatchel W, et al. Canagliflozin Improves Glycaemia in Subjects With Type 2 Diabetes on Metformin Plus Sulphonylurea - Poster presented at CODHy. 2012 Nov 8; 2012.

(92) Vercruysse F, Charpentier G, Wilding J, Hollander P, Gonzalez-Galves G, Mathieu C, et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin Plus Sulphonylurea Over 52 Weeks - Poster presented at EASD. 2013 Sep 23; 2013.

(93) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3012 - 26-week Core Double-Blind period. 2012 Apr 5.

(94) Janssen Research & Development L. Clinical Study Report - JNJ-28431754 DIA3012 - 52-week extension double-blind period. 2013 May 23.

(95) Forst T, Guthrie R, Goldenberg R, Vijapurkar U, Yee J, Meininger G., et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes on Metformin and Pioglitazone - Poster presented at CODHy. 2012 Nov 8; 2012.

(96) Rosenstock J, Davies M, Dumas R, Desai M, Alba M, Capuano G, et al. Effects of Canagliflozin Added on to Basal Insulin With or Without Other Antihyperglycemic Agents in Type 2 Diabetes - Poster presented at ADA. 2013 Jun 21; 2013.

(97) Woo V, Davies M, de Zeeuw D, Bakris G, Usiskin K, Gassmann-Mayer C, et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes With Moderate Renal Impairment - Poster presented at CODHy. 2012 Nov 8; 2012.

(98) Yale J-F, Bakris G, Xi L, Figueroa K, Wajs E, Usiskin K, et al. Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycemia and Is Well Tolerated in Type 2 Diabetes Mellitus Subjects With Moderate Renal Impairment - Poster presented at ADA. 2012 Jun 8; 2012.

(99) Yale JF, Bakris G, Cariou B, Nieto J, Wajs E, Figueroa K, et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes Mellitus and Chronic Kidney Disease Over 52 Weeks – Poster presented at ADA. 2013 Jun 21; 2013.

(100) Woo V, Davies M, de Zeeuw D, Bakris G, Perkovic V, Mayer C, et al. Canagliflozin Is Effective and Generally Well Tolerated in Subjects With Type 2 Diabetes Mellitus and Stage 3 Chronic Kidney Disease - Poster presented at ADA. 2013 Jun 21; 2013.

(101) Nieto J, Yale J-F, Barkis G, Cariou B, Wajs E, Figueroa K, et al. Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes Mellitus and Chronic Kidney Disease Over 52 Weeks. 2013 Sep 23; 2013.

(102) Wysham C, Woo V, Mathieu M, Alba M, Capuano G, Meininger G. Canagliflozin Added on to Dipeptidyl Peptidase-4 Inhibitors or Glucagon-like Peptide-1 Agonists With or Without Other Antihyperglycemic Agents in Type 2 Diabetes Mellitus - Poster presented at ADA. 2013 Jun 21; 2013.

(103) National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. http:, publications.nice.org.uk/pmg9, editors. 4-4-2013.
Ref Type: Online Source

(104) Hartemann-Heurtier A, Halbron M, Golmard JL, Jacqueminet S, Bastard JP, Rouault C, et al. Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract 2009 Oct;86(1):37-43.

(105) Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions – version 5.1.0. 2011.
Ref Type: Online Source

(106) Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011. 10-10-2013.
Ref Type: Online Source

(107) Whitehead A. Meta-analysis of controlled clinical trials (Statistics in Practice). 2002.

(108) Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-Analysis in Medical Research. 2000.

(109) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-60.

(110) Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004 Oct 30;23(20):3105-24.

(111) Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2002 Oct 23;64(4):583-639.

(112) MRC Biostatistics Unit. The BUGS Project - Deviance Information Criterion. 2012. 10-10-2013.
Ref Type: Online Source

(113) Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997 Jun;50(6):683-91.

(114) Dias S, Welton NJ, Sutton AJ, Caldwell DM, u G, des AE. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials. 2011. 10-10-2013.
Ref Type: Online Source

(115) Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011 Feb;64(2):163-71.

(116) Spiegelhalter DJ, Thomas A, Best NG, Lunn D. WinBUGS User Manual version 1.4. January 2003. 2003. 10-10-2013.
Ref Type: Online Source

(117) Janssen Research & Development. Endocrinologic and Metabolic Drugs Advisory Committee – Briefing Document Available for Public release - Canagliflozin as an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus. 2012 Dec 11.

(118) Janssen Research & Development. Summary of Clinical Safety - Canagliflozin As an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Anti-hyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus. 2012 May 19. Report No.: EDMS-ERI-43601880:1.0.

(119) Janssen Research & Development, Endocrinologic and Metabolic Drugs Advisory Committee. INVOKANA™ (canagliflozin) tablets, for oral use [package insert]. 2013 Jan 10.

(120) Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003 Apr;26(4):1176-80.

(121) Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998 Sep 12;317(7160):703-13.

(122) Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. Diabet Med 2008 Mar;25(3):245-54.

(123) The Swedish Insitute for Health Economics (IHE). Systematic Literature Review Of Economic Simulation Models Of T2dm And Cost-Effectiveness Studies Of Canagliflozin, Sglt-2 Inhibitors, And Relevant Treatment Comparators From The Uk Perspective. 2013.
Ref Type: Unpublished Work

(124) NICE. Guide to the methods of technology appraisal 2013. http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9 . 4-4-2013. 10-10-2013.
Ref Type: Online Source

(125) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996 Aug 3;313(7052):275-83.

(126) Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabet Med 2003 Jun;20(6):442-50.

(127) Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002 Jul;22(4):340-9.

(128) Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006 Aug;22(8):1523-34.

(129) Lane S, Levy AR, Sambrook J, Mukherjee J, Tildesley H. The Impact on Utilities of Weight Loss and Weight Gain Among Canadian Patients with Type 2 Diabetes. 2012.

(130) Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Econ 2005 Mar;14(3):217-30.

(131) Willis M, Asseburg C, He J. Validation of economic and health outcomes simulation model of type 2 diabetes mellitus (ECHO-T2DM). J Med Econ 2013 Aug;16(8):1007-21.

(132) The Swedish Institute for Health Economics (IHE). ECHO-T2DM 1.4 - Technical Report. 2013 Oct 9.

(133) Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 Oct;47(10):1747-59.

(134) The Swedish Institute for Health Economics (IHE), IMS, Willis M, Knudsen M. Cross-Validation Using Two Economic Simulation Models Of T2DM To Assess The Reliability Of Cost-Effectiveness Evidence. 2013.
Ref Type: Unpublished Work

(135) Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health 2012 Sep;15(6):796-803.

(136) Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value Health 2012 Sep;15(6):843-50.

(137) American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. Diabetes Care 2004 Sep;27(9):2262-5.

(138) Barhak J, Isaman DJ, Ye W, Lee D. Chronic disease modeling and simulation software. J Biomed Inform 2010 Oct;43(5):791-9.

(139) Eddy DM, Schlessinger L. Validation of the archimedes diabetes model. Diabetes Care 2003 Nov;26(11):3102-10.

(140) Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P, et al. A health policy model of CKD: 1. Model construction, assumptions, and validation of health consequences. Am J Kidney Dis 2010 Mar;55(3):452-62.

(141) Mueller E, Maxion-Bergemann S, Gultyaev D, Walzer S, Freemantle N, Mathieu C, et al. Development and validation of the Economic Assessment of Glycemic Control and Long-Term Effects of diabetes (EAGLE) model. Diabetes Technol Ther 2006 Apr;8(2):219-36.

(142) Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin 2004 Aug;20 Suppl 1:S27-S40.

(143) McEwan P, Peters JR, Bergenheim K, Currie CJ. Evaluation of the costs and outcomes from changes in risk factors in type 2 diabetes using the Cardiff stochastic simulation cost-utility model (DiabForecaster). Curr Med Res Opin 2006 Jan;22(1):121-9.

(144) Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013 Sep;56(9):1925-33.

(145) Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil 2011 Jun;18(3):393-8.

(146) Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Cederholm J. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract 2011 Aug;93(2):276-84.

(147) NICE. Clinical Guidelines CG34 - Management of hypertension in adults in primary care: partial update. 2006.
Ref Type: Online Source

(148) NICE. NICE clinical guideline 67. Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008. 2-6-2013.
Ref Type: Online Source

(149) The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. Am J Med 1991 Apr;90(4):450-9.

(150) Janssen. Canagliflozin_DoF_11/10/2013_OR_ MDS_3: Cegedim Strategic Data for Canagliflozin HTA Submissions. 2013.
Ref Type: Unpublished Work

(151) European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010.
Ref Type: Online Source

(152) NHS England, BMA, NHS Employers. 2013/14 general medical services (GMS) contract quality and outcomes framework (QOF) - Guidance for GMS contract 2013/14. 2013.
Ref Type: Online Source

(153) Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical Inertia in People With Type 2 Diabetes: A retrospective cohort study of more than 80,000 people. Diabetes Care 2013 Jul 22.

(154) Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011 May;96(5):1301-10.

(155) Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2008 Aug;30(8):1448-60.

(156) Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A, Gause-Nilsson I. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. Diabetes Metab Res Rev 2010 Oct;26(7):540-9.

(157) Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006 Dec 7;355(23):2427-43.

(158) Bagust A, Hopkinson PK, Maier W, Currie CJ. An economic model of the long-term health care burden of Type II diabetes. Diabetologia 2001 Dec;44(12):2140-55.

(159) Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W, et al. Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes Care 1997 May;20(5):735-44.

(160) Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F, et al. Model of complications of NIDDM. I. Model construction and assumptions. Diabetes Care 1997 May;20(5):725-34.

(161) Association of the British Pharmaceutical Industry (ABPI). The Code of Practice for the Pharmaceutical Industry Second 2012 Edition. 16-8-2012.
Ref Type: Online Source

(162) Janssen. Advisory Board Minutes - December 2012. 2013.
Ref Type: Unpublished Work

(163) Janssen. Advisory Board Minutes - May 2013. 2013.
Ref Type: Online Source

(164) Oxford Outcomes, Shingler S, Fordham B, Lloyd A. Utilities for Type 2 Diabetes Mellitus. 31-5-2013. 31-5-2013.
Ref Type: Unpublished Work

(165) Oxford Outcomes, Shingler S, Fordham B, Lloyd A. Utilities for Type 2 Diabetes Mellitus: Regression Analysis Results. 5-7-2013. 5-7-2013.
Ref Type: Unpublished Work

(166) Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab 2011 Sep;13(9):814-22.

(167) Eli Lilly and Company Ltd. STA submission - Exenatide once-weekly (BYDUREON) for the treatment of T2DM. 17-6-2011.
Ref Type: Online Source

(168) Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999 May;15(3):205-18.

(169) Wexler DJ, Grant RW, Wittenberg E, Bosch JL, Cagliero E, Delahanty L, et al. Correlates of health-related quality of life in type 2 diabetes. Diabetologia 2006 Jul;49(7):1489-97.

(170) Nyirjesy P, Sobel JD. Genital mycotic infections in patients with diabetes. Postgrad Med 2013 May;125(3):33-46.

(171) Geerlings SE. Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment. Int J Antimicrob Agents 2008 Feb;31 Suppl 1:S54-S57.

(172) Goswami R, Dadhwal V, Tejaswi S, Datta K, Paul A, Haricharan RN, et al. Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. J Infect 2000 Sep;41(2):162-6.

(173) Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med 1999 Dec 16;341(25):1906-12.

(174) Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001 Jun;24(6):1069-78.

(175) Pi-Sunyer FX. The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. Postgrad Med 2009 Sep;121(5):94-107.

(176) Alva ML, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: estimating the bias due to unobserved heterogeneity using the UKPDS. Trials 12[(Suppl 1):A64]. 2013.
Ref Type: Journal (Full)

(177) Grandy S, Fox KM. Change in health status (EQ-5D) over 5 years among individuals with and without type 2 diabetes mellitus in the SHIELD longitudinal study. Health Qual Life Outcomes 2012;10:99.

(178) Davies M, Speight J. Patient-reported outcomes in trials of incretin-based therapies in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2012 Oct;14(10):882-92.

(179) Grandy S, Fox KM, Bazata DD. Association of Self-Reported Weight Change and Quality of Life, and Exercise and Weight Management Behaviors Among Adults with Type 2 Diabetes Mellitus: The SHIELD Study. Cardiol Res Pract 2012;2012:892564.

(180) YHEC, Bartlett.C., Mahon J, Arber M, Hill C, Glanville J, et al. A Systematic Review of Health Reported Quality of Life in Type 2 Diabetes Mellitus Patients Treated with Anti-Diabetic Therapies. 2013. 8-8-2013.
Ref Type: Unpublished Work

(181) Oxford Outcomes, Shingler S, Fordham B, Lloyd A. Utilities for T2DM and associated adverse events: Literature Review Summary Document. 2013.
Ref Type: Unpublished Work

(182) Office for National Statistics. 2011 Census, Key Statistics and Quick Statistics for local authorities in the United Kingdom. 2013.
Ref Type: Online Source

(183) Burstrom K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. Qual Life Res 2001;10(7):621-35.

(184) Schunk M, Reitmeir P, Schipf S, Volzke H, Meisinger C, Thorand B, et al. Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany. Diabet Med 2012 May;29(5):646-53.

(185) Sparring V, Nystrom L, Wahlstrom R, Jonsson PM, Ostman J, Burstrom K. Diabetes duration and health-related quality of life in individuals with onset of diabetes in the age group 15---34 years -- a Swedish population-based study using EQ-5D. BMC Public Health 2013 Apr 22;13(1):377.

(186) National Audit Office, Department of Health. The management of adult diabetes services in the NHS. 2013.
Ref Type: Online Source

(187) Department of Health. National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts. 2013. 2-10-2013.
Ref Type: Online Source

(188) The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines . 1-12-2012. 2-6-2013.
Ref Type: Online Source

(189) BASHH. United Kingdom National Guideline on the Management of Vulvovaginal Candidiasis (2007). 2007. 10-10-2013.
Ref Type: Online Source

(190) UK National Screening Committee. Annual Report: English National Screening Programme for Diabetic Retinopathy. 2011. 2-6-2013.
Ref Type: Online Source

(191) British Medical Association, Royal Pharmaceutical Society. British National Formulary No.65. 2013.

(192) Curtis L. Unit Costs of Health and Social Care (2012). 2012. 10-10-2013.
Ref Type: Online Source

(193) The UK Renal Registry. The Fifth Annual Report. 2002. 9-10-2013.
Ref Type: Online Source

(194) Janssen, Schroeder MD, Girod I. The Cost of Co-morbidities and Complications in Type 2 Diabetes Mellitus. Results of a Systematic Literature Review: Resource identification, measurement and valuation studies. 2013.
Ref Type: Unpublished Work

(195) Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care 2002 Feb;11(2):70-4.

(196) The Information Centre for Health and Social Car. Prescribing for Diabetes in England: 2005/6 to 2010/11. 2011.
Ref Type: Online Source

(197) The National Prescribing Centre (NPC). Cardiovascular — type 2 diabetes. Data focused commentary: Type 2 diabetes: Self-monitoring blood glucose. 2012.
Ref Type: Online Source

(198) Thompson G, Willis M, Johansen P, Neslusan C, Schroeder M, Girod I. Assessment of the key drivers of the cost-effectiveness in the economic modelling of canagliflozin (CANA) versus glimepiride (GLIM) in the treatment of Type 2 diabetes mellitus (T2DM) in the UK setting. 2013.
Ref Type: Unpublished Work

(199) Schroeder M, Willis M, Johansen P, Girod I, Neslusan C, Thompson G. Impact Of Patient Weight Trajectory On Cost-Effectiveness Of Treatments Of Type 2 Diabetes Mellitus (T2DM). 2013.
Ref Type: Unpublished Work

(200) Mount Hood Modelling Group. Mount Hood Challenge (6th). 2013. 10-10-2013.
Ref Type: Online Source

(201) Palmer AJ, Clarke P, Gray A, Leal J, Lloyd A, Grant D, et al. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. Value Health 2013 Jun;16(4):670-85.

(202) Mount Hood Modelling Group. Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 2007 Jun;30(6):1638-46.

(203) Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988 Nov 18;260(19):2864-71.

(204) Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004 Aug 21;364(9435):685-96.

(205) Thomason MJ, Colhoun HM, Livingstone SJ, Mackness MI, Betteridge DJ, Durrington PN, et al. Baseline characteristics in the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with Type 2 diabetes. Diabet Med 2004 Aug;21(8):901-5.

(206) Gerstein HC, Bosch J, Pogue J, Taylor DW, Zinman B, Yusuf S. Rationale and design of a large study to evaluate the renal and cardiovascular effects of an ACE inhibitor and vitamin E in high-risk patients with diabetes. The MICRO-HOPE Study. Microalbuminuria, cardiovascular, and renal outcomes. Heart Outcomes Prevention Evaluation. Diabetes Care 1996 Nov;19(11):1225-8.

(207) HOPE study investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000 Jan 22;355(9200):253-9.

(208) Sasaki A, Uehara M, Horiuchi N, Hasegawa K, Shimizu T. A 15 year follow-up study of patients with non-insulin dependent diabetes mellitus (NIDDM) in Osaka, Japan. Long-term prognosis and causes of death. Diabetes Res Clin Pract 1996 Sep;34(1):47-55.

(209) Bristol Myers Squibb, AstraZeneca EEIG. SPC for Dapagliflozin. 7-5-2013. 10-10-2013.
Ref Type: Online Source

(210) Gonzalez EL, Johansson S, Wallander MA, Rodriguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 2009 Apr;63(4):332-6.

(211) Holden SH, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, et al. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. Diabetes Obes Metab 2013 Sep;15(9):844-52.

(212) Janssen. Canagliflozin_DoF_11/10/2013_OR_ MDS_1: Cegedim Strategic Data for Canagliflozin HTA Submissions. 2013. 11-10-2013.
Ref Type: Online Source

(213) Datamonitor. Treatment Algorithms: Type 2 Diabetes – Novel classes drive fragmentation of treatment choices in type 2 diabetes. 2013.
Ref Type: Online Source

(214) Janssen. Canagliflozin_DoF_11/10/2013_OR_ MDS_2: IMS Regimen Volume Growth Data for Canagliflozin HTA submissions. 2013.
Ref Type: Unpublished Work