NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes [ID1160]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]

Contents:

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

NICE National Institute for Health and Care Excellence

Ertugliflozin in triple therapy for treating type 2 diabetes **Pre-meeting briefing**

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

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

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

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

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

[redacted]

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Definition of terms

Sodium–glucose co-transporter 2 inhibitors (SGLT-2 inhibitors)	
Ertugliflozin (ERTU)	**Referred to collectively hereafter as ‘flozins’**
Canagliflozin (CANA)	
Dapagliflozin (DAPA)	
Empagliflozin (EMPA)	
Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors)	
Such as sitagliptin, saxagliptin and linagliptin	**Referred to collectively hereafter as ‘gliptins’**

Key issues

- The company's submission focusses on a triple therapy regimen of a flozin with metformin and a gliptin because ertugliflozin (ERTU) has been studied in this combination
  - the combination of a flozin with metformin and a gliptin has not been considered or approved previously by NICE
  - the company believes that this regimen is sufficiently used in the UK for it to be regarded as standard therapy, and therefore no other triple therapy regimens are included as comparators
  - Does the committee accept the company's approach?
- The key clinical trial data comes from VERTIS SITA 2. Is the committee satisfied with the evidence for the efficacy and safety of ERTU compared with placebo?
- There is no direct evidence comparing ERTU with other flozins and the company conducted an indirect comparison. Does the committee accept the company's conclusions that ERTU has similar efficacy and safety to other flozins in the proposed triple therapy regimen?
- Does the committee accept the company's cost-minimisation approach based on the assumption that the flozins have similar efficacy and safety and only differ in terms of drug acquisition costs?
- The ERG highlights that the triple therapy regimen proposed by the company costs more than other triple therapy regimens used in clinical practice. What is the committee's view of the cost relative to other triple therapy combinations?

[redacted]

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Background

- Type 2 diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from reduced secretion of the hormone insulin or reduced tissue sensitivity to insulin (known as insulin resistance)
- If not managed effectively, type 2 diabetes can lead to kidney failure, blindness, limb amputation, hypertension, damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication and is the greatest cause of morbidity and premature death
  - life expectancy is reduced by up to 10 years in people with diabetes
- There are over 3 million people aged 17 and over in England with type 2 diabetes, however many people are undiagnosed so this may be conservative
- Prevalence is rising because of increased prevalence of obesity, low physical activity and higher life expectancy after diagnosis because of better cardiovascular risk protection
  - particularly prevalent in people of African, South Asian and Caribbean family origin

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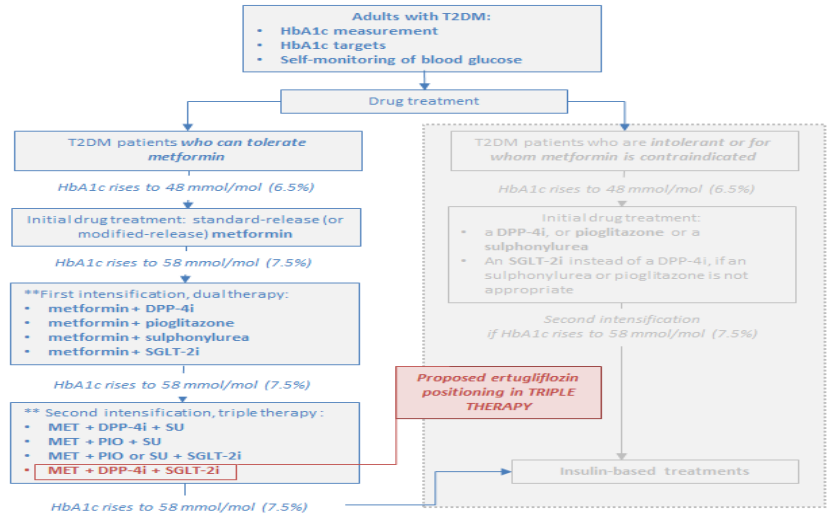
Details of the technology

Technology	Ertugliflozin (Steglatro, MSD)
Marketing authorisation	Adults aged 18 years and older with type 2 diabetes to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes **This STA covers the triple therapy indication only. Monotherapy and dual therapy indications to be appraised in subsequent FTA**
Mechanism of action	Sodium–glucose co-transporter 2 inhibitor (SGLT2i): Reduces conservation of glucose by kidneys, leading to loss of glucose in urine
Administration & dosage	5 mg once daily for monotherapy, increasing to 15 mg once daily if additional glycaemic control is needed. In combination therapy, dosage should be individualised using the recommended daily dose of 5 mg or 15 mg
List price and average cost of treatment	Ertugliflozin (Steglatro®) 5 mg * 28 tablets: £[redacted] per pack Ertugliflozin (Steglatro®) 15 mg * 28 tablets: £[redacted] per pack

Treatment Pathway for type 2 diabetes

Current clinical pathway (NG28) and proposed positioning of ertugliflozin (ERTU) combination therapy with metformin and gliptin



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Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; MET, metformin; DPP4-I (gliptin), dipeptidyl peptidase 4 inhibitor; SGLT-2i (flozin), sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; PIO, pioglitazone

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Source: Figure 1 (page 13 of the company submission)

Current management of type 2 diabetes

- NICE guideline (NG) 28 'Type 2 diabetes in adults: management' recommends reinforcing advice on diet, lifestyle and adherence to drug treatment
- If there is still inadequate glycaemic control, NG28 recommends several options as monotherapy. Following this initial therapy, if there is still inadequate glycaemic control, dual therapy is recommended
- This appraisal focuses on **triple therapy options** if there is inadequate glycaemic control following dual therapy
  - NG28 recommends triple therapy (metformin plus a sulfonylurea plus either a gliptin or pioglitazone), or insulin based treatment
  - TAs 315, 336 and 418 recommend the flozins CANA, EMPA and DAPA either with metformin plus a sulphonylurea or metformin plus pioglitazone. The flozins are also recommended with insulin, with or without other antidiabetic drugs

[redacted]

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First treatment for type 2 diabetes is diet and physical activity. However, as compliance is usually poor, drugs are needed with treatment initially starting with metformin. Unless weight is lost, type 2 diabetes is a progressive disease and more drugs are usually required.

The second drug is usually a sulphonylurea (SU) such as gliclazide, but may be pioglitazone, because SUs can cause hypoglycaemia (low blood glucose). Both SUs and pioglitazone cause weight gain. SUs work by stimulating insulin release from the pancreas, so over time they lose effectiveness (beta cell capacity in the pancreas declines). When a third drug is needed, there are several oral options:

- A gliptin (sitagliptin being most common)
- Pioglitazone, if drug 2 was a sulphonylurea, or vice versa.
- A flozin

Injected glucose lowering drugs including GLP-1 analogues such as long-acting exenatide, injected once a week and insulin, are usually added later in the treatment pathway.

Decision problem

	NICE scope	Company submission	Rationale if different from scope
Population	Adults with type 2 diabetes that is inadequately controlled on combination therapy with anti-diabetic agents	As per scope	
Intervention	ERTU in triple therapy	As per scope	
Comparator	• Sulfonylureas • DPP-4is • Pioglitazone • SGLT-2is • GLP-1 mimetics • Insulin	SGLT-2is (gliptins)	Evidence base for ERTU in triple therapy is with metformin + a gliptin only. The company believes the only relevant comparators are other flozins used in a triple therapy regimen with the same background therapies
Outcomes	• Mortality • Complications of diabetes • HbA1c/glycaemic control • Changes in cardiovascular risk factors • Adverse events • Health-related quality of life	As per scope	
Economic analysis	Cost-utility analysis	Cost-minimisation analysis	An indirect comparison showed similar efficacy and safety of all flozins. Company considered cost-minimisation analysis the most appropriate form of economic evaluation

Anti-hyperglycaemic agents used in triple therapy in the UK (moving annual total)

- Company reports that flozins are only used in triple therapy as add on to metformin with a sulfonylurea/gliptin, based on data from a panel of 150 general practices (800 GPs) in the UK
- The metformin + gliptin+ flozin combination already accounts for XXXX of triple therapy (equating to about 1.2 million people in the UK)
- Based on this, the company's proposed positioning of ERTU in triple therapy is with metformin and a gliptin compared with other flozins with the same background therapy

Triple therapy	Moving annual total 2017	
	patients	%
MET + SU + PIO	23,806	7.8
MET + SU + gliptin	138,287	45.1
MET + SU + GLP-1	21,172	6.9
MET + SU + flozin	45,792	15.0
MET + gliptin + PIO	10,059	3.3
MET + gliptin + GLP-1	1,724	0.5
MET + gliptin + flozin	34,775	XXX
Other	30,656	10.0
Total	306,271	100

Abbreviations:
SU: sulphonylureas
MET: metformin
PIO: thiazolidinedione
GLP-1: glucagon-like peptide-1
Gliptin: DPP-4 inhibitor
Flozin: SGLT-2 inhibitor

[redacted]

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Clinical expert comments

- Aim of treatment is to maintain control of blood glucose levels so that glycated haemoglobin (HbA1c) is 53 mmol/mol or less. Treatment should reduce the incidence and progression of complications of diabetes and minimise adverse events
- Pathway of care well defined in the NHS and based on NG28 – the treatment options after metformin, and before insulin is required, can vary depending on the clinical condition of the patient and co-morbidities
  - NG28 does not reflect new cardiovascular (CV) outcome data with flozins that has led to changes in most other international guidelines that support use of flozins in patients with pre-existing CV disease
- ERTU in triple therapy is likely to add another option to the flozins currently available in the NHS and is likely to work in the same way as other flozins
- Flozins can be more effective in people with type 2 diabetes who have normal kidney function but elevated Hba1c and are overweight or obese
- Treatment is likely to be less effective in people with renal impairment and stopped when estimated glomerular filtration rate (eGFR) falls below 30 mls/min. As eGFR is routinely monitored in patients with diabetes, additional monitoring is unlikely to be required
- Adverse effects are polyuria and UTIs / genital infections. These are unpleasant but not usually severe. Rare events such as diabetic ketoacidosis not reported in trials for ERTU and CV outcomes not yet available
- Emerging data also suggest flozins are renoprotective in diabetes

[redacted]

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Clinical expert statements from the Royal College of Pathologists and Professor of Medicine at the University of Liverpool and Aintree University Hospital NHS Foundation Trust

Improvement in HbA1c, reduction in cardiovascular events/deaths and weight reduction are also important outcomes

Clinical effectiveness

[redacted]

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Company's clinical evidence: VERTIS SITA 2

Design	Randomised, double-blind, placebo-controlled, phase III study: Part A: 26–week, double-blind, placebo–controlled treatment period Part B: 26-week active placebo extension treatment period
Population (Part A only) (n=462)	Adults with type 2 diabetes who have inadequate glycaemic control (HbA1c 7.0-10.5%) on metformin at a dose ≥1500 mg/day and on sitagliptin at a dose of 100 mg/day
Intervention	ERTU 5 mg (n=156) ERTU 15 mg (n=153)
Comparator	Placebo (n=153)
Location	104 international study sites in 12 countries from Europe, North America and selected other countries. No UK sites or patients included in the trial
Primary outcome	• Change in HbA1c from baseline to week 26
Other outcomes	• Change in fasting plasma glucose, body weight and blood pressure • Proportion of patients with HbA1c <7.0% • Proportion receiving glycaemic rescue therapy • Adverse events • Health related quality of life
Duration of study	52 weeks

[redacted]

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Source: Table 5 (page 17) of the company submission. Please see pages 17-22 of the company submission for more information

Trial eligibility criteria included adults with a diagnosis of type 2 diabetes in accordance with American Diabetes Association (ADA) guidelines, ≥18 years, BMI ≥18.0 kg/m2, inadequate glycaemic control on metformin therapy (≥1500 mg/day for at least 8 weeks) and be on sitagliptin (100 mg/day for ≥8 weeks, and HbA1c between 7.0-10.5%, (53–91 mmol/mol) at screening visit. People on this regimen for less than 8 weeks, or at a lower dose of metformin, or used metformin in combination with a DPP-4i other than sitagliptin were adjusted to the appropriate medication

The efficacy and safety outcomes at week 26 (Phase A) used as evidence of comparability to other flozins

The patient, the investigator and the sponsor involved in the treatment or clinical evaluation of the patients, were unaware of treatment group assignments. Patients' treatment assignments were unblinded at the completion of the 26-week part A to the sponsor to permit authoring of the clinical study report. Personnel associated with the conduct of the study, as well as trial site personnel and patients, remained blinded and were not unblinded until after Phase B of the study was completed.

Although there are no UK patients in the VERTIS SITA2 trial, there are Western European patients (France, Norway and Spain) and the company considers that the clinical findings are generalisable to the UK.

At 26 weeks, 78% of the placebo group, 89% of the ertugliflozin 5mg and 91% of the ertugliflozin 15mg group remained on allocated treatment. The corresponding figures at week 52 were 48%, 77% and 76%. By 26 weeks, rescue treatment was required in 1.3% of the ertugliflozin 5mg group, 2% of the ertugliflozin 15mg group, and 16.3% of those on placebo.

Baseline characteristics in VERTIS SITA 2

VERTIS SITA 2	PBO	ERTU 5 mg	ERTU 15 mg	TOTAL
n	153	156	153	462
Age, mean (SD) years	58.3 (9.2)	59.2 (9.3)	59.7 (8.6)	59.1 (9.0)
Sex, %	Male: 65.4 Female: 34.6	Male: 51.9 Female: 48.1	Male: 53.6 Female: 46.4	Male: 56.9 Female: 43.1
Body weight (kg), mean (SD)	86.4 (20.8)	87.6 (18.6)	86.6 (19.5)	86.9 (19.6)
BMI, mean (SD) kg/m^2	30.3 (6.40)	31.2 (5.5)	30.9 (6.1)	30.8 (6.0)
Disease duration (years), mean (SD)	9.44 (5.55)	9.88 (6.13)	9.20 (5.32)	9.51 (5.68)

Abbreviations: BMI, body mass index; kg, kilogram; PBO; placebo, SD, standard deviation

[redacted]

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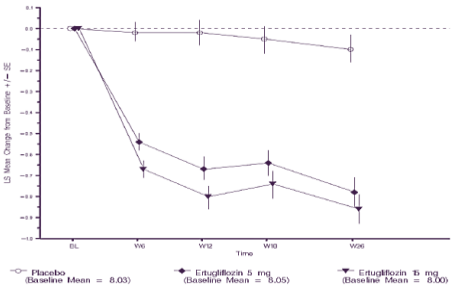
Source: Table 7 (page 23) of the company submission

Baseline characteristics of the patients were generally similar between groups with the exception of sex, where there was a higher proportion of males in the placebo group versus the ertugliflozin group. The mean age was 59.1 years; the mean duration of the disease was 9.51 years and the overall median metformin dose at baseline was 2000 mg/day.

Clinical effectiveness results (1)

Primary efficacy outcome: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-value)
ERTU 5 mg	-0.69 (-0.87, -0.50);<0.001
ERTU 15 mg	-0.76 (-0.95, -0.58); <0.001)

Secondary efficacy outcome: Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	n	Number (%) with HbA1c <7.0% at W26	Adjusted Odds Ratio (OR) relative to PBO 95%% CI; p-value)
PBO	153	26 (17.0)	-
ERTU 5 mg	156	50 (32.1)	3.16 (1.74, 5.72; <0.001)
ERTU 15 mg	153	61 (39.9)	4.43 (2.44, 8.02; <0.001)

Source: Figure 3 (page 28 of company submission) and Table 10 (page 29 of company submission)

The least square (LS) mean reductions from baseline in HbA1c to week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups than in the placebo group. In the ertugliflozin groups, reductions from baseline in HbA1c were observed at week 6 and 12, with subsequent further reductions at week 26. Reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. There was minimal change from baseline in HbA1c to week 18 in the placebo group although a small reduction in HbA1c was observed at week 26.

The corresponding changes from baseline to week 26 for HbA1c in mmol/mol are:

- ertugliflozin 5 mg vs. placebo = [95%CI] = -7.51 [-9.50, -5.51]
- ertugliflozin 15 mg vs. placebo = [95%CI] = -8.34 [-10.35, -6.33]

The raw proportion of people with HbA1c <7.0% was almost twice as great in the ertugliflozin 5 mg group and was over twice as great in the ertugliflozin 15 mg group as it was in the placebo group. Model-based odds of having an HbA1c <7.0% at week 26 were

significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group.

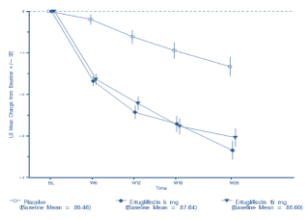
At 26 weeks, 17% of the placebo group achieved the HbA1c target of <7.0%, falling to 14% by week 52. At 26 weeks, 32% of the ertugliflozin 5 mg achieved that target, as did 40% of the ertugliflozin 15mg arm. By 52 weeks, the corresponding ertugliflozin figures were 33% and 33%. So most patients would be considered for further intensification of treatment.

Of those still on allocated treatment at 26 weeks, the mean reductions in HbA1c were 0.3% on placebo, 0.9% on ertugliflozin 5mg and 0.8% on ertugliflozin 15mg. Of those still on allocated treatment at 52 weeks, the reductions in HbA1c were 0.7%, 1.0% and 1.0% on placebo, ertugliflozin 5 and 15mg respectively (but only 48% were still on placebo, so the 0.7% reduction reflects selection out of patients with poor control).

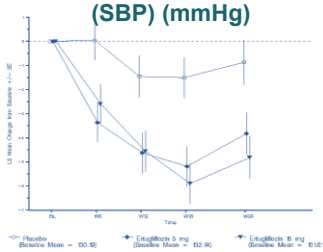
Clinical effectiveness results (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

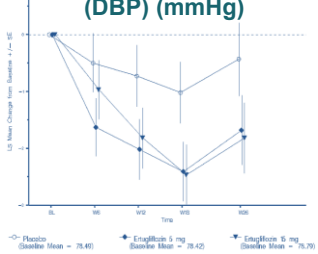
Body Weight (kg)



Systolic blood pressure (SBP) (mmHg)



Diastolic blood pressure (DBP) (mmHg)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-2.03 (-2.65, -1.40); <0.001	-1.72 (-2.35, -1.09) ; <0.001
SBP (mmHg)	-2.93 (-5.36, -0.49); 0.019	-3.94 (-6.39, -1.50); 0.002
DBP (mmHg)	-1.24 (-2.97, 0.48); 0.157	-1.38 (-3.11, 0.36); 0.119

Abbreviations: cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; FAS, full analysis set

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Source: Figure 4. 5 and 6(page 30-32 of company submission)

Weight loss by 26 weeks was 1.3kg, 3.4kg and 3.0kg on placebo, ertugliflozin 5 and 15mg respectively. By week 52, weight loss was mostly maintained on ertugliflozin, 3.5Kg on 5mg and 2.8mg on ertugliflozin 15mg, whereas a little weight (0.3kg) was regained by the placebo group (perhaps partly due to weight gain with rescue glimepiride – the 52 week weight results include all patients).

Systolic blood pressure fell by 0.9 mmHg in the placebo arm, and by 3.8 mmHg and 4.8 mmHg in the ertugliflozin arms. The fall on placebo was not maintained to 52 weeks but was in the ertugliflozin arms.

Adverse events (AEs)

VERTIS SITA 2	PBO N = 153	ERTU5 N = 156	ERTU15 N = 153
Overall Safety (excluding rescue and including rescue)[a], n (%)			
AEs related to study drug [b]	13 (8.5)	17 (10.9)	22 (14.4)
SAE related to study drug [b]	0 (0)	0 (0)	1 (0.7)
Genital mycotic infection (women)	1 (1.9)	6 (8.0)	**9 (12.7)***
Genital mycotic infection (men)	0 (0)	**4 (4.9)***	3 (3.7)
Urinary tract infection	3 (2.0)	4 (2.6)	7 (4.6)

* p< 0.05 versus placebo
[a] week 26 safety analyses, data following initiation of glycaemic rescue were excluded from incidence of 'one or more AEs' and from 'AEs related to study drug'
[b] investigator assessed
Abbreviations: PBO, placebo; AE, adverse event; SAE, serious adverse event

[redacted]

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Source: Table 27 (page 51 of the company submission). Please also see pages 49-52 of the company submission and pages 10-12 of the ERG report for more information

Network meta-analysis and cost effectiveness

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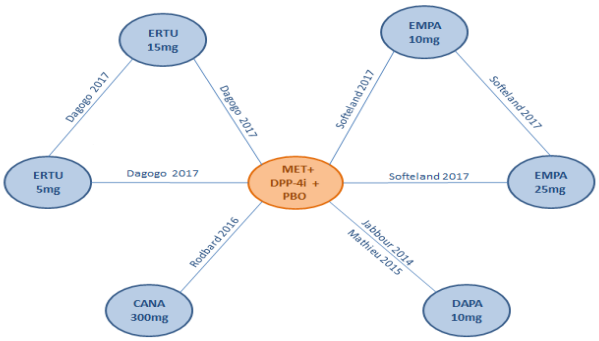
Company's network meta-analysis (NMA)

- Compared ERTU with other flozins on a background of metformin and a gliptin
- No other comparators in scope were included - company believes the only relevant comparators are other flozins with the same background therapies
- Included 5 RCTs (VERTIS SITA 2 (Dagogo 2018 - ERTU); Jabbour 2014 (DAPA); Mathieu 2015 (DAPA); Rodbard 2016 (CANA); Softeland 2017 (EMPA)
- Outcomes: **continuous**: change in HbA1c, weight and SBP. **Binary**: HbA1c in target; UTIs; genital mycotic infections. All measured at week 24 to 26



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Source: Figure 7, page 38 of the company submission. See also tables 12 and table 13 in the CS (pages 35 and 36)

In the absence of direct evidence comparing ertugliflozin in triple therapy with other flozins in triple therapy, the company carried out network meta-analyses (NMAs) to indirectly estimate relative effects.

Dapagliflozin 10mg arms from the two dapagliflozin trials included in the NMA were treated as distinct interventions in without explanation, but presumably because the results at 26 weeks were rather different.

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Company's NMA results

Continuous outcomes

- Change in HbA1c: ERTU 5 and 15 mg were statistically superior to DAPA 10mg (if using Jabbour 2014 but no differences if using Mathieu 2015)
- Weight change: [redacted]
- Change in SBP: no statistically significant differences between flozins

Binary outcomes

- HbA1c at target (<7.0%): no statistically significant differences between flozins
- All AEs / UTIs: no statistically significant differences between flozins

Company's conclusion

- ERTU has similar efficacy and safety in triple therapy to other flozins

[redacted]

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Please see pages 39-48 of the company submission and pages 15-16 of the ERG report for more information

The reduction in HbA1c after 26 weeks with dapagliflozin in Jabbour 2014 trial was only 0.4%, which contrasts with the higher reduction in the Mathieu 2015 trial (0.72%, placebo adjusted). There were only minor differences in baseline differences between these trials. Patients in Jabbour 2014 were more overweight (94kg versus 86kg) but had a lower baseline HbA1c (7.8% versus 8.2%) which seems insufficient to explain the difference in efficacy estimates. With longer follow-up, the reductions were more similar at 0.6% and 0.74% at 48 and 52 weeks.

ERG critique: VERTIS SITA 2

- Good quality trial showing that ERTU is effective in improving glycaemic control vs placebo
- Key issue is that the triple therapy regimen of a flozin with metformin + gliptin has not been considered previously by NICE (only flozin with metformin + sulfonylurea/pioglitazone)
  - ERG considers it reasonable to extrapolate from clinical equivalence shown in trials of triple therapy with metformin + gliptin, to triple therapy with metformin and either sulfonylurea/pioglitazone
- The company used the full analysis set (FAS) population (defined as patients who received at least one dose of study treatment and who had at least one measurement of the outcome. This could result in unhealthier patients being underrepresented in the FAS population
  - ERG noted there were no major imbalances of baseline characteristics across the arms of VERTIS SITA 2 in the FAS population
- VERTIS FACTORIAL trial not included by the company provides further evidence on the effectiveness of ERTU in triple therapy. Results were comparable to VERTIS-SITA 2 results at 26 and 52 weeks

[redacted]

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Please see pages 9-10 of the ERG report for more information

ERG critique: company NMA

- Included trials were of good quality and broadly similar
- 3 different gliptins (sitagliptin, saxagliptin and linagliptin) were used in studies included in the NMA. The efficacy of these was assumed to be equal to allow a broader connected network. ERG agrees that this assumption is reasonable
- ERG carried out their NMA for the primary outcome which produced similar results to those presented by the company. There were no changes to estimates of effect size or statistical significance for the ERTU comparisons
- Although absolute equivalence is not proven, the company's NMA shows no clinically significant differences in glucose-lowering efficacy amongst the flozins:
  - effect on HbA1c of DAPA in the Jabbour 2014 trial at 26 weeks was smaller than in other DAPA trial but by 52 weeks the effect had increased to close to that of ERTU
- Instead of an NMA, ERG considers a simpler comparison of clinical effectiveness could have been carried out against just one flozin approved by NICE:
  - ERG compared VERTIS SITA 2 with the trial by Mathieu and colleagues of DAPA in combination with sitagliptin and metformin and concluded that this comparison provides reasonable evidence that ERTU is at least as effective as DAPA

[redacted]

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Please see pages 12-16 of the ERG report for more information

Company's economic analysis

- Company considered cost minimisation to be the most appropriate form of economic analysis because the results of the NMA showed that all flozins have similar health benefits
- Only drug acquisition costs were considered in the cost minimisation analysis as there are no differences in testing, initiation, administration or monitoring costs between flozins
- 1 year time horizon was considered sufficiently long to capture any differences between the treatments

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Drug acquisition costs

Therapy	Price per pack	Price per tablet	Dose per tablet	Daily dose	Annual cost
Background therapy					
Metformin	£0.90 per 28 pack	£0.03	500mg	2000 mg	£43.83
Gliptin (Sitagliptin)	£33.26 per 28 pack	£1.19	100mg	100 mg	£434.65
Intervention					
ERTU	£[redacted] per 28 pack	£[redacted]	5 mg or 15 mg	5 mg or 15 mg	£[redacted]
Comparators					
CANA	£39.20 per 30 pack	£1.31	100 mg or 300mg	100 mg or 300mg	£478.48
DAPA	£36.59 per 28 pack	£1.31	10 mg	10 mg	£478.48
EMPA	£36.59 per 28 pack	£1.31	10 mg or 25 mg	10 mg or 25 mg	£478.48
Combination					
Met + gliptin +ERTU		£[redacted]			£[redacted]
Met + gliptin +CANA		£2.53			£956.96
Met + gliptin +DAPA		£2.53			£956.96
Met + gliptin+EMPA		£2.53			£956.96

[redacted]

24

Source: Table 30 (page 57 of the company submission)

CONFIDENTIAL

Base-case results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs vs. ERTU
Metformin + gliptin + ERTU 5 mg /15 mg	£[redacted]	-	-	
Metformin + gliptin + CANA100 mg /300 mg	£956.96	-	-	£[redacted]
Metformin + gliptin + DAPA 5 mg /10 mg	£956.96	-	-	£[redacted]
Metformin + gliptin + EMPA 10 mg /25 mg	**£956.96**	-	-	£[redacted]

- CANA, DAPA and EMPA all have an annual cost of £478.48 (£1.31 per day * 365.25 days)
- ERTU is [redacted] to the NHS with an annual cost of per day * 365.25 days), producing an annual [redacted]

[redacted]

25

Source: Table 33 (page 60 of the company submission)

The company notes that the primary limitation of the cost-minimisation analysis is that the assumptions of equal efficacy and safety are not based on head to head comparisons from a randomised controlled equivalence trial. Additionally, the NMA for triple therapy only comprises of five trials as data was not available for all outcomes and the NMA networks did not converge for some safety outcomes (genital mycotic infections, NSHE and SHE). However, the company states that the NMA was populated with data from a SLR of RCTs. The studies included were quality assessed using the York Centre for Reviews and Dissemination checklist and found to be of high quality.

CONFIDENTIAL

ERG critique of company's cost-minimisation analysis

- Company's justification of a cost-minimisation approach on the basis of NMA results showing similar efficacy and safety is valid
- Assumptions of cost minimisation analysis are reasonable (no differences in administration/monitoring costs of flozins and 1 year time horizon)
- ERG agrees that ERTU results in an [redacted]
- Company's case, based on prescribing data, is that the triple therapy regimen of a flozin + metformin + gliptin is sufficiently used in UK for it to be considered standard therapy. However, it is relatively expensive compared with other triple therapy regimens
  - could be argued that company's proposed regimen is appropriate only when patients cannot take either SU or PIO

Combination	Annual cost
Metformin + SU + PIO	£76
Metformin + gliclazide* MR + PIO	£108
Metformin + SU + gliptin	£479
Metformin + gliclazide + flozin	£568
Metformin + gliptin+ PIO	£471
Metformin + gliptin+ flozin	£927

*Based on past appraisals gliclazide is ERG's preferred SU based on efficacy and AEs

[redacted]

26

Source: Table 7 (page 22 of the ERG report). Please see pages 21-23 of the ERG report for more information

Equalities issues

- No equality issues have been raised by the company or patient and professional groups

[redacted]

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Key issues

- The company's submission focusses on a triple therapy regimen of a flozin with metformin and a gliptin because ERTU has been studied in this combination
  - the combination of a flozin with metformin and a gliptin has not been considered or approved previously by NICE
  - the company believes that this regimen is sufficiently used in the UK for it to be regarded as standard therapy, and therefore no other triple therapy regimens are included as comparators
  - Does the committee accept the company's approach?
- The key clinical trial data comes from VERTIS SITA 2. Is the committee satisfied with the evidence for the efficacy and safety of ERTU compared with placebo?
- There is no direct evidence comparing ERTU with other flozins and the company conducted an indirect comparison. Does the committee accept the company's conclusions that ERTU has similar efficacy and safety to other flozins in the proposed triple therapy regimen?
- Does the committee accept the company's cost-minimisation approach based on the assumption that flozins have similar efficacy and safety and only differ in terms of drug acquisition costs?
- The ERG highlights that the triple therapy regimen proposed by the company costs more than other triple therapy regimens used in clinical practice. What is the committee's view of the cost relative to other triple therapy combinations?

[redacted]

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Authors

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[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ertugliflozin in triple therapy for treating type 2 diabetes [ID1160] [redacted]

Document B

Company evidence submission

30th August 2018

File name	Version	Contains confidential information	Date
		Yes	30th August 2018

Contents

Tables and figures

Abbreviations

AE	Adverse event
ADA	American diabetes association
AG	Assessment group
AHA	Anti-hyperglycaemic agents
ANCOVA	Analysis of covariance
ASaT	All subjects as treated
BL	Baseline
BMI	Body mass index
CANA	Canagliflozin
CHMP	Committee for Medicinal Products for Human Use
cLDA	Constrained longitudinal data analysis
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DAO	Data as observed
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DPP-4i	Dipeptidyl peptidase 4 inhibitor
DSU	Decision support unit
ECG	Electrocardiogram
EMA	European Medicine Agency
eGFR	Estimated glomerular filtration rate
EMPA	Empagliflozin
EPAR	European public assessment report
ERG	Evidence review group
ERTU	Ertugliflozin
FAS	Full analysis set
FEM	Fixed effect model
FPG	Fasting plasma glucose
GLUT1-4	Glucose transporter 1,2,3 and 4
GLP-1	Glucose-dependent insulinotropic peptide
GP	General practitioner
HbA1c	Haemoglobin A1 c
HDL-c	High-density lipoprotein
HRQoL	Health-related quality of life
HOMA-β	Homeostatic model assessment β cell
ICER	Incremental cost-effectiveness ratio
IR	Including rescue (approach)
ITT	Intention-to-treat population
IVRS	Interactive voice response system
LDL-c	Low-density lipoprotein
LINA	Linagliptin
LS	Least square
LYG	Life years gained
MA	Marketing authorization
MAT	Moving annual total
MET	Metformin
Mg	Milligram
MI	Myocardial infarction

MSD	Merck Sharp & Dohme Ltd
N	Number of patients per treatment group
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NPH	Neutral protamine Hagedorn
NSHE	Non-severe hypoglycaemic event
N/A	Not applicable
OR	Odds ratio
PBO	Placebo
PP	Per protocol
PPG	Post-prandial glucose
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REM	Random effect model
S	Screening
SA	Sensitivity analysis
SAE	Serious adverse event
SAXA	Saxagliptin
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SITA	Sitagliptin
SLR	Systematic literature review
SGLT-1	Sodium-glucose cotransporter-1
SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
SHE	Severe hypoglycaemia
SmPC	Summary of product characteristics
SU	Sulphonylurea
TA	Technology appraisal
TC	Total cholesterol
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedone
UGE	Urinary glucose excretion
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary tract infections
V	Visit
W	Week

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission focuses on part of the ertugliflozin (Steglatro®) marketing authorisation: triple therapy regimen with metformin and a dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of type 2 diabetes mellitus (T2DM).

The proposed population, patients with inadequate glycaemic control on a stable dose of metformin and a DPP-4i is narrower than the marketing authorization because the evidence base on ertugliflozin is limited to this triple therapy regimen.

Please see Table 1 below for a summary of the National Institute for Health and Care Excellence (NICE) decision problem.

Table 1 - The decision problem

	Final scope issued by NICE (August 2018)	Decision problem addressed in the company submission (August 2018)	Rationale if different from the final NICE scope
Population	Adults with T2DM inadequately controlled on combination therapy with anti-diabetic agents	Adults with T2DM inadequately controlled on combination therapy with anti-diabetic agents	
Intervention	Ertugliflozin in a triple therapy regimen	Ertugliflozin in a triple therapy regimen	
Comparator(s)	• Sulfonylureas • DPP-4is • Pioglitazone • Sodium-glucose co-transporter 2 inhibitor (SGLT-2is) • GLP-1 mimetics • Insulin	• SGLT-2is	As stated in Section B.1.1, the ertugliflozin evidence in a triple therapy regimen is confined to the following combination: metformin + DPP-4i + ertugliflozin. MSD believes that the only relevant comparators are other SGLT-2is used in a triple therapy regimen with the same background therapies.
Outcomes	• Mortality. • Complications of diabetes, including cardiovascular, renal and eye. • HbA1c/glycaemic control. • Body mass index (BMI). • Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including urinary tract infections (UTIs), genital mycotic infections and malignancies. • Health-related quality of life (HRQoL).	• Mortality. • Complications of diabetes, including cardiovascular, renal and eye. • HbA1c/glycaemic control. • BMI. • Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including UTIs, genital mycotic infections and malignancies. • HRQoL.	

	Final scope issued by NICE (August 2018)	Decision problem addressed in the company submission (August 2018)	Rationale if different from the final NICE scope
Economic Analysis	Cost-utility analysis	Cost-minimisation analysis	As the results of the network meta-analysis (NMA) revealed that the efficacy and safety of all SGLT-2is were similar in triple therapy, a cost-minimisation analysis was considered the most appropriate form of economic evaluation
Subgroups to be considered	None	None	

Abbreviations: NICE, National Institute for Health and Care Excellence; T2DM, type 2 diabetes mellitus; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium –glucose co-transporter 2 inhibitor; GLP-1, glucagon-like peptide 1

B.1.2 Description of the technology being appraised

The summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) [1] for the indication being appraised have been included in Appendix C.The technology being appraised (ertugliflozin) is described in the Table 2 below.

Table 2 - The technology being appraised: ertugliflozin in combination with metformin and a DPP-4i

UK approved name and brand name	Ertugliflozin (Steglatro®)
Mechanism of action	Ertugliflozin is an inhibitor of SGLT-2 and possesses a high selectivity over glucose transport via sodium-glucose co-transporter 1 (SGLT-1) and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion (UGE) and thereby reducing plasma glucose and HbA1c in patients with T2DM
Marketing authorisation/CE mark status	• Date of Marketing authorisation: 21st March 2018
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ertugliflozin has been approved by the EMA for: Adults aged 18 years and older with T2DM to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes
Method of administration and dosage	Ertugliflozin should be taken orally once daily in the morning, with or without food. In monotherapy, the recommended starting dose of ertugliflozin is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed. In combination therapy the dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of ertugliflozin 5 mg or ertugliflozin 15 mg.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	• Ertugliflozin (Steglatro®) 5 mg * 28 tablets: £[redacted] per pack • Ertugliflozin (Steglatro®) 15 mg * 28 tablets: £[redacted] per pack
Patient access scheme (if applicable)	N/A

Abbreviations: SGLT-2i, sodium –glucose co-transporter 2 inhibitor; T2DM, type 2 diabetes mellitus; mg, milligram; N/A, not applicable

B.1.3 Health condition and position of the technology in the treatment pathway

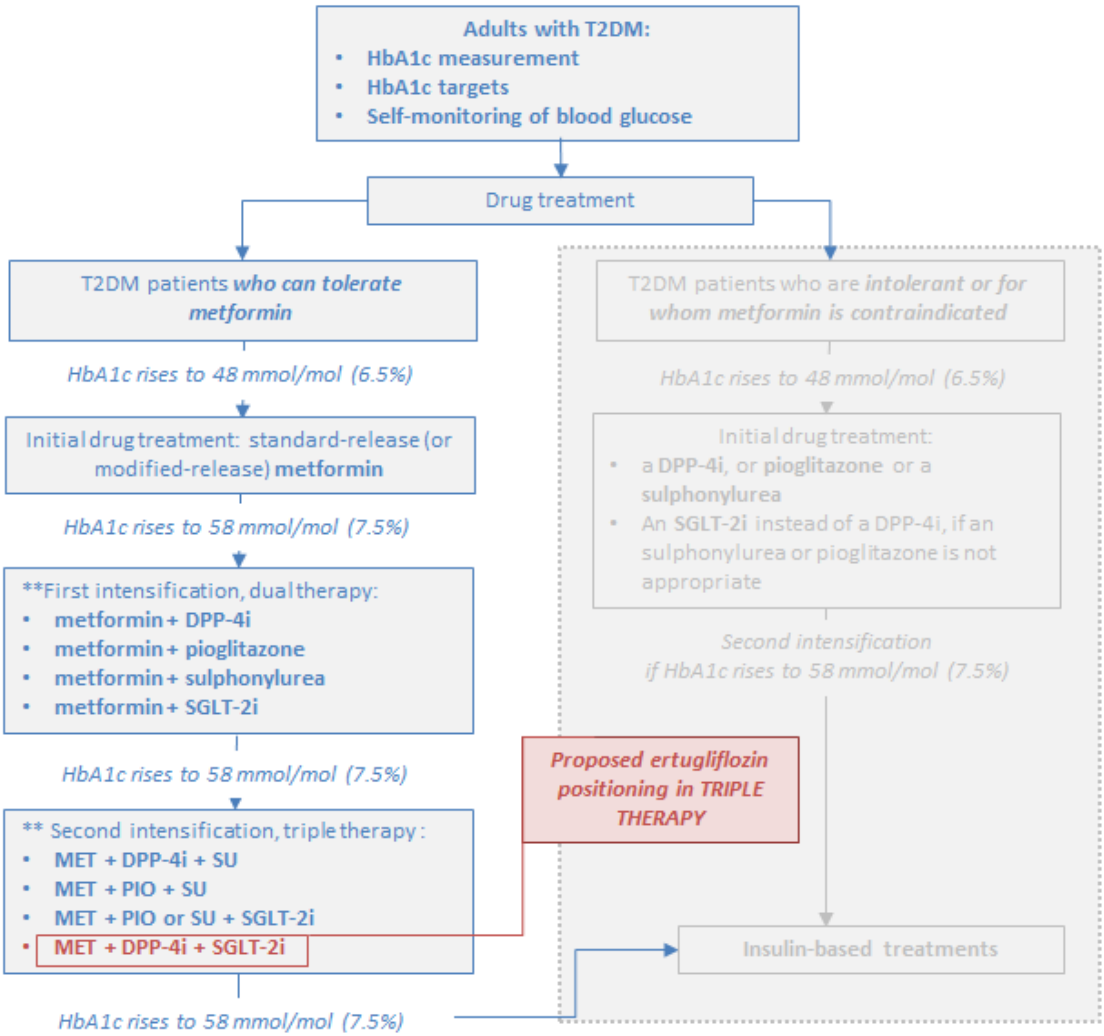
B.1.3.1 Brief disease overview

T2DM is a progressive metabolic disease that leads to a decline of the pancreatic β-cells function. Elevated blood concentrations of glucose are the typical manifestation of this disorder, defined as hyperglycaemia. This phenomenon is induced by the hormone insulin; this may be present in lower concentrations in the body or there may be a resistance in its action [2]. Patients affected by T2DM and inadequately controlled with treatments may develop comorbidities and cardiovascular complications that include: retinopathies, nephropathies, neuropathies, peripheral vascular disease, hypertension and cardiovascular disease [2]. It is estimated that worldwide 415 million people suffer from T2DM [3], of which ~3.1 million are in England [4].

B.1.3.2 Clinical pathway and ertugliflozin proposed positioning

The clinical pathway of care depicted below in Figure 1, reflects the latest NICE pathway for "Managing blood glucose in adults with type 2 diabetes" [5] and the algorithm for blood glucose lowering therapy in adults with T2DM included in NICE Guideline (NG) 28 [4]: "Type 2 diabetes in adults", which was revised in April 2017 and accounts for SGLT-2is like ertugliflozin.

Figure 1- Current T2DM clinical pathway (NG28) and proposed ertugliflozin combination therapy positioning with metformin and DPP-4i



**Support the person aim for an HbA1c level of 48 mmol/mol or 53 mmol/mol
Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; MET, metformin; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

Table 3 below summarises the moving annual total (MAT) of antihyperglycaemic agents (AHA) used in triple therapy (in order of administration) for December 2017 [6].

The table clearly shows that SGLT-2is are only used in triple therapy in combination with 'metformin + sulphonylureas (SU)' or 'metformin + DPP-4i'. The metformin + DPP-4i + SGLT-2i combination already accounts for 11.4% of triple therapy. Ertugliflozin proposed positioning in triple therapy focuses on adding it to a background of 'metformin + DPP-4i'.

Table 3 - UK MAT of AHA use in triple therapy

Triple therapy	MAT 2017 [6]	
	Patients	*%*
SU + MET + TZD	23,806	7.8
MET + SU + DPP-4i	138,287	45.1
MET + SU + GLP-1	21,172	6.9
MET + SU + SGLT-2i	45,792	15.0
MET + TZD + DPP-4i	10,059	3.3
MET + DPP-4i + GLP-1	1,724	0.5
MET + DPP-4i + SGLT-2i	34,775	**11.4**
Other	30,656	10.0
Total	306,271	100

Abbreviations: MAT, moving annual total; SU, sulphonylureas; MET, metformin; TZD, thiazolidinedione; GLP-1, glucagon-like peptide – 1; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT-2i, sodium-glucose co-transporter-2; TZD, thiazolidinedione

B.1.4 Equality considerations

MSD has not identified any equality issues.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to identify clinical studies relevant to this submission. The first SLR was designed to identify randomised controlled trials (RCTs) on the efficacy and safety of ertugliflozin and other pharmacological interventions (other SGLT-2is) for the treatment of adult patients with uncontrolled T2DM. The searches for this SLR were originally conducted on the 19th December 2016 and updated on the 11th August 2017 and 8th May 2018.

The second SLR was designed to identify interventional non-RCTs evidence supporting the efficacy and safety of ertugliflozin for the treatment of uncontrolled T2DM. Searches for this SLR were conducted in August 2017 and May 2018. From the original and the SLR updates:

1. RCTs SLR: A total of 8 citations were identified:
   - Five RCTs for ***triple therapy*** were included in the NMA. The ertugliflozin RCTs identified as relevant for the purposes of this submission was the VERTIS SITA2 study
2. Non-RCTs SLR: No citations were identified and therefore none were included in accordance with the inclusion and exclusion criteria described in Appendix D.

Full details of the SLR process and methods used to identify and select the clinical evidence relevant to the appraisal of ertugliflozin in triple therapy have been included in Appendix D. The SLRS also sought evidence for monotherapy and dual therapy. A summary of the studies identified through the SLR and included in the NMA is presented in Table 4.

Table 4 - Studies identified through the SLR and included in the NMA

First author, year	Location(s)	Previous treatment	Arm 1	Arm 2	Arm 3	Study duration (weeks)
VERTIS SITA2 [7-10]	Australia, Brazil, Canada, France, Korea, New Zealand, Norway, Spain, Taiwan, USA	metformin ≥1500 and sitagliptin 100 mg for ≥8 weeks	metformin + sitagliptin 100 mg + placebo	metformin + sitagliptin 100 mg + ertugliflozin 5 mg	metformin + sitagliptin 100 mg + ertugliflozin 15 mg	26
Jabbour 2014 [11, 12]	Argentina, Germany, Mexico, Poland, UK, USA	metformin ≥1500 and 10 week dose-stabilisation of sitagliptin 100 mg. 52% of patients were on metformin + sitagliptin 100 mg prior to study commencement	metformin + sitagliptin 100 mg + placebo	metformin + sitagliptin 100 mg + dapagliflozin 10 mg		24
Mathieu 2015 [13, 14]	USA, Czech Republic, Mexico, Poland, Puerto Rico, Romania, Russian Federation, UK	metformin ≥1500 for ≥8 weeks or metformin ≥1500 and DPP-4i ≥8 weeks	metformin + saxagliptin 100 mg + placebo	metformin + saxagliptin 100 mg + dapagliflozin 10 mg		24
Rodbard 2016 [15, 16]	Australia, Canada, France, Germany, USA	metformin ≥1500 and sitagliptin 100 mg for ≥12 weeks	metformin + sitagliptin 100 mg + placebo	metformin + sitagliptin 100 mg + canagliflozin 300 mg		24
Softeland 2017 [17, 18]	Australia, Brazil, Canada, France, Korea, New Zealand, Norway, Spain, Taiwan, USA	metformin ≥1500 for ≥12 weeks	metformin + linagliptin 5 mg + placebo	metformin + linagliptin 5 mg + empagliflozin 10 mg	metformin + linagliptin 5 mg + empagliflozin 25 mg	24

Abbreviations: SLR, systematic literature review; NMA, network meta-analysis

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Trial design of RCTs involving the intervention of interest

The efficacy and safety of ertugliflozin in combination with metformin and a DPP-4i have been studied in a randomised, double-blind, placebo - controlled Phase 3 clinical study. A summary of the clinical trial [8-10] is presented in Table 5 below.

Please note for clarity that the ertugliflozin 15 mg dose used in the VERTIS SITA2 study was administered as 5 mg and 10 mg tablets; only the 5 mg and 15 mg tablets will be marketed in the UK.

Table 5 - Clinical effectiveness evidence from the VERTIS SITA2 study

<table>
<tr><th>Study</th><th>VERTIS SITA2 [8-10]</th></tr>
<tr><td>Study design</td><td>A Phase 3, 52-week, multicentre, double-blind, randomised, placebo-controlled, parallel – group study divided into two phases:
- phase A, a 26–week, double-blind, placebo–controlled treatment period
- phase B, a 26-week active–controlled treatment period</td></tr>
<tr><td>Population</td><td>Adults with T2DM, diagnosed in accordance with the American Diabetes Association (ADA) guidelines, with inadequate glycaemic control (HbA1c 7.0-10.5% [53-91 mmol/mol]) on metformin therapy at a dose ≥1500 mg/day and on sitagliptin at a dose of 100 mg/day.</td></tr>
<tr><td>Intervention(s)</td><td>Ertugliflozin 5 mg (N=156)
Ertugliflozin 15 mg (N=153)

Phase A: patients were randomised to ertugliflozin 5 mg or ertugliflozin 15 mg while maintaining metformin at a stable dose of ≥1500 mg/day and sitagliptin 100 mg/day up to week 26. Patients were instructed to take:

<table>
<tr><th>Background therapy</th><th>Arms</th><th>Medication administered</th></tr>
<tr><td rowspan="4">MET ≥1500 and SITA100</td><td rowspan="2">ERTU5</td><td>ERTU5 tablet</td></tr>
<tr><td>Matching PBO for ERTU10</td></tr>
<tr><td rowspan="2">ERTU15</td><td>ERTU5 tablet</td></tr>
<tr><td>ERTU10 tablet</td></tr>
</table>

Patients were prescribed with glycaemic rescue therapy in the form of open-label glimepiride (or insulin glargine if glimepiride was considered inappropriate) when exceeding the following thresholds:

- Fasting plasma glucose (FPG) > 270 mg/dL after randomisation up to week 6
- FPG > 240 mg/dL after week 6 through week 12
- FPG > 200 mg/dL after week 12 through week 26

Phase B: double-blind (investigators and patients) extension period where patients randomised to ertugliflozin remain on their randomised treatments until week 52.</td></tr>
<tr><td>Comparator(s)</td><td>Placebo (N=153)

Phase A: patients were randomised to placebo while maintaining metformin at a stable dose of ≥1500 mg/day and sitagliptin 100 mg/day.</td></tr>
</table>

<table>
<tr><td></td><td colspan="3">Patients were instructed to take:

<table><tr><th>Background therapy</th><th>Arms</th><th>Medication administered</th></tr><tr><td rowspan="4">MET ≥1500 and SITA100</td><td rowspan="2">PBO</td><td>Matching PBO for ERTU5</td></tr><tr><td>Matching PBO for ERTU10</td></tr><tr><td rowspan="2">PBO</td><td>Matching PBO for ERTU5</td></tr><tr><td>Matching PBO for ERTU10</td></tr></table>
Patients were prescribed with glycaemic rescue therapy in the form of open-label glimepiride (or insulin glargine if glimepiride was considered inappropriate) when exceeding the following thresholds:

- FPG > 270 mg/dL after randomisation up to week 6
- FPG > 240 mg/dL after week 6 through week 12
- FPG > 200 mg/dL after week 12 through week 26

Phase B: double-blind (investigators and patients) extension period where patients randomised to placebo remain on their randomised treatments until week 52</td></tr>
<tr><td>Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>Indicate if trial used in the economic model</td><td>No. Clinical data was not required for cost-minimisation modelling</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="3">• Mortality.
• Complications of diabetes, including cardiovascular, renal and eye.
• HbA1c / glycaemic control.
• BMI.
• Frequency and severity of hypoglycaemia.
• Changes in cardiovascular risk factors.
• Adverse effects of treatment, including urinary tract infections, genital infections and malignancies.
• HRQoL.</td></tr>
<tr><td>All other reported outcomes</td><td colspan="3">- HbA1c <7.0%.
- FPG.
- Patients receiving glycaemic rescue therapy.
- Hypovolemia.
- Haemoglobin.
- HOMA-β cell function.
- HDL-c, LDL-c.</td></tr>
</table>

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; PPG, post-prandial glucose; ERTU5/10/15, ertugliflozin 5, 10 and 15 mg; MET, metformin; PBO, placebo; BMI, body mass index; UTIs, urinary tract infections; HRQoL, health-related quality of life; HOMA- β, homeostatic model assessment β cell

B.2.2.2 RCTs excluded from further discussion

Summarised below in Table 6 are the RCTs that report ertugliflozin in combination with metformin and a DPP-4i but that were excluded from this submission. The rationale for exclusion is provided within the table.

Table 6 – ertugliflozin RCTs excluded from this submission

Study details	Population	Intervention & Comparator	Rationale for exclusion
VERTIS FACTORIAL [19, 20] Phase 3, completed	Patients with T2DM who have inadequate glycaemic control on metformin	All on a background of metformin: • SITA100 + ERTU5 vs. ERTU15 • SITA100 + ERTU15 vs. ERTU5 • SITA100 + ERTU5 m vs. SITA100 • SITA100 + ERTU15 vs. SITA100	The triple therapy focus of this submission is ertugliflozin compared to other SGLT-2is on a background of metformin + DPP-4is. The background therapy of the VERTIS FACTORIAL study is metformin only.
VERTIS SITA [21, 22] Phase 3, completed	Patients with T2DM who have inadequate glycaemic control despite diet and exercise	• SITA100 + ERTU5 vs. PBO • SITA100 + ERTU15 vs. PBO	The triple therapy focus of this submission is ertugliflozin compared to other SGLT-2is on a background of metformin + DPP-4is. The background therapy of the VERTIS SITA study is diet and exercise only.

Abbreviations: T2DM, type 2 diabetes mellitus; ERTU5/15, ertugliflozin 5 and 15 mg; MET, metformin; PBO, placebo; SITA100, sitagliptin 100 mg

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Key aspects of listed RCTs

As described in Section B.1.1, ertugliflozin in combination with metformin and a DPP-4i has been approved by the EMA for the treatment of patients with T2DM. All aspects of the included trial methodologies are reported below. A summary of the baseline characteristics of the participants in these trials is presented in Table 7.

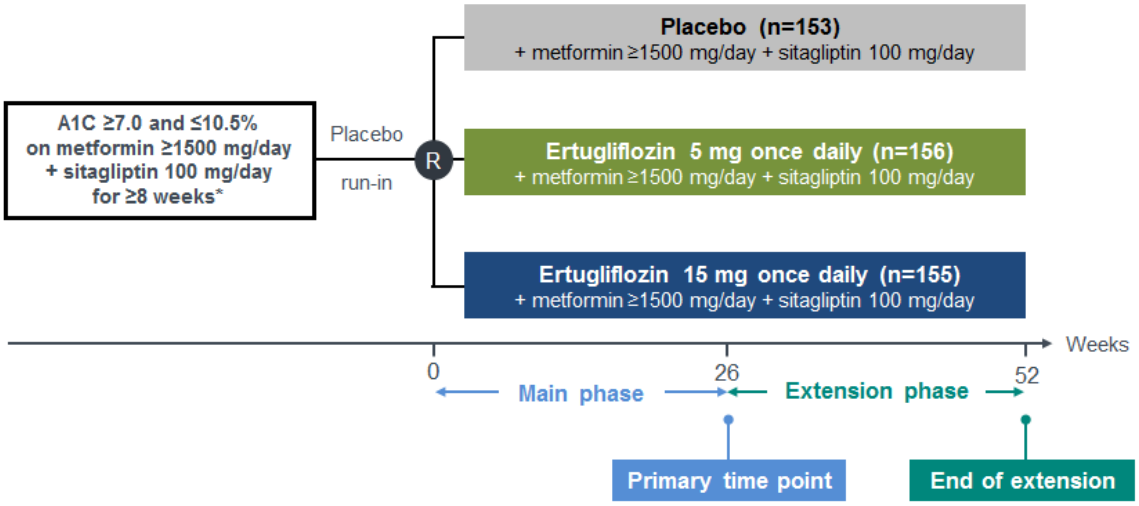
VERTIS SITA2 Study [7-10]

Trial design

The VERTIS SITA2 study is a 52-week, double-blind, multi-center, randomised, placebo-controlled, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 26-week double-blind active placebo extension (Phase B). The efficacy and safety outcomes at week 26 (Phase A) will be used as evidence of comparability to other SGLT-2is in this submission. This study aims to evaluate the efficacy and tolerability of ertugliflozin 5 mg and 15 mg versus placebo in people with T2DM and inadequate glycaemic control on metformin at a dose ≥1500 mg/day and on sitagliptin at a dose of 100 mg/day for at least 8 weeks.

VERTIS SITA2 enrolled 464 patients with a diagnosis of T2DM according to ADA guidelines. The duration of the trial was for up to approximately 69 weeks (with 10 clinic visits) for each patient. Please see the trial design diagram in Figure 2 for a graphical representation.

Figure 2 - VERTIS SITA2 trial design diagram



* Patients on one of the following regimens were also eligible to enter the screening period, and could enrol in the trial if they met entry criteria after the wash-out / dose titration / stabilization period:

- On metformin ≥1500 mg/day + sitagliptin 100 mg/day <8 weeks
- On metformin ≥1500 mg/day + other DPP-4i or a SU
- On metformin <1500 mg/day + any DPP-4i

Abbreviations: HbA1c, haemoglobin A1c

A double-blind/masking technique was used in this study. Ertugliflozin and matching placebo were packaged identically so that blinding was maintained. The patient, the investigator and the sponsor personnel who were involved in the treatment or clinical evaluation of the patients, were unaware of treatment group assignments. Patients' treatment assignments were unblinded at the completion of the 26-week Phase A to the sponsor to permit authoring of the clinical study report (CSR). Personnel associated with the conduct of the study, as well as trial site personnel and patients, remained blinded and were not unblinded until after Phase B of this study was completed.

Randomisation occurred centrally using an interactive voice response system (IVRS). Patients were assigned randomly in a 1:1:1 ratio to ertugliflozin 5 mg (N=156), ertugliflozin 15 mg (N=155; only 153 analysed due to two patients not receiving study medication), or placebo once daily (N=153) using a computer-generated randomization schedule. Randomisation was stratified according to use of a sulfonylurea at the first visit. All randomised participants had to be on a stable dose of metformin (≥1500 mg/day) and sitagliptin 100 mg until completion of the study at week 52.

Given that the results at week 26 (Phase A) will provide the evidence of ertugliflozin 5 mg and 15 mg comparability to the other SGLT-2is in the scope, Phase B of the VERTIS SITA2 study will not be discussed further. However, for completeness, the main efficacy and safety results are presented in Appendix M.

Eligibility criteria

To be considered for inclusion in the study, male and female patients had to have a diagnosis of T2DM in accordance with ADA guidelines, be aged ≥18 years, a BMI ≥18.0 kg/m2, inadequate glycaemic control on metformin therapy (≥1500 mg/day for at least 8 weeks) and be on sitagliptin (100 mg/day) for ≥8 weeks, and have a HbA1c between 7.0-10.5%, (53–91 mmol/mol) at the screening visit. All patients who were on this regimen for less than 8 weeks, or at a lower dose of metformin, or used metformin in combination with a DPP-4i other than sitagliptin, were adjusted to the appropriate medication and if they met the abovementioned criteria they entered the study. As illustrated in Figure 2, participants on this therapy regimen for <8 weeks and/or on lower doses of metformin and/or another DPP-4 inhibitor at screening were eligible to take part in the study matching the above therapy criteria after an appropriate dose adjustment, stabilisation, or washout period.

The exclusion criteria comprised of patients diagnosed with T1DM, medical history of ketoacidosis, eGFR <60 mL/min/1.73m^2 or serum creatinine ≥115 µmol/L (1.3 mg/dL) in men or ≥106 µmol/L (1.2 mg/dL) in women, history of cardiovascular event within 3 months of screening, treatment in the previous 12 weeks with insulin of any type of AHAs other than metformin, DPP-4 inhibitors or SUs; uropathy or FPG >14.4 mmol/L (260 mg/dL) prior to the placebo-run in.

Settings and locations

The trial was conducted in 12 countries, including 104 trial centres: 5 in Argentina, 5 in Bulgaria, 4 in Colombia, 10 in Czech Republic, 5 in Finland, 4 in Hungary, 9 in Israel, 6 in Malaysia, 9 in Romania, 7 in Slovakia, 12 in the Republic of Korea, and 28 in the United States.

Trial drugs and concomitant medications

Patients were given ertugliflozin 5 mg, ertugliflozin 15 mg or placebo as oral tablets once daily for 52 weeks at approximately the same time (morning) each day. Additionally, metformin (≥1500 mg/day) and sitagliptin (100 mg/day) were also given as background therapies.

The AHAs taken by the patient at any time prior to Visit 1/Screening, and any other medications taken within 8 weeks of Visit 1/Screening, were recorded. Concomitant medications (including glycaemic rescue therapy) taken during the trial were also recorded. The following medications were prohibited while patients were receiving study medication during the double-blind treatment period: other antihyperglycaemic medications not under investigation in VERTIS SITA2, corticosteroids and weight-loss medications.

The investigator or patient's physician/healthcare provider was permitted to make adjustments in the patient's non-AHA therapies throughout the trial if clinically warranted. Specific medications permitted during the study were: blood pressure and lipid-altering medications, hormonal replacement therapy and birth control medications, thyroid hormone replacement therapy and supplements and/or traditional medicines

Outcomes specified in the scope

VERTIS SITA2 study outcomes were pre-specified and they are aligned to the outcomes described in the scope (see Section B.1.1).

The primary efficacy endpoint was the change from baseline in HbA1c to week 26 followed by pre-specified secondary endpoints all evaluated at week 26 that included: change in FPG, body weight and blood pressure (SBP and DBP), proportion of patients with HbA1c <7.0%, patients who received glycaemic rescue therapy, fasting measure of β- cell function and changes in EQ-5D-3L.

The safety and tolerability of ertugliflozin was evaluated through the assessment of pre-specified AEs following a tiered approach. Tier 1 AEs evaluated AEs of special interest such as genital mycotic infections, UTIs, symptomatic hypoglycaemia and hypovolemia. Other AEs and changes in laboratory parameters that were not pre-specified as Tier 1 endpoints were classified as belonging to Tier 2 or Tier 3, based on the number of events observed.

B.2.3.2 Baseline characteristics of the participants in the VERTIS SITA2 study

Baseline characteristics of the patients were generally similar between groups with the exception for the gender category, where a higher proportion of males in the placebo group versus the ertugliflozin groups was found (Table 7). The mean age was 59.1 years; the mean duration of the disease was 9.51 years and the overall median metformin dose at baseline was 2000 mg/day.

Table 7 - The baseline characteristics of participants in the VERTIS SITA2 trial by treatment groups (All Subjects as Treated = ASaT)

VERTIS SITA2 [7-10]	PBO	ERTU5	ERTU15	TOTAL
n	153	156	153	462
Demographics				
Age, mean (SD) years	58.3 (9.2)	59.2 (9.3)	59.7 (8.6)	59.1 (9.0)
Gender, n (%)	Male: 100 (65.4) Female: 53 (34.6)	Male: 81 (51.9) Female: 75 (48.1)	Male: 82 (53.6) Female: 71 (46.4)	Male: 263 (56.9) Female: 199 (43.1)
Body weight (kg), mean (SD)	86.4 (20.8)	87.6 (18.6)	86.6 (19.5)	86.9 (19.6)
BMI, mean (SD) kg/m^2	30.3 (6.40)	31.2 (5.5)	30.9 (6.1)	30.8 (6.0)
Disease indicators				
Disease duration (years), mean (SD)	9.44 (5.55)	9.88 (6.13)	9.20 (5.32)	9.51 (5.68)
Background AHA therapy at screening:				
MET, n (%)	153 (100.0)	156 (100.0)	153 (100.0)	462 (100.0)
DPP-4i, n (%)	102 (66.7)	107 (68.6)	100 (65.4)	309 (66.9)
Sulfonamides, urea derivates, n (%)	52 (34.0)	52 (33.3)	54 (35.3)	158 (34.2)
No. agents 2	152 (99.3)	152 (97.4)	152 (99.3)	456 (98.7)
No. agents 3+	1 (0.7)	4 (2.6)	1 (0.7)	6 (1.3)
HbA1c %, mean (SD)	8.03 (0.93)	8.05 (0.86)	8.00 (0.83)	8.03 (0.88)
FPG mmol/L, mean	9.4	9.3	9.5	9.4

VERTIS SITA2 [7-10]	PBO	ERTU5	ERTU15	TOTAL
eGFR mL/min/1.73m^2, mean (SD)	**30 to <60**: 1 (0.7) **60 to <90**: 79 (51.6) **≥90**: 73 (47.7)	**30 to <60**: 3 (1.9) **60 to <90**: 79 (51.6) **≥90**: 73 (47.7)	**30 to <60**: 4 (2.6) **60 to <90**: 85 (55.6) **≥90**: 64 (41.8)	**30 to <60**: 8 (1.7) **60 to <90**: 257 (55.6) **≥90**: 197 (42.6)

Abbreviations: ERTU, ertugliflozin; PBO, placebo; MET, metformin; mg, milligram; n, sample size; BMI, body mass index; kg, kilogram; AHA, anti-hyperglycaemic agent; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SD, standard deviation; DPP-4i, dipeptidyl peptidase 4 inhibitor

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the VERTIS SITA2 trial population, hypothesis-objective, statistical analysis and data management are summarised in Table 8 below.

Table 8 - Summary of the statistical analyses for the VERTIS SITA2 ertugliflozin study

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Triple therapy				
VERTIS SITA2 [7-10]	Ertugliflozin is superior to placebo in patients with T2DM and inadequate glycaemic control on a stable dose of metformin and sitagliptin	All outcomes analysed followed a planned testing procedure with ertugliflozin 15 mg assessed first, followed by ertugliflozin 5 mg. If a test in the ordered testing procedure did not meet statistical significance, subsequent tests were considered nominal and were thus not used for declaring statistical significance but only as a measure of strength of association between the endpoint and the treatment effect. • The full analysis set (FAS) population was used for most efficacy endpoints, which included all randomised patients who took at least one dose of study medication and had at least one measurement of the outcome variable. The primary analysis model for continuous efficacy endpoints was a cLDA model proposed by Liang and Zeger [23]. The model	The trial aimed to randomise approximately 405 patients in a 1:1:1 ratio among the 3 treatment groups. This sample size provided 97% power to detect a true difference of 0.5% in the mean change from baseline in HbA1c between a given ertugliflozin dose and placebo based on a 2-sided test at a 5% level of significance, with a	Efficacy • Missing data were handled implicitly by a longitudinal data analysis (LDA) model. Logistic regression was used to evaluate the proportion of patients with HbA1c. • Sensitivity analyses were performed that did not rely on the "Missing at Random" assumption underlying the primary methodology Safety • In the absence of safety data the safety analysis used data as observed (DAO), i.e. no

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		included terms for treatment, prior AHAs (metformin + DPP-4i / metformin + SU), baseline eGFR, time, and the interaction of time by treatment. • The ASaT population was used for the safety analysis, time-to-rescue analysis and for summarising baseline characteristics, patient disposition and compliance. It consisted of all randomised patients who took at least one dose of study medication Safety and tolerability were assessed following a tiered-approach. Symptomatic hypoglycaemia and AEs associated with UTIs, male and female genital mycotic infections and hypovolemia were considered to be pre-specified safety parameters (Tier 1) for which p-values and 95% CIs for between-treatment differences were provided using the Miettinen and Nurminen method [24]. Other safety parameters were considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters. Continuous measures such as changes from baseline in laboratory, ECG, and vital sign parameters were considered Tier 3, except for lipid parameters which belonged to Tier 2. Summary statistics for baseline, on-treatment, and change (or percent change) from baseline values were provided by treatment group in table format and plotted with the corresponding standard errors.	SD of 1.0 and assuming a dropout rate of 19%.	imputation for missing data/missing value excluded Patient withdrawal If a patient withdrew consent from participating in the trial, no further evaluations were performed, and no additional data collected. Patients who discontinued treatment with study medication for reasons other than withdrawn consent attended the clinic for a Study Medication Discontinuation Visit followed by a post-treatment telephone call 14 days after the last dose of study medication.

Abbreviations: T2DM, type 2 diabetes mellitus; FAS, full analysis set; ASaT, all subjects as treated; ECG, electrocardiogram

Full details of the numbers of participants eligible to enter the trial are included in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

B.2.5.1 Validity of the RCTs results

The quality of each source of evidence identified in Section B.2.2 has been appraised in order to assess the validity and robustness of the overall design and execution of the VERTIS SITA2 study.

B.2.5.2 Quality assessment methods

The York Centre for Reviews and Dissemination quality assessment tool [25] was chosen to assess the quality and risk of bias of the RCTs identified through the SLR, which incorporates the criteria for assessment of risk of bias and generalisability suggested by NICE [26].

B.3.5.3 Routine clinical practice in England

The VERTIS SITA2 trial reflects current clinical practice in England and Wales for patients on metformin and a DPP-4i requiring second treatment intensification to reach their HbA1c goal. The change in HbA1c over time is the primary efficacy outcome of the VERTIS SITA2 trial presented in Section B.2.2, which reflects current clinical practice in England and Wales for evaluating treatments in patients with T2DM (NG28 [5]). The remaining secondary efficacy (change in weight, FPG and SBP) and safety (AEs, hypoglycaemia, UTIs and genital mycotic infections) outcomes are all clinically relevant to both physicians and patients for assessing the progression of the disease and the need for treatment intensification.

B.3.5.4 Summary of results of the quality assessment of the ertugliflozin RCTs

As can be seen in Table 9, the results of the quality assessment indicate that the VERTIS SITA2 study is of good quality. Please refer to Appendix D for a complete quality assessment of each trial identified through the SLR.

Table 9 - Summary of quality assessment for the VERTIS SITA2 trial reporting ertugliflozin in triple therapy

Study ID and publications	VERTIS SITA2 [7-10]
	Triple therapy
Was the randomisation method adequate?	Yes
Was the allocation adequately concealed?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis?	No
Did the authors of the study publication declare any conflicts of interest?	Yes

Abbreviations: ID, identity

B.2.6 Clinical effectiveness results of the relevant trials

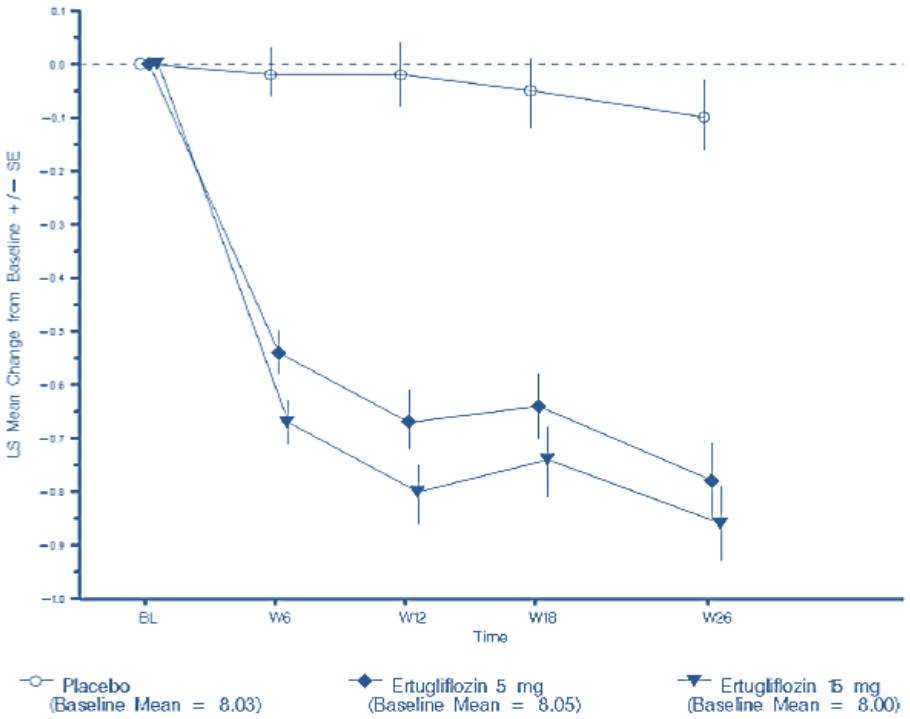
All data from the VERTIS SITA2 trial are presented excluding glycaemic rescue therapy to avoid the confounding influence of the rescue therapy (e.g. glimepiride or insulin glargine). As described in Table 8, the FAS population was used for the majority of the efficacy endpoints, whereas the ASaT was used for all safety and tolerability outcomes.

B.2.6.1 VERTIS SITA2: Phase A - primary efficacy outcome at week 26

HbA1c change from baseline to week 26

The least square (LS) mean reductions from baseline in HbA1c to week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups than in the placebo group, as shown in Figure 3. In the ertugliflozin groups, reductions from baseline in HbA1c were observed at week 6 and 12, with subsequent further reductions seen at week 26. The reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. In the placebo group, there was essentially no change from baseline in HbA1c to week 18; a small reduction in HbA1c was observed at week 26.

Figure 3 - HbA1c (%) change from baseline to week 26 - (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-0.69 (-0.87, -0.50)	<0.001
ERTU15	-0.76 (-0.95, -0.58)	<0.001

Abbreviations: HbA1C, haemoglobin A1c; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least square; SE, standard error; W, week; FAS, full analysis set

The corresponding changes from baseline to week 26 for HbA1c in mmol/mol are:

- ertugliflozin 5 mg vs. placebo = [95%CI] = -7.51 [-9.50, -5.51]
- ertugliflozin 15 mg vs. placebo = [95%CI] = -8.34 [-10.35, -6.33]

B.2.6.2 VERTIS SITA2: Phase A - secondary efficacy outcomes at week 26

Proportion of patients with HbA1c <7.0% (<53 mmol/mol) at week 26

Table 10 shows the analysis of the proportion of patients with an HbA1c <7.0% (<53 mmol/mol) at week 26. The raw proportion of patients with an HbA1c <7.0% was almost twice as great in the ertugliflozin 5 mg group and was over twice as great in the ertugliflozin 15 mg group as it was in the placebo group. The model-based odds of having an HbA1c <7.0% at week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group.

Table 10 - Analysis of patients with HbA1c <7.0% at week 26 - (logistic regression using multiple imputation; FAS)

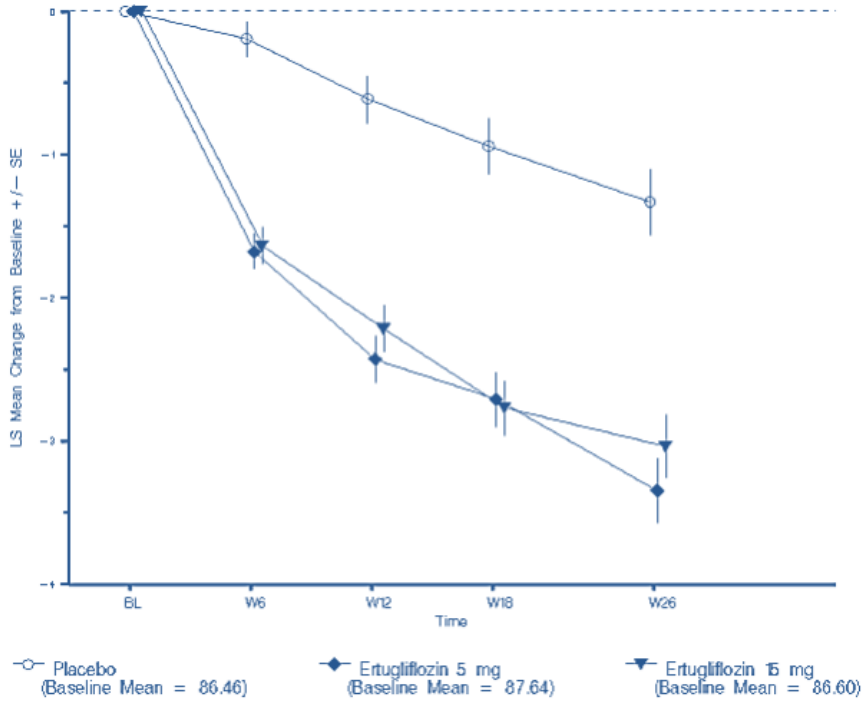
Treatment	N	Number (%) of patients with HbA1c <7.0% (raw proportion)	Adjusted odds ratios relative to PBO*		
			Point estimate	95% CI	p-Value
PBO	153	26 (17.0)			
ERTU5	156	50 (32.1)	3.16	(1.74 , 5.72)	<0.001
ERTU15	153	61 (39.9)	4.43	(2.44 , 8.02)	<0.001

* Adjusted ORs based on logistic regression model fitted with fixed effects for treatment, prior AHA, covariates for baseline HbA1c and eGFR. Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.
Abbreviations: HbA1C, haemoglobin A1c; OR, odd ratio; FAS, full analysis set; PBO, placebo; ERTU, ertugliflozin; N, sample size

Body weight change from baseline to week 26

The LS mean reductions from baseline in body weight at week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group, as shown in Figure 4. In both ertugliflozin groups and in the placebo group, body weight decreased from baseline to week 6 and continued to decrease at each subsequent time point through to week 26. The size of the decrease in body weight was numerically greater in both of the ertugliflozin groups than it was in the placebo group at each time point.

Figure 4 - Body weight (Kg) LS mean change from baseline to week 26 - (cLDA, FAS)



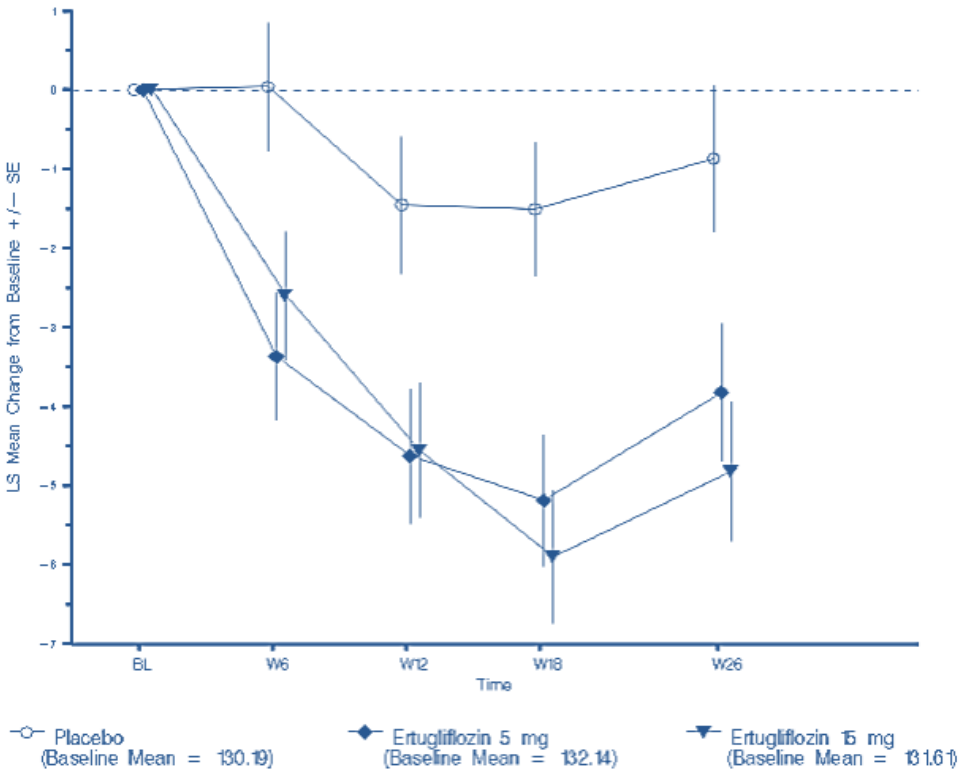
	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-2.03 (-2.65, -1.40)	<0.001
ERTU15	-1.72 (-2.35, -1.09)	<0.001

Abbreviations: kg, kilogram; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least square; SE, standard error; W, week; FAS, full analysis set

SBP change from baseline to week 26

The LS mean reductions from baseline in SBP at week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups than in the placebo group, as shown in Figure 5. In both ertugliflozin groups, SBP decreased from baseline at each time point through week 18 and then increased slightly at week 26. In the placebo group, SBP decreased at week 12, remained stable at week 18, and then increased slightly at week 26. Changes from baseline in SBP to week 26 were similar for the ertugliflozin 5 mg and ertugliflozin 15 mg groups.

Figure 5 - SBP (mmHg) LS mean change from baseline to week 26 - (cLDA, FAS)



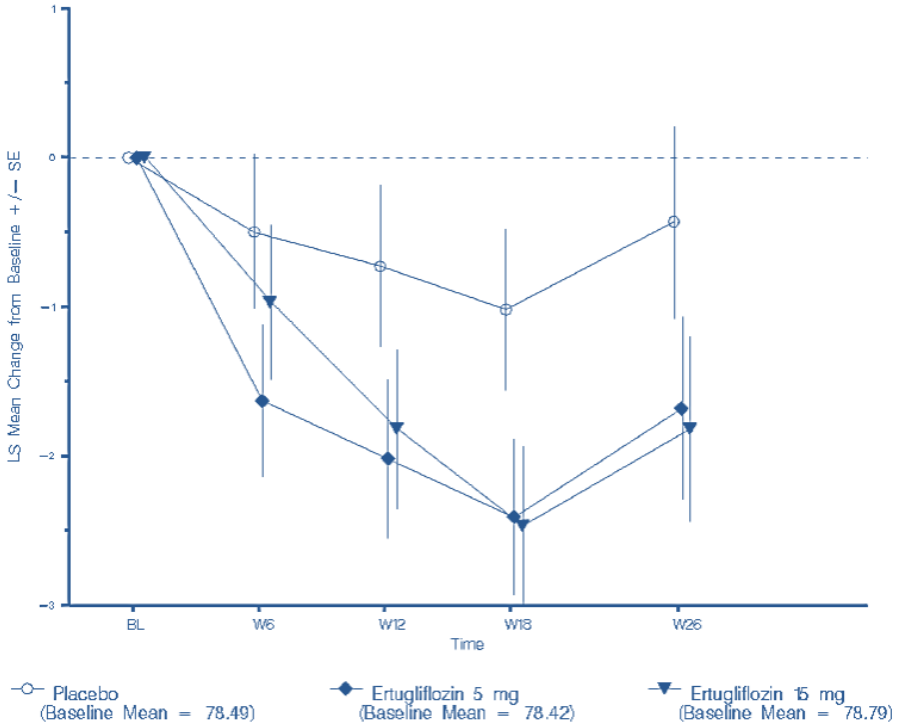
	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-2.93 (-5.36, -0.49)	0.019
ERTU15	-3.94 (-6.39, -1.50)	0.002

Abbreviations: SBP, systolic blood pressure; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least square; SE, standard error; ,W, week; FAS, full analysis set

DBP change from baseline to week 26

LS mean changes from baseline in DBP to week 26 are plotted in Figure 6. Similar to SBP, DBP decreased from baseline at each time point through to week 18 in both ertugliflozin groups and then increased slightly at week 26. A similar pattern for DBP was seen in the placebo group; however, the reduction from baseline was lower at each time point relative to the ertugliflozin groups.

Figure 6 - DBP (mmHg) LS mean change from baseline to week 26 - (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-1.24 (-2.97, 0.48)	0.157
ERTU15	-1.38 (-3.11, 0.36)	0.119

Abbreviations: DBP, diastolic blood pressure; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least square; SE, standard error; W, week; FAS, full analysis set

EQ-5D-3L

Table 11 shows the results of the analysis of change from baseline in EQ-5D-3L score to week 26. No meaningful changes from baseline in the EQ-5D-3L score were observed in any of the treatment groups.

Table 11 - EQ-5D-3L score change from baseline to week 26 (cLDA, FAS)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
PBO ERTU5 ERTU15	152 150 149	0.90 (0.144) 0.88 (0.166) 0.89 (0.182)	120 139 134	0.91 (0.139) 0.90 (0.149) 0.91 (0.142)	153 155 151	0.01 (-0.01, 0.04) 0.0 (-0.02, 0.03) 0.02 (-0.00, 0.04)
Pairwise comparison			**Differences in LS means (95% CI)***		**p-Value**	
ERTU 5 mg vs. PBO ERTU 15 mg vs. PBO			-0.01 (-0.04, 0.02) 0.01 (-0.02, 0.04)		0.598 0.675	
Conditional pooled SD of change from baseline					0.12	

Abbreviations: FAS, full analysis set; cLDA, constrained longitudinal data analysis; PBO, placebo; ERTU, ertugliflozin; N, sample size; SD, standard deviation; CI, confidence interval

*Based on cLDA model with fixed effects for treatment, time, prior AHA, baseline eGFR (continuous), menopausal status randomisation stratum and the interaction of time by treatment. Time was treated as a categorical variable

B.2.7 Subgroup analysis

To assess whether the treatment effect at week 26 was consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the primary endpoint (change in HbA1c) was estimated and plotted. The classification variables were baseline HbA1c levels ≤ or > median and HbA1c categories <8.0%; ≥8.0 to <9.0%; ≥9.0% and <10%; ≥10%. This was a pre-planned subgroup analysis. The consistency of the treatment effect was assessed in the context of the repeated measures ANCOVA (RMANCOVA) method. This model adjusted for treatment, prior AHAs, subgroup, eGFR, and treatment-by-subgroup interaction. Time was treated as a categorical variable and time-specific versions of each term listed above at each week was used to acknowledge the repeated nature of the measurements. An unstructured covariance matrix was used to model the correlation among repeated measurements. Treatment effects and nominal 95% CIs by category for the classification variables listed above are reported in Appendix E. Formal statistical testing of treatment-by-subgroup interactions was not performed.

A post-hoc subgroup analysis for gender was included because there was a higher proportion of males in the placebo group (65.4%) compared with the ertugliflozin 5 mg group (51.9%) and the 15 mg group (53.6%) as reported in Section B.2.3.2. Both HbA1c and gender subgroup analyses results for the primary outcome are presented in Appendix E excluding glycaemic rescue therapy, to avoid the confounding influence of the rescue therapy (e.g. glimepiride or insulin glargine).

Moreover, post-hoc subgroup analyses clinically relevant to the England and Wales practices were developed. These include the percentage of patients reaching the HbA1c

target (<7.0%) by their HbA1c baseline band; and changes in SBP by their SBP baseline band in accordance with the concomitant use (or not) of hypertensive medications (diuretics and β blockers). Results of these analyses are available in Appendix E.

B.2.8 Meta-analysis

Based on the current data availability for the SGLT-2is in triple therapy, a NMA was considered to be the most appropriate approach (see Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Summary of trials

Trials included in the NMA were identified through the SLR and are presented in Table 12**Error! Reference source not found.**. An overview of the baseline characteristics and the outcomes reported in all included studies are provided in Table 13 and Table 14, respectively.

The full network of evidence identified in the SLR for ertugliflozin in triple therapy is presented in Figure 7. It should be noted that the evidence networks are based solely on the treatments compared in the studies identified. As all outcomes of interest were not reported in each trial, outcome-specific evidence networks are reported in Appendix N for completeness.

The background therapy of interest for the appraisal of ertugliflozin in triple therapy is metformin + DPP-4i.

Table 12 - Summary of the RCTs used to carry out the NMA

Trial identifier	ERTU5	ERTU15	CANA100	CANA300	DAPA10	EMPA10	EMPA25
Dagogo 2018 - NCT02036515 [7-10]	✓	✓					
Jabbour 2014 - NCT00984867 [11, 12]					✓		
Mathieu 2015 - NCT01646320 [13, 14]					✓		
Rodbard 2016 - NCT02025907 [15, 16]			✓	✓ (titrated)			
Softeland 2017 - NCT01734785 [17, 18]						✓	✓

Abbreviations: TA, technology appraisal; ERTU, ertugliflozin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin

Table 13 - Baseline characteristics of all included studies

Triple therapy studies included											
Study	**Arms**	**N**	**Age (years)**	**Duration of disease (years)**	**Female (%)**	**HbA1c (%)**	**Weight (kg)**	**BMI (kg/m2)**	**SBP (mmHg)**	**DBP (mmHg)**	**FPG (mg/dL)**
Dagogo 2018 [7-10]	**MET + SITA + PBO**	153	58.3	9.9	35%	8.0	86.4	30.3	130	NR	170
	MET + SITA + ERTU5	156	59.2	9.2	48%	8.1	87.6	31.2	132	NR	168
	MET + SITA + ERTU5	153	59.7	9.4	46%	8.0	86.6	30.9	132	NR	172
	Total/Avg	462	59.1	9.5	43%	8.0	86.9	30.8	131	NR	170
Jabbour 2014 [11, 12]	**MET + SITA + PBO**	113	56.6	6.5	41%	7.9	94.2	NR	NR	NR	165
	MET + SITA + DAPA10	113	56.8	6.7	41%	7.8	94.0	NR	NR	NR	167
	Total/Avg	226	56.7	6.6	41%	7.9	94.1	NR	NR	NR	166
Mathieu 2015 [13, 14]	**MET + SAXA + PBO**	129	55.0	8.0	53%	8.2	88.2	32.2	NR	NR	177
	MET + SAXA + DAPA10	146	55.2	7.2	56%	8.2	85.8	31.2	NR	NR	179
	Total/Avg	275	55.1	7.6	54%	8.2	87.0	31.7	NR	NR	178
Rodbard 2016 [15, 16]	**MET + SITA + PBO**	94	57.5	10.1	48%	8.4	90.0	31.7	NR	NR	180
	MET + SITA + CANA	99	57.4	9.8	38%	8.5	94.1	32.3	NR	NR	186
	Total/Avg	193	57.5	10.0	43%	8.5	92.1	32.0	NR	NR	183
Softeland 2017 [17, 18]	**MET + LINA + PBO**	108	55.9	NR	44%	8.0	82.3	29.6	130	NR	164
	MET + LINA + EMPA10	109	54.3	NR	39%	8.0	88.4	31.2	130	NR	167
	MET + LINA + EMPA25	110	55.4	NR	35%	8.0	84.4	29.9	131	NR	169
	Total/Avg	217	55.1	NR	42%	8.0	85.4	30.4	130	NR	166

Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin; NR, not reported

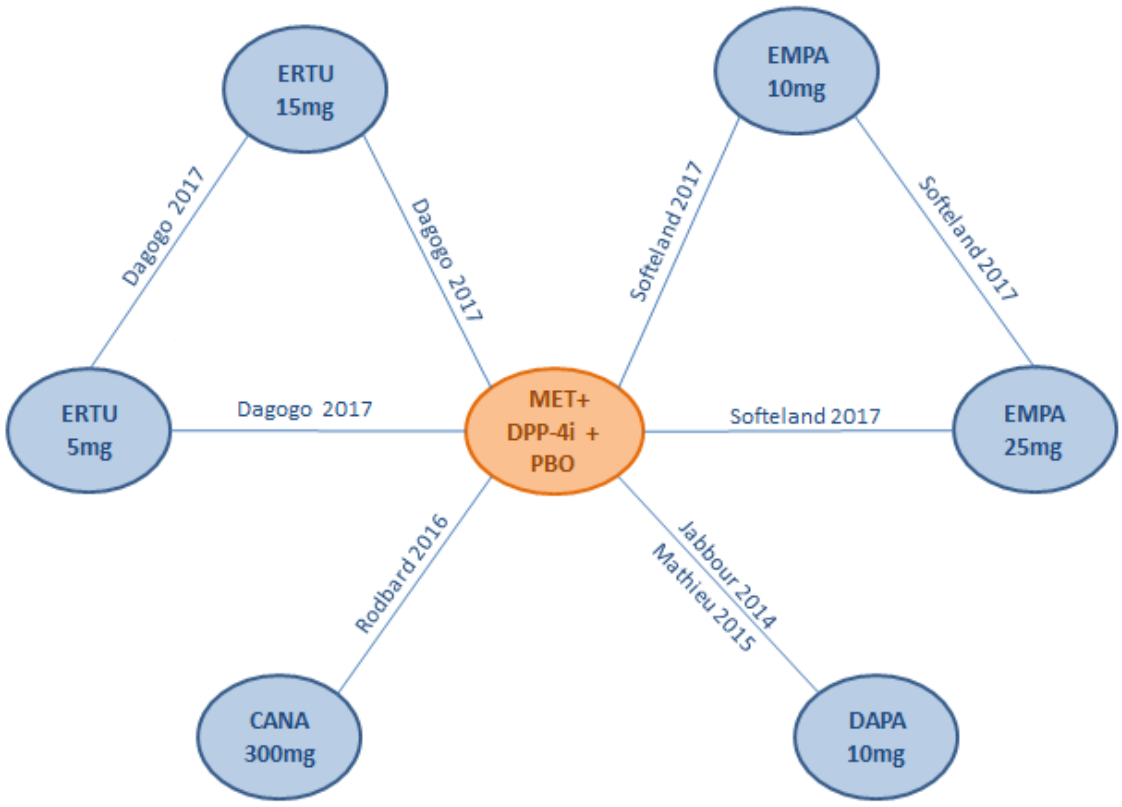
Table 14 - Outcomes reported by included studies informing the NMA

Reference	Arms	N	HbA1c change (%)	Weight change (kg)	SBP (mm/hg)	DBP (mm/hg)	HbA1c in target (%)	NSHE (%)	SHE (%)	UTIs (%)	Genital mycotic infection (%)	AEs (%)
Triple therapy												
Dagogo 2018 [7-10]	SITA+ERTU5	156	-0.78	-3.4	-3.8	/	32%	4%	0.0%	3%	3%	42%
	SITA+ERTU15	153	-0.86	-3.0	-4.8	/	40%	2%	0.0%	5%	2%	44%
Jabbour 2014 [11, 12]	SITA+PBO	153	-0.09	-1.3	-0.9	/	17%	3%	0.6%	2%	0%	48%
	SITA+PBO	113	0.00	-0.4	NR	/	12%	4%	0.0%	10%	17%	NR
	SITA+DAPA10	113	-0.40	-2.5	NR	/	22%	5%	0.7%	8%	1%	NR
Mathieu 2015 [13, 14]	SAXA+PBO	129	-0.10	-0.4^	2.0**	/	13%	0%	NR	6%	1%	59%
	SAXA+DAPA10	146	-0.82	-1.9^	-1.9**	/	37%	0%	NR	5%	5%	56%
Rodbard 2016 [15, 16]	SITA+PBO	94	-0.01	-1.6^	0.1^	/	12%	2%	0.0%	2%	1%	40%
	SITA+CANA	99	-0.91	-3.4^	-5.8^	/	32%	4%	0.0%	2%	6%	44%
Softeland 2017 [17, 18]	LINA+PBO	108	0.14	-0.3^	-1.7	/	17%	1%	0.0%	7%	2%	68%
	LINA+EMPA10	109	-0.65	-3.1^	-3.0	/	37%	0%	0.0%	7%	2%	55%
	LINA+EMPA25	110	-0.56	-2.5^	-4.3	/	33%	3%	0.0%	4%	5%	52%

Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; NSHE, non-severe hypoglycaemic event; SHE, severe hypoglycaemic event; UTI, urinary tract infection; GTI, genital tract infections; AE, adverse event; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin; NR, not reported

^ Data sourced from clinicaltrials.gov ** SE not able to be imputed, therefore the study is unable to be included in the network

Figure 7 - Full network of evidence: triple therapy



Abbreviations: PBO, placebo; ERTU, ertugliflozin; CANA, canagliflozin; EMPA, empagliflozin; DAPA, dapagliflozin; MET, metformin; mg, milligram; DPP-4i, dipeptidyl peptidase-4 inhibitor

B.2.9.2 NMA base case definition

The NMA base case was defined as:

- The FAS population was used in the ertugliflozin trial for the efficacy outcomes.
- The ASaT population was used in the ertugliflozin trial for the safety outcomes.
- The outcome time point was either 24 or 26 weeks for all the included studies.
- The efficacy outcomes assessed were: HbA1c, weight, SBP and HbA1c at target (i.e. <7%).
- The safety outcomes assessed were: overall AEs, UTIs, genital mycotic infections.

B.2.9.3 NMA results

The NMA conducted consisted of both continuous and binary outcomes. For the continuous outcomes (change in HbA1c, weight and SBP) the median of the mean difference from baseline was presented. The median odds ratio (OR) was presented for binary outcomes (HbA1c in target, AEs, UTIs and genital mycotic infections). Additional binary safety outcomes (NSHE and SHE) were not considered appropriate for inclusion in the NMA due to the number of zero events across in this line of therapy.

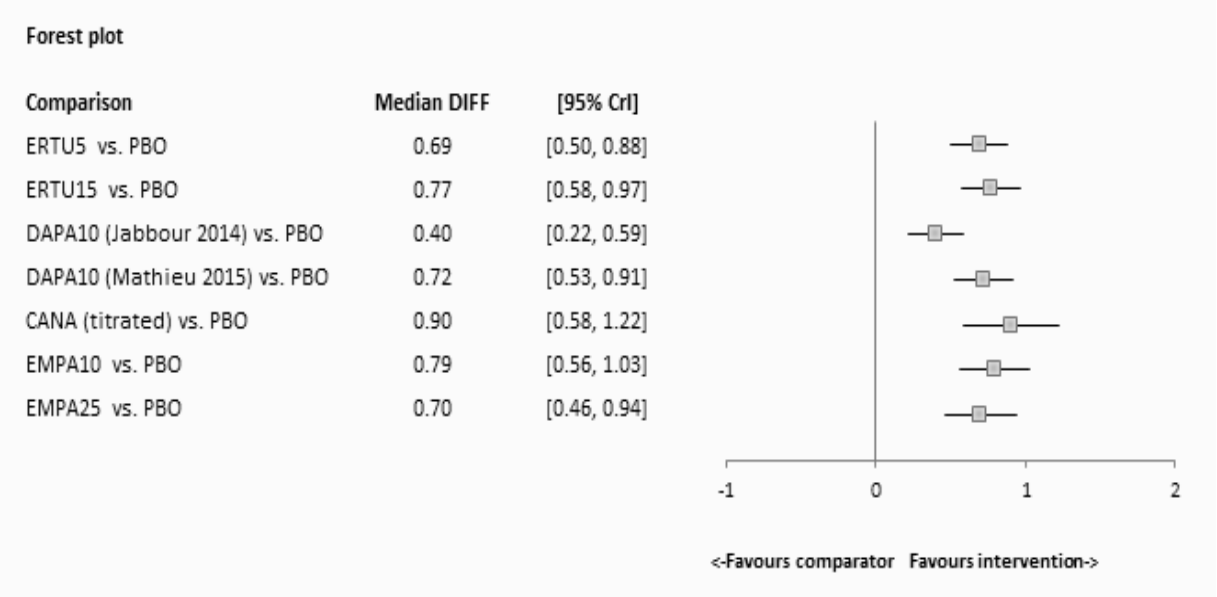
The results of the NMA are summarised in both forest plots and tables. NMA summary statistics are also presented (Table 16, Table 18, Table 20, Table 22, Table 24 and Table 26) to give context for the model selection (random effect model (REM) or fixed effect model (FEM)). The forest plots display the results obtained from comparing each SGLT-2i to placebo (Figure 8, Figure 9, Figure 10, Figure 11, Figure 12 and Figure 13). Within tables that show results of the indirect comparison between SGLT-2is,), the median differences and ORs were reported for continuous (Table 15, Table 17, Table 19) and binary outcomes (Table 21, Table 23 and Table 25), respectively. The associated 95% credible intervals (CrI) for the selected base cases were also included. Significant results, defined as a CrI not including 0 for continuous outcomes and 1 for binary outcomes, were highlighted in bold in the tables. Results for the non-selected model and the deviance information criterion (DIC) can be found in Appendix P. The results are broken down into continuous efficacy outcomes, binary efficacy outcomes and binary safety outcomes.

- **Continuous efficacy outcomes**

HbA1c (%) change from baseline to week 26

Canagliflozin had the largest effect sizes for change from baseline in HbA1c (Figure 8) when compared with placebo. For the indirect comparison of SGLT-2i, the only statistically significant results were ertugliflozin 5 mg and 15 mg being superior to dapagliflozin 10 mg (Table 15).

Figure 8 - Base case – HbA1c (%) change from baseline to week 24 - 26 (continuous outcome – FEM)



Background therapy: metformin + DPP-4is
Abbreviations: HbA1c, haemoglobin A1c; FEM, fixed effect model; vs, versus; CrI, credible interval

Table 15 - HbA1c change (%) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	**-0.29 (-0.56 to -0.02)**	**-0.37 (-0.64 to -0.10)**
DAPA10 (Mathieu 2015)	[redacted]	-0.05 (-0.32 to 0.22)
CANA (titrated)	[redacted]	0.13 (-0.24 to 0.50)
EMPA10	0.10 (-0.21 to 0.41)	[redacted]
EMPA25	[redacted]	-0.07 (-0.38 to 0.24)

Background therapy: metformin + DPP-4is
Bold values indicate significant results (CrI does not include 0)

Table 16 - Hba1c (%) change from baseline – NMA summary statistics

	FEM	REM
DIC	-15.132	-15.139
Total residual deviance (95% CrI)	12.02 (4.41 to 23.33)	12.01(4.41 to 23.33)
SD	2.5 (0.13 to 4.87)	
Data points	12	

Abbreviations: HbA1c, haemoglobin A1c; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

Weight change (kg) change from baseline to week 26

All SGLT-2is significantly reduced body weight when compared with placebo (Figure 9). Empagliflozin 10 mg produced the largest reduction in weight. In the indirect comparison of SGLT2-is, [redacted] was superior to [redacted] (Table 17).

Figure 9 - Base case – Weight change (kg) from baseline to week 24 - 26 (continuous outcome – FEM)

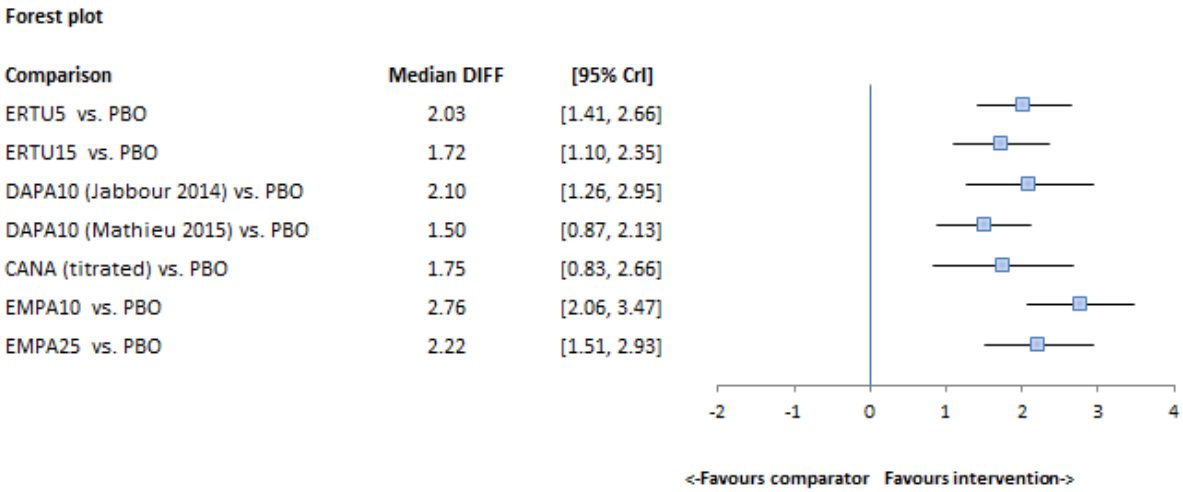


Table 17 - Weight Change (kg) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	0.07 (-0.99 to 1.13)	0.38 (-0.68 to 1.43)
DAPA10 (Mathieu 2015)	[redacted]	-0.22 (-1.1 to 0.66)
CANA (titrated)	[redacted]	0.03 (-1.08 to 1.14)
EMPA10	0.73 (-0.21 to 1.68)	[redacted]
EMPA25	[redacted]	0.50 (-0.45 to 1.45)

Background therapy: metformin + DPP-4is
Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Table 18 - Weight change (kg) change from baseline – NMA summary statistics

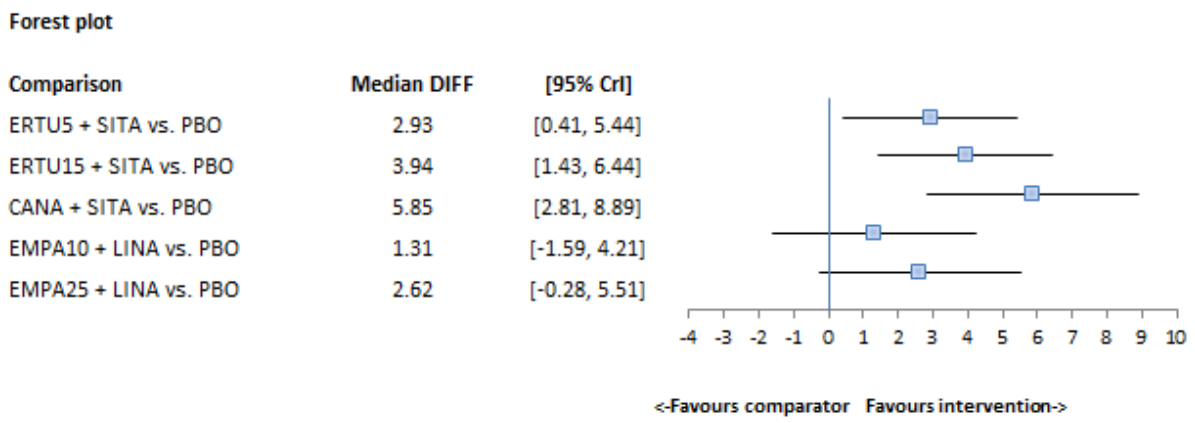
	FEM	REM
DIC	13.674	13.662
Total residual deviance (95% CrI)	12.02 (4.41 to 23.33)	12.01 (4.41 to 23.33)
SD	2.5 (0.12 to 4.88)	
Data points	12	

Abbreviations: kg, kilogram; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

SBP (mmHg) change from baseline to week 26

The benefits of dapagliflozin on SBP could not be assessed as neither of the dapagliflozin studies reported SBP. For this outcome, both doses of ertugliflozin and titrated canagliflozin reduced SBP versus placebo (Figure 10). There were no differences between SGLT-2is in the indirect comparison (Table 19).

Figure 10 - Base case – SBP (mmHg) change from baseline to week 26 (continuous outcome – FEM)



Background therapy: metformin + DPP-4is
Abbreviations: SBP, systolic blood pressure; FEM, fixed effect model; vs, versus; CrI, credible interval;

Table 19 - SBP Change (mmHg) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	--	--
DAPA10 (Mathieu 2015)	--	--
CANA (titrated)	[redacted]	1.91 (-2.04 to 5.86)
EMPA10	-1.62 (-5.46 to 2.22)	[redacted]
EMPA25	[redacted]	-1.32 (-5.15 to 2.52)

Background therapy: metformin + DPP-4is
Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model;

Table 20 - SBP (mmHg) change from baseline – NMA summary statistics

	FEM	REM
DIC	30.563	30.576
Total residual deviance (95% CrI)	7.99 (2.18 to 17.52)	8 (2.17 to 17.54)
SD	2.5 (0.12 to 4.88)	
Data points	8	

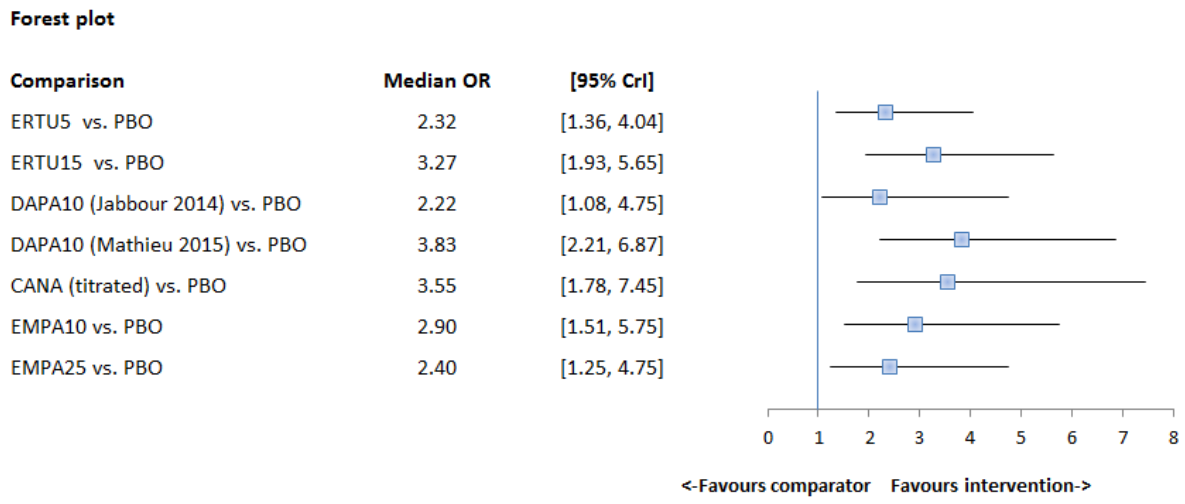
Abbreviations: SBP, systolic blood pressure; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

- **Binary efficacy outcome**

HbA1c <7.0% (<53 mmol/mol) at week 26

All SGLT-2is were significantly better than placebo in maintaining HbA1c levels in target (<7.0%) (Figure 11). Canagliflozin and dapagliflozin 10 mg had the largest median OR for HbA1c in target (<7.0%) (Figure 11). No significant differences were found between SGLT-2is in the indirect comparison (Table 21).

Figure 11 - Base case – Hba1c (%) within target (<7.0%) at week 24 - 26 (binary outcome – FEM)



Background therapy: metformin + DPP-4is
Abbreviations: HbA1c, haemoglobin A1c; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 21 - HbA1c in target (<7.0%) median odds ratio (CrI): FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	[redacted]	[redacted]
DAPA10 (Mathieu 2015)	[redacted]	[redacted]
CANA (titrated)	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Background therapy: metformin + DPP-4is
Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Table 22 - HbA1c in target (<7.0%) – NMA summary statistics

	FEM	REM
DIC	82.907	Did not converge
Total residual deviance (95% CrI)	12.08 (4.43 to 23.51)	Did not converge
SD	Did not converge	
Data points	12	

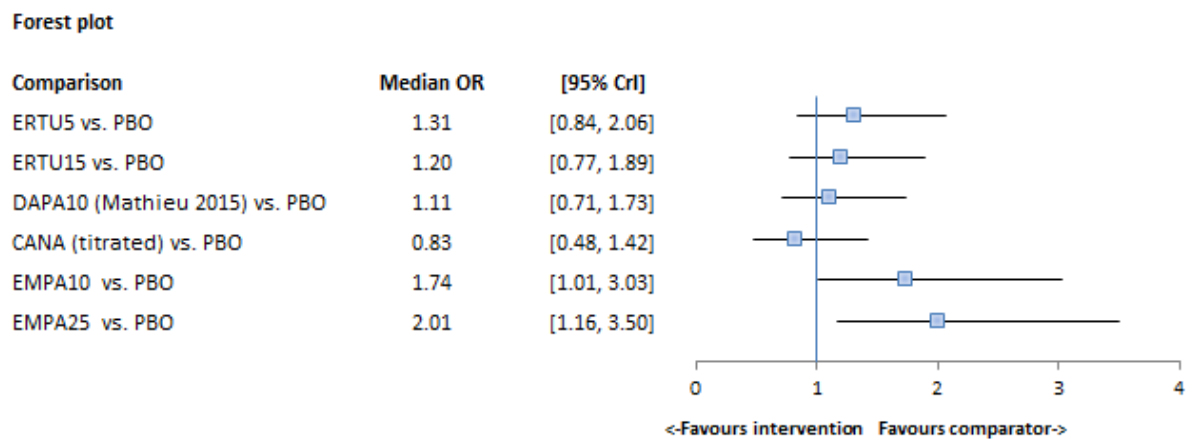
Abbreviations: HbA1c, haemoglobin A1c; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

- **Binary safety outcomes**

AEs at week 26

Empagliflozin 10 mg and 25 mg had statistically significant differences when compared with placebo (Figure 12). In the SGLT2-is comparison, no differences were found (Table 23).

Figure 12 - Base case – AEs at week 24 - 26 (binary outcome, FEM)



Background therapy: metformin + DPP-4is
Abbreviations: AEs, adverse events; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 23 - AEs median odds ratio (CrI): FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	--	--
DAPA10 (Mathieu 2015)	[redacted]	[redacted]
CANA (titrated)	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Background therapy: metformin + DPP-4is
*Dose titration
Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Table 24 - AEs - NMA summary statistics

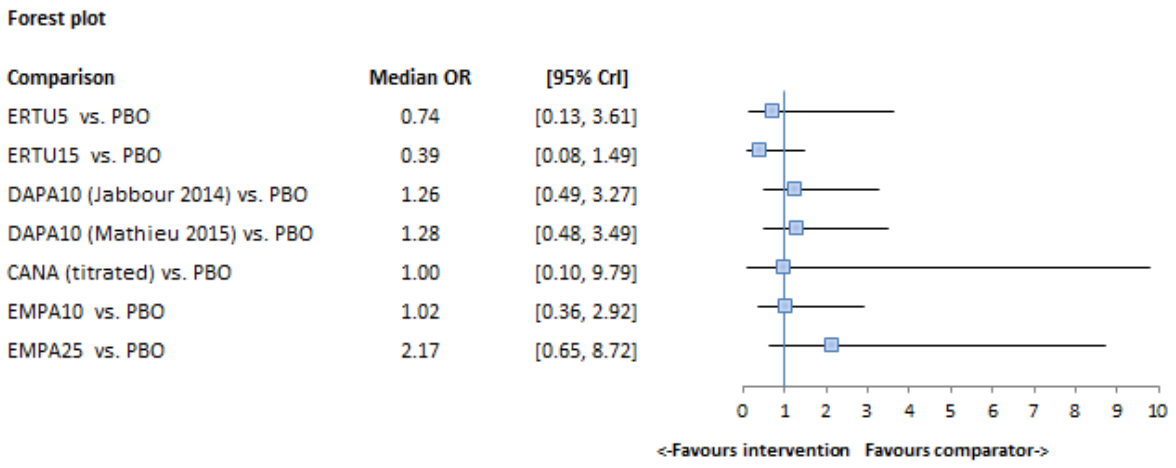
	FEM	REM
DIC	73.081	Did not converge
Total residual deviance (95% CrI)	10.04 (3.26 to 20.58)	Did not converge
SD	Did not converge	
Data points	10	

Abbreviations: AEs, adverse events; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

UTIs at week 26

No statistically significant differences were found between SGLT-2is and placebo in UTIs (Figure 13) and there were no significant differences between SGLT-2is (Table 25).

Figure 13 - Base case – UTIs at week 24 - 26 (binary outcome – FEM)



Background therapy: metformin + DPP-4is

Abbreviations: UTIs, urinary tract infections; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 25 - UTIs median odds ratio (CrI): FEM

	ERTU5	ERTU15
DAPA10 (Jabbour 2014)	[redacted]	[redacted]
DAPA10 (Mathieu 2015)	[redacted]	[redacted]
CANA (titrated)	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Background therapy: metformin + DPP-4is
Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Table 26 - UTIs - NMA summary statistics

	FEM	REM
DIC	66.499	Did not converge
Total residual deviance (95% CrI)	12.46 (4.58 to 24.23)	Did not converge
SD	Did not converge	
Data points	12	

Abbreviations: UTIs, urinary tract infections; NMA, network meta-analysis; FEM, fixed effect model, REM, random effect model; DIC, deviance information criterion; SD, standard deviation; CrI, credible interval

Neither the FEM nor the REM converged for the genital mycotic infection outcome, attributed to the small number of RCTs and small numbers of patients affected, particularly in the placebo arms. Non-converged results are available in Appendix Q.

B.2.9.4 Assessment of heterogeneity and inconsistency

Inconsistency, which occurs due to an imbalance of effect modifiers between treatment comparisons and leads to biased estimates of treatment effect [27] is usually assessed by performing a series of Bucher tests to test for conflicts between direct and indirect evidence. However, there was a lack of closed loops with direct and indirect evidence available in this case and, as a result, no inconsistency tests could be conducted.

The statistical heterogeneity in treatment effect estimates was evaluated using between study variance (i.e. square root of the standard deviation of underlying effects across trials) with 95% CrI [28], where the REM converged. Heterogeneity was also assessed via assessment of study quality, which is presented in details in Appendix D.

Though the available data was limited, included studies for triple therapy were similar in terms of age, gender, starting HbA1c, BMI, SBP and FPG. The included studies in triple therapy potentially introduced heterogeneity into the analysis given differences in treatment approaches, specifically through the use of different DPP-4is as a baseline therapy (sitagliptin [3 RCTs], saxagliptin [1 RCT] and linagliptin [1 RCT]) in combination with

metformin. In order to create a network it has been assumed that the DPP-4is were equivalent. Moreover, the only included canagliflozin study had titration (as such, patients were neither high nor low dose). Please note that canagliflozin plus sitagliptin [15, 16] was interpreted as high dose, as the majority of patients on canagliflozin 100 mg, titrated to the 300 mg dose (90.7%), with the majority of these titrating by week 8 (97.2%). However, this approach allowed the investigation of the relative efficacy of ertugliflozin against all SGLT-2is in this triple therapy combination and to inform the network with data coming from five RCTs. Alternatively, only three studies (those in which sitagliptin was used as DPP-4i [7-10] [11, 12] [15, 16]) would have informed the network and, as a result, only an indirect comparison against dapagliflozin 10 mg and canagliflozin (titrated) would have been possible.

For of all the outcomes, there were too few studies to perform sensitivity analyses through meta-regression controlling for potential effect modifiers. In conclusion, these limitations do not appear to have impacted the NMA results. A stringent inclusion and exclusion criteria were applied to identify studies and they were all found to be of good quality (Appendix D). It is believed that the findings are generalisable to T2DM patients being treated by NHS England and Wales.

B.2.10 Adverse reactions

B.2.10.1 Evidence from VERTIS SITA2

Details on overall AEs incidence across arms, drug-related AEs, genital mycotic infections, UTIs, discontinuation and SAEs are reported in Table 27.

Treatment with ertugliflozin was well-tolerated in this trial. The overall incidences of AEs, SAEs (with no deaths), and discontinuation number due to AEs did not different significantly across treatment groups. There was a small numerical increase in the number of patients who discontinued due to AEs in the ertugliflozin 5 mg group relative to the placebo and ertugliflozin 15 mg groups.

Hypoglycaemia is associated with increased morbidity and mortality. SGLT-2is, in general, are associated with a low incidence of hypoglycaemia due to their glucose-dependent mechanism of action [29]. In this study, the incidence of hypoglycaemia with the addition of ertugliflozin to metformin and sitagliptin was low and similar to the addition of placebo.

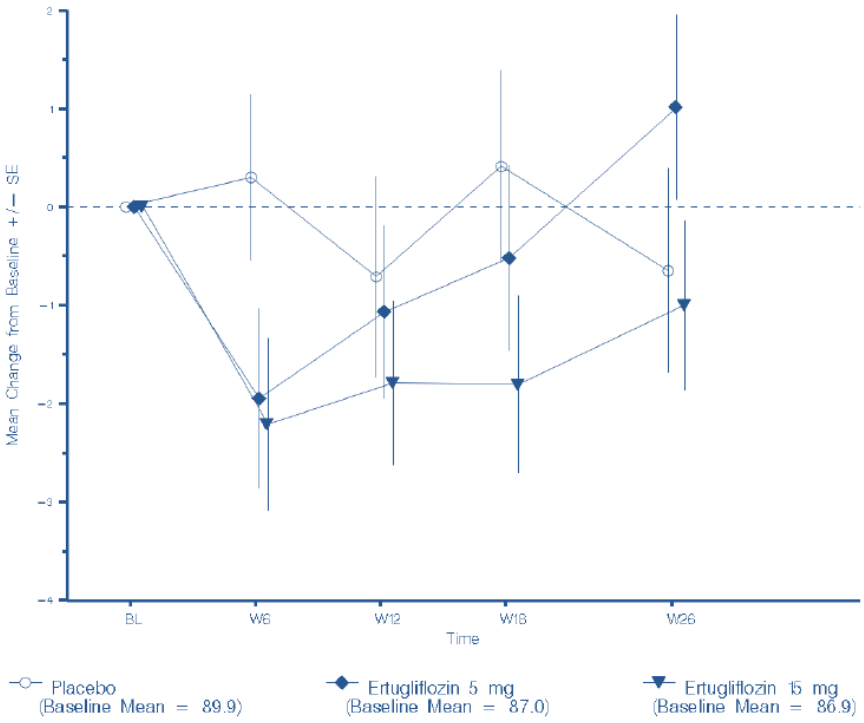
The incidence of UTIs was generally low and not meaningfully different between the ertugliflozin and placebo groups.

Genital mycotic infections occurred more frequently in the ertugliflozin groups in both male and female patients, compared to placebo. Two patients in the ertugliflozin 5 mg group and none in the ertugliflozin 15 mg or placebo groups discontinued study medication due to a genital mycotic infection.

Although treatment with SGLT-2is causes osmotic diuresis, which may lead to AEs related to volume depletion, the incidence of hypovolemia AEs was low in this study. Hypovolemia AEs were reported for one patient in the ertugliflozin 5 mg group and one patient in the placebo group; none were reported in the ertugliflozin 15 mg group.

In this study, the mean eGFR decreased modestly from baseline at week 6 in the ertugliflozin 5 mg and 15 mg groups but returned to baseline in the ertugliflozin 5 mg group and increased toward baseline in the ertugliflozin 15 mg group at week 26 (Figure 14). Small mean changes around the baseline value were observed in the placebo group through week 26.

Figure 14 - Mean change from baseline in eGFR (mL/min/1.73m2) over time (Mean ± SE; APaT: excluding rescue approach)



Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate; SE, standard error; W, week

The proportions of patients who had a decrease >30% in eGFR from baseline (at least one occurrence or at the last on-treatment assessment) were low for the ertugliflozin and placebo groups. One patient in the placebo group and none in the ertugliflozin groups had a decrease >50% in eGFR from baseline. Three patients in the ertugliflozin 15 mg group experienced an eGFR decrease that met discontinuation criteria; eGFR levels subsequently returned to or towards baseline in all 3 patients.

Summary statistics of mean percentage change from baseline in lipid parameters (median percent change for triglycerides), showed that lipid effects with ertugliflozin treatment were generally similar to those observed with placebo except for HDL, which increased at week 26 in the ertugliflozin groups (Appendix L).

Further information and results on safety evaluations and laboratory values is provided in Appendix L.

B.2.10.2 Summary of adverse reactions

Table 27 - Summary of adverse events for the VERTIS SITA2 study at week 26

VERTIS SITA2 [7-10]	PBO N = 153	ERTU5 N = 156	ERTU15 N = 153
Overall Safety (ER and IR)[a], n (%)			
One or more AEs	74 (48.4)	65 (41.7)	67 (43.8)
AEs related to study drug[b]	13 (8.5)	17 (10.9)	22 (14.4)
One or more SAEs	5 (3.3)	7 (4.5)	3 (2.0)
SAE related to study drug[b]	0 (0)	0 (0)	1 (0.7)
AEs leading to discontinuation	1 (0.7)	5 (3.2)	1 (0.7)
Death	0 (0)	0 (0)	0 (0)
Tier 1 AEs			
Genital mycotic infection (women)	1 (1.9)	6 (8.0)	9 (12.7)*
Genital mycotic infection (men)	0 (0)	4 (4.9)*	3 (3.7)
Urinary tract infection	3 (2.0)	4 (2.6)	7 (4.6)
Symptomatic hypoglycaemia[c]	4 (2.6)	6 (3.8)	1 (0.7)
Hypovolemia	1 (0.7)	1 (0.6)	0 (0)
Other AEs by SOC			
Vascular disorders (hypertension)	3 (2.0)	1 (0.6)	2 (1.3)
Eye disorders (diabetic retinopathy)	1(0.7)	0 (0.0)	2 (1.3)
Cardiac disorders[d]	2(1.3)	2 (1.3)	0 (0.0)

* p<0.05 versus placebo.
[a] For Week 26 safety analyses, data following initiation of glycaemic rescue were excluded from incidence of 'one or more AEs' and from 'AEs related to study drug'
[b] As reported by the investigator
[c] Event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required)
[d] Including: supraventricular extra systoles, acute myocardial infarction, angina pectoris
Abbreviations: ERTU, ertugliflozin; PBO, placebo; AE, adverse events; SAE, Serious adverse event; UTIs, urinary tract infections

B.2.10.3 Brief overview on the safety of the technology being appraised

Treatment with ertugliflozin (both the 5 and 15 mg dose strengths) for 26 weeks is generally well-tolerated, with a low and not clinically relevant incidence of symptomatic hypoglycaemia, UTI, or hypovolemia AEs, but results in a higher incidence, as shown with the use of other SGLT-2is, of genital mycotic infections in male and female subjects relative to placebo. The overall safety profile of ertugliflozin observed in this study is consistent with that reported in similarly designed efficacy and safety studies of other SGLT-2i on a background of metformin and a DPP-4i [7-18].

B.2.11 Ongoing studies

VERTIS SITA2 is the only study providing evidence for the use of both dosages of ertugliflozin (5 mg and 15 mg) in people with T2DM and inadequately controlled on metformin and DPP-4i therapies. No further evidence for this indication will become available in the next 12 months.

B.2.12 Innovation

MSD believes that ertugliflozin will substantially improve the HRQoL of patients with inadequate glycaemic control on a stable dose of metformin and a DPP-4i.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of clinical benefits and harms of ertugliflozin

In the VERTIS SITA2 trial, subjects with T2DM and inadequate glycaemic control receiving antihyperglycaemic therapy with metformin ≥1500 mg/day and sitagliptin 100 mg/day, the addition of treatment with ertugliflozin (both the 5 and 15 mg dose strengths) for 26 weeks relative to placebo:

- provided clinically meaningful reductions from baseline in HbA1c and FPG;
- resulted in a greater proportion of subjects with an HbA1c <7% (<53 mmol/mol);
- reduced body weight and SBP;
- was well-tolerated, without a meaningful difference in the incidence of symptomatic hypoglycaemia, UTI, or hypovolemia AEs, but with higher incidence of genital mycotic infections in male and female subjects

The results of the NMA comparing ertugliflozin to canagliflozin, dapagliflozin and empagliflozin revealed that the efficacy and safety of all the SGLT-2is were similar. There were some examples where statistically significant differences were found between the SGLT-2is in the indirect comparison; both doses of ertugliflozin were significantly better at

reducing HbA1c (%) than dapagliflozin 10 mg. [redacted] Ertugliflozin is at least as efficacious and well tolerated as its comparators canagliflozin, dapagliflozin and empagliflozin.

B.2.13.2 Strengths and limitations of clinical evidence from VERTIS SITA2

Ertugliflozin in a triple therapy regimen has demonstrated significant improvement in HbA1c in T2DM subjects, alongside reducing body weight and blood pressure as additional benefits. It is well tolerated and its safety profile is similar to that of other SGLT-2is in the same indications, with a low and acceptable incidence of UTIs and genital mycotic infections.

The VERTIS SITA2 trial has strong internal validity minimising the possibility of bias. Patients were randomised using an IVRS and double-blinding was employed so the patients and investigators were unaware of treatment allocation. The balance of the treatment arms at baseline confirms that randomisation was appropriately conducted. Ideally intention to treat (ITT) analysis would have been employed for the efficacy analysis; however the authors of the VERTIS SITA2 trial felt that the FAS population was the most appropriate form of analysis. The same approach to analysing triple therapy data was also used by Jabbour et al., 2014 (dapagliflozin) [11, 12] and Softeland et al., 2017 (empagliflozin) [17, 18]. A detailed quality assessment of the VERTIS SITA2 trial is reported in Appendix D.

The clinical evidence reflects the decision problem addressed in this submission (Section B.1.1). The outcomes reported reflect the key benefits experienced by patients and those regularly monitored by clinicians i.e. HbA1c, blood pressure and weight (NG 28). Although there are no UK patients in the VERTIS SITA2 trial, there are western European patients (France, Norway and Spain) and the clinical findings should be generalisable to the UK. The overall findings from the VERTIS SITA2 study support ertugliflozin as an effective and well tolerated option for treating patients with T2DM in the NHS in England and Wales.

This medicine does not meet the end of life criteria.

B.3 Cost effectiveness

Summary

- The results of the NMA comparing ertugliflozin to canagliflozin, dapagliflozin and empagliflozin in triple therapy on a background of metformin with a DPP-4i (presented in detail in section 2.9) revealed that the efficacy and safety of all the SGLT-2is were similar. The exceptions were ertugliflozin 5 mg and 15 mg being significantly better at HbA1c reduction than dapagliflozin 10 mg; and empagliflozin 10 mg being significantly better than ertugliflozin 15 mg at weight reduction.
- In light of the NMA results a cost-minimisation analysis was considered to be the most appropriate form of economic evaluation.
- Only drug acquisition costs were considered in the cost-minimisation analysis.
- In the base case analysis ertugliflozin was found to be cost-saving compared to all other SGLT-2is in triple therapy providing an annual saving per patient of £94.97.
- It can be concluded that ertugliflozin is a cost-effective use of NHS resources in England and Wales and should be introduction as an alternative therapy option for the treatment of T2DM in triple therapy on a background of metformin with DPP-4i.

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify evidence to support the evaluation of ertugliflozin as a mono, dual and triple therapy for T2DM patients. A single review was performed to identify relevant studies in T2DM that included published economic evaluations, studies reporting EQ-5D utility values and studies reporting cost and resource use data. In this appraisal the focus will be on results applicable to triple therapy.

Full details of the search strategy of the single economic SLR are presented in Appendix G. A total of 4,644 articles were identified through electronic database searching and a further 2,635 through supplementary searches. Of these, a total of 97 publications were ultimately included, comprising 78 publications reporting on 73 unique economic evaluations, 8 publications reporting on 6 unique EQ-5D utility studies and 11 publications reporting on 10 unique cost and resource use studies.

No previous economic evaluations for ertugliflozin in combination with metformin and a DPP-4i as a treatment for T2DM were identified; therefore a de novo health economic analysis was conducted for the purposes of this appraisal.

Full details of the economic evaluations included in the SLR and the quality assessments of these economic evaluations can be found in Appendix G.

B.3.2 Economic analysis

Of the 73 unique economic evaluations, 31 considered triple therapy (32 publications). Where the efficacy and safety of the interventions were found to be similar or greater at a similar or lower cost than the comparator treatments, a cost minimisation approach was frequently adopted. Of the 31 economic evaluations, nine (29%) conducted a cost-minimisation analysis (one did both cost-minimisation and cost-utility analyses).

As SGLT-2is on a background of metformin with DPP-4is have not been evaluated, a simple de novo cost-minimisation model was developed.

B.3.2.1 Patient population

The patient group assessed in the economic evaluation are adults with T2DM that are inadequately controlled on metformin and a DPP-4i. This population is a subset of that defined in the scope and in the marketing authorisation, but is consistent with the trial evidence [7-10].

B.3.2.2 Model structure

As the results of the NMA comparing ertugliflozin on a background of metformin and DPP-4i to the other licensed SGLT-2is (canagliflozin, dapagliflozin and empagliflozin) revealed that the efficacy (HbA1c, weight change, SBP and HBA1c within target) and safety (AEs and UTIs) of all SGLT-2is were similar in triple therapy, a cost-minimisation analysis was considered the most appropriate form of economic evaluation.

A cost-minimisation model was developed in Microsoft Excel 2010. As there are no differences in testing, initiation, administration or monitoring costs between SGLT-2is, only drug acquisition costs were considered in the cost minimisation analysis. The model and analysis have a one year time horizon as this is sufficiently long to capture any differences between the treatments. As a time horizon of one year was modelled, a discount rate was not applied.

Table 28 - Features of the economic analysis

	Previous appraisals			Current appraisal	
Factor	**TA315 [30]**	**TA336 [31]**	**TA418 [32]**	**Chosen values**	**Justification**
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime (40 years)	1 year	It is long enough to reflect all important differences in costs or outcomes between the treatments being compared
Treatment waning effect?	HbA1c drift was assumed to be 0.14% for SGLT-2is	Not reported	Not reported.	None applied	Efficacy and safety are assumed to be equal for the treatments compared in a cost-minimisation analysis
Source of utilities	Bagust and Beale, 2005 [33] , Currie et. al 2006 [34], Janssen UK Study (TA315) [30]	Utilities were sourced from numerous publications. The predominant sources were UKPDS 62 [35], Sullivan et al., 2011 [36]	Health Survey for England, 2003 [37], UKPDS 62 [35], Currie et al., 2006 [34], Barry et al., 1997 [38] (ref), Bagust and Beale, 2005 [33]	Not applicable.	Only cost are considered in a cost-minimisation.
Source of costs	Drug acquisition costs were taken from British National Formulary (BNF) [39], procedure costs were taken from the National Schedule of Reference Costs 2011-12 [40]	Drug acquisition costs were taken from the BNF [41]. Event cost were sourced from Clarke et al., 2003 [42]	Drug acquisition costs were taken from the BNF [43], complication were taken from UKPDS 65 [42], 84 [44], Curtis 2013 [45]	Drug acquisition costs were taken from the NHS drug tariff [46]	Reports the latest drug list prices as collated by the NHS.

Abbreviations: TA, technology appraisal; HbA1c, haemoglobin A1c; SGLT-2is, sodium-glucose co-transporter 2 inhibitor; UKPDS, United kingdom Prospective Diabetes Study; NHS, National Health Services

B.3.2.2 Intervention technology and comparators

As outlined in Section B.1.3.2, 11.4% of triple therapy is made up of SGLT-2is on a background of metformin plus DPP-4is. The background, intervention and comparator treatments are implemented in the cost-minimisation analysis according to their marketing authorisations (see Table 29).

Table 29 - Intervention and comparators

Therapy	Units
Background therapy	
Metformin	2000 mg OD
DPP-4i (Sitagliptin)	100 mg OD
Intervention	
Ertugliflozin	5 mg or 15 mg OD
Comparators	
Canagliflozin	100 mg or 300mg OD
Dapagliflozin	10 mg OD
Empagliflozin	10 mg or 25 mg OD

Abbreviations: OD, once daily

No explicit treatment continuation rule has been assessed. In the cost-minimisation analysis, the cost for one patient concordant with treatment over a one year period is compared for the intervention and the comparators.

B.3.3 Clinical parameters and variables

As the results of the NMA revealed that the efficacy (HbA1c, weight change, SBP and HBA1c within target) and safety (AEs and UTIs) of all SGLT-2is were similar in triple therapy, a cost-minimisation analysis was considered the most appropriate form of economic evaluation. The cost-minimisation analysis assumes that the efficacy and safety of the SGLT-2is are equivalent.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-3L was administered at baseline, 26 and 52 weeks in the VERTIS SITA2 trial for patients receiving both doses of ertugliflozin and placebo [7-10]. The mean change from baseline in EQ-5D scores was negligible. HRQL data were not collected as part of the Jabbour et a.l., 2014 [11, 12], Mathieu et. al., 2015 [13, 14], Rodbard et. al., 2016 [15, 16] or Softeland et. al., 2017 [17, 18] trials.

B.3.4.2 Mapping

Not applicable.

B.3.4.3 Health-related quality-of-life studies

In line with the NICE guide to the methods of technology appraisal, a SLR to identify relevant utility studies was performed. Full details of the search strategy can be found in Appendix G and the results can be found in Appendix H.

The date inclusion criterion was confined to literature published after the systematic reviews conducted for the multiple technology appraisal of SGLT-2is, TA390 [47]. A total of 8 publications (6 studies) were included in the SLR that reported EQ-5D health-state utility values for patients with T2DM.

B.3.4.4 Adverse reactions

Adverse events that patients would consider significant, events that impact on areas of their health related quality of life (HRQoL) such as UTIs and genital mycotic infections reduce the patients QoL. As the NMA suggest there are no meaningful differences between ertugliflozin and its comparators, a cost-minimisation analysis was conducted and adverse event decrements were not modelled.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As the NMA results indicate that there are no statistically significant differences between the SGLT-2is in triple therapy in terms of efficacy and safety, HRQoL was not modelled. Health effects identified in the literature, and excluded as a cost-minimisation is the most appropriate form of economic evaluation, include [48]:

- angina pectoris
- myocardial infarction (MI)
- congestive heart failure (CHF)
- stroke, peripheral vascular disease
- diabetic retinopathy
- macular edema
- cataracts
- hypoglycemia
- ketoacidosis
- nephropathy (comprising microalbuminuria, gross proteinuria, and end-stage renal disease)

- neuropathy
- foot ulcer and amputation
- pulmonary edema
- depression, in addition to nonspecific
- mortality

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR to identify relevant cost and resource use data was performed. Full details of the search strategy can be found in Appendix G and the results in Appendix I. A total of 11 publications reporting on 10 unique studies were identified for the treatment of T2DM.

B.3.5.1 Intervention and comparators' costs and resource use

As there are no differences in administration and monitoring costs, and the NMA indicates that the SGLT-2is have similar efficacy and safety, diabetes treatment and AEs costs have been assumed to be the same between ertugliflozin and its comparators; the cost-minimisation has been confined to drug acquisition costs alone. This is consistent with the resource use assumptions applied in TAs 390 [47], 288 [49], 315 [30], 336 [31] and 418 [32]. Table 30 and Table 31 present the drug acquisition costs, dosage, and annual cost of ertugliflozin and the comparators treatments in triple therapy.

Table 30 - Drug acquisition costs

Therapy	Price per pack	Price per tablet	Dose per tablet	Daily dose	Annual cost
Background therapy					
Metformin	£0.90 per 28 pack	£0.03	500mg	2000 mg	£43.83
DPP-4i (Sitagliptin)	£33.26 per 28 pack	£1.19	100mg	100 mg	£434.65
Intervention					
Ertugliflozin	£[redacted] per 28 pack	£[redacted]	5 mg or 15 mg	5 mg or 15 mg	£[redacted]
Comparators					
Canagliflozin	£39.20 per 30 pack	£1.31	100 mg or 300mg	100 mg or 300mg	£478.48
Dapagliflozin	£36.59 per 28 pack	£1.31	10 mg	10 mg	£478.48
Empagliflozin	£36.59	£1.31	10 mg or 25 mg	10 mg or 25 mg	£478.48

Therapy	Price per pack	Price per tablet	Dose per tablet	Daily dose	Annual cost
	per 28 pack				
Combination					
Met + DPP-4i + ertugliflozin		£[redacted]			£[redacted]
Met + DPP-4i + canagliflozin		£2.53			£956.96
Met + DPP-4i + dapagliflozin		£2.53			£956.96
Met + DPP-4i + empagliflozin		£2.53			£956.96

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitor

Table 31 - Unit costs associated with the technology in the economic model (annual costs)

Items	ERTU	Reference in submission	CANA	DAPA	EMPA	Reference in submission
Technology cost	£[redacted]	B.1.2	£478.48	£478.48	£478.48	**Error! Reference source not found.**
Back ground therapy (Met + DPP-4i)	£43.83 + £434.65	**Error! Reference source not found.**	£43.83 + £434.65	£43.83 + £434.65	£43.83 + £434.65	**Error! Reference source not found.**
Mean cost of technology treatment	-	-	-	-	-	-
Administration cost	-	-	-	-	-	-
Monitoring cost	-	-	-	-	-	-
Tests	-	-	-	-	-	-
Total	£[redacted]		£956.96	£956.96	£956.96	-

Abbreviations: Met, metformin; DPP-4i, dipeptidyl peptidase 4 inhibitor; ERTU, ertugliflozin; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin

B.3.5.2 Health-state unit costs and resource use

As the NMA results comparing ertugliflozin to the other licensed SGLT-2is (canagliflozin, dapagliflozin and empagliflozin) on a background of metformin and a DPP-4i revealed that the efficacy (HbA1c, weight change, SBP and HBA1c within target) of all SGLT-2is were similar in triple therapy, a cost-minimisation analysis will be conducted and no health states will be modelled.

B.3.5.3 Adverse reaction unit costs and resource use

As the NMA results comparing ertugliflozin to the other licensed SGLT-2is (canagliflozin, dapagliflozin and empagliflozin) on a background of metformin and DPP-4i revealed that the safety (AEs and UTIs) of all SGLT-2is were similar in triple therapy, a cost-minimisation analysis will be conducted and no adverse event states will be modelled.

B.3.5.4 Miscellaneous unit costs and resource use

There are no miscellaneous unit costs and resource use

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The inputs for the base case analysis are summarised in Table 32.

Table 32 - Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Drug acquisition costs			
Metformin	£48.83 (Table 30)	As these are list prices there is no uncertainty to assess.	B.3.5
DPP-4i (Sitagliptin)	£434.65 (Table 30)		B.3.5
Ertugliflozin	£[redacted] (Table 30)		B.1.1
Dapagliflozin	£478.48 (Table 30)		B.3.5
Canagliflozin	£478.48 (Table 30)		B.3.5
Empagliflozin	£478.48 (Table 30)		B.3.5

Abbreviations: CI, confidence interval

B.3.6.2 Assumptions

The assumptions applied in the cost-minimisation analysis are summarised in

Assumption	Justification
1. Ertugliflozin and the other SGLT-2is have equal efficacy.	NMA, B.2.9
2. Ertugliflozin and the other SGLT-2is have the same adverse event profile.	NMA, B.2.9 and B.2.10
3. As there are no differences in health outcomes life years gained and quality adjusted life years will not be estimated	Based on assumptions 1 and 2
4. There are no differences between ertugliflozin and the other SGLT-2is in terms of testing, administration, initiation or monitoring.	SPCs [39, 41, 43]

Abbreviations: NMA, network meta-analysis

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case analysis is presented in Table 33 for ertugliflozin compared to the other SGLT-2is on a background of metformin with DPP-4is. As both metformin and DPP-4i costs are the same for all comparators, [redacted]. Canagliflozin [39], dapagliflozin [43] and empagliflozin [41] all have an annual cost of £478.48 (£1.31 per day * 365.25 days). Ertugliflozin [redacted] to the NHS with an annual cost of £[redacted] (£[redacted] per day * 365.25 days), producing an annual [redacted].

Table 33 - Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs. ertugliflozin (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Met + DPP-4i + ertugliflozin 5 mg /15 mg	£[redacted]	-	-		-	-	-	-
Met + DPP-4i + canagliflozin 100 mg /300 mg	£956.96	-	-	£[redacted]	-	-	-	-
Met + DPP-4i + dapagliflozin 5 mg /10 mg	£956.96	-	-	£[redacted]	-	-	-	-
Met + DPP-4i + empagliflozin 10 mg /25 mg	£956.96	-	-	£[redacted]	-	-	-	-

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

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

As a one year cost-minimisation analysis based on drug acquisition list prices has been conducted, probabilistic, deterministic and scenario analyses are not required.

B.3.8.2 Deterministic sensitivity analysis

Not applicable.

B.3.8.3 Scenario analysis

Not applicable.

B.3.8.4 Summary of sensitivity analyses results

Sensitivity analyses were not required as the analysis is based on list prices.

B.3.9 Subgroup analysis

No clinically relevant subgroups were identified and as a result no subgroup analysis was required.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The validation of the cost-minimisation model was assessed using internal (verification) validity. Verification was conducted by one economist and assessed using the techniques of extreme value analysis (substituting minimum and maximum values for appropriate parameter values), logical consistency tests and using parallel inputs for all costs.

B.3.11 Interpretation and conclusions of economic evidence

The cost-minimisation analysis demonstrated that ertugliflozin is a [redacted] alternative therapy to the other SGLT-2is (canagliflozin, dapagliflozin and empagliflozin) in triple therapy on a background of metformin and a DPP-4i. Ertugliflozin provides [redacted] annually per patient [redacted].

The primary limitation of the cost-minimisation analysis is that the assumptions of equal efficacy and safety are not based on head to head comparisons from a randomised controlled equivalence trial. Additionally the NMA for triple therapy only comprises of five trials, data was not available for all outcomes and the NMA networks did not converge for

some safety outcomes (genital mycotic infections, NSHE and SHE). However, it should be noted that the NMA was populated with data from a SLR of RCTs. The studies included were quality assessed using the York Centre for Reviews and Dissemination checklist [25] and found to be of high quality.

The cost-minimisation finding is robust as the analysis is based on the TA418 [32] committee assumptions for common resource use. The results of the cost-minimisation analysis are generalisable to adults with T2DM in England and Wales who require an SGLT-2i as triple therapy with metformin and a DPP-4i.

It should be noted that the treatment of T2DM is individualised for each patient and that all existing treatments have advantages and disadvantages and do not enable all T2DM patients to achieve and maintain their target HbA1c levels. The introduction of ertugliflozin as triple therapy on a background of metformin and DPP-4i adds an additional treatment option. The SGLT-2i mechanism of action increases renal glucose excretion providing clinically significant glucose reduction alongside a decrease in blood pressure and weight loss.

In summary, it can be concluded that the introduction of ertugliflozin will result in a [redacted] therapy for the NHS in England and Wales, supporting its implementation as a valuable treatment alternative for patients with T2DM.

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B.5 Appendices

Appendix C: Summary of product characteristics and European public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Other outcomes in the VERTIS SITA2 trial

Appendix M: Overview on Phase B results of the VERTIS SITA2 trial

Appendix N: NMA – outcome-specific diagrams

Appendix O: Effect modifiers

Appendix P: NMA – additional base-case results

Appendix Q: NMA – non converged analyses

Appendix R: WinBUGS code

Appendix s: References

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

C.1 Ertugliflozin 5 mg and 15 mg tablets

FINAL TEXT
11 April 2018

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Steglatro® 5 mg film-coated tablets
Steglatro® 15 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Steglatro 5 mg film-coated tablets
Each tablet contains 5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid).

Excipient(s) with known effect
Each tablet contains 28 mg of lactose (as monohydrate).

Steglatro 15 mg film-coated tablets
Each tablet contains 15 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid).

Excipient(s) with known effect
Each tablet contains 85 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Steglatro 5 mg film-coated

tablets
Pink, 6.4 x 6.6 mm, triangular-shaped, film-coated tablets debossed with “701” on one side and plain on the other side.

Steglatro 15 mg film-coated tablets
Red, 9.0 x 9.4 mm, triangular-shaped, film-coated tablets debossed with “702” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Steglatro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

(For study results with respect to combinations and effects on glycaemic control see sections 4.4, 4.5, and 5.1.)

4.2 Posology and method of administration

Posology
The recommended starting dose of ertugliflozin is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed.

When ertugliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia (see sections 4.4, 4.5, and 4.8).

In patients with volume depletion, correcting this condition prior to initiation of ertugliflozin is recommended (see section 4.4).

If a dose is missed, it should be taken as soon as the patient remembers. Patients should not take two doses of Steglatro on the same day.

Special populations

Renal impairment
Assessment of renal function is recommended prior to initiation of Steglatro and periodically thereafter (see section 4.4).

Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 or CrCl less than 60 ml/min (see section 4.4).

Steglatro should be discontinued when eGFR is persistently less than 45 ml/min/1.73 m^2 or CrCl is persistently less than 45 ml/min.

Steglatro should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as it is not expected to be effective in these patients.

Hepatic impairment
No dose adjustment of ertugliflozin is necessary in patients with mild or moderate hepatic impairment. Ertugliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see section 5.2).

Elderly (≥ 65 years old)
No dose adjustment of ertugliflozin is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 4.8). There is limited experience with Steglatro in patients ≥ 75 years of age.

Paediatric population
The safety and efficacy of ertugliflozin in children under 18 years of age have not been established. No data are available.

Method of administration
Steglatro should be taken orally once daily in the morning, with or without food. In case of swallowing difficulties, the tablet could be broken or crushed as it is an immediate-release dosage form.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Steglatro should not be used in patients with type 1 diabetes mellitus.

Hypotension/Volume depletion
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Steglatro (see section 4.8), particularly in patients with impaired renal function (eGFR less than 60 ml/min/1.73 m^2 or CrCl less than
60 ml/min), elderly patients (≥ 65 years), patients on diuretics, or patients on anti-hypertensive therapy
with a history of hypotension. Before initiating Steglatro, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms after initiating therapy.

Due to its mechanism of action, ertugliflozin induces an osmotic diuresis and increases serum creatinine and decreases eGFR. Increases in serum creatinine and decreases in eGFR were greater in patients with moderate renal impairment (see section 4.8).

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving ertugliflozin. Temporary interruption of treatment with ertugliflozin should be considered until the fluid loss is corrected.

Diabetic ketoacidosis
Rare cases of DKA, including life-threatening and fatal cases, have been reported in clinical trials and post-marketing in patients treated with sodium glucose co-transporter-2 (SGLT2) inhibitors, and cases have been reported in clinical trials with ertugliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l
(250 mg/dl). It is not known if DKA is more likely to occur with higher doses of ertugliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with ertugliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with ertugliflozin may be restarted once the patient's condition has stabilised.

Before initiating ertugliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin

requirements due to acute medical illness, surgery, or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of ertugliflozin in patients with type 1 diabetes have not been established and ertugliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Impairment in renal function
The efficacy of ertugliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2).

Steglatro should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min. Steglatro should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl is persistently below 45 ml/min due to a reduction of efficacy.

Monitoring of renal function is recommended as follows:
- Prior to ertugliflozin initiation and periodically during treatment (see section 4.2).
- More frequently in patients with an eGFR below 60 ml/min/1.73 m^2 or a CrCl below 60 ml/min.

Hypoglycaemia with concomitant use with insulin and insulin secretagogues
Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue, which are known to cause hypoglycaemia (see section 4.8). Therefore, a lower dose of insulin or insulin secretagogue may be required to minimise the risk of hypoglycaemia when used in combination with ertugliflozin (see sections 4.2 and 4.5).

Genital mycotic infections
Ertugliflozin increases the risk of genital mycotic infections. In trials with SGLT2 inhibitors, patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections (see section 4.8). Patients should be monitored and treated appropriately.

Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infections. The incidence of urinary tract infections was not notably different in the ertugliflozin 5 mg and 15 mg groups (4.0% and 4.1%) and the placebo group (3.9%). Most of the events were mild or moderate and no serious case was reported. Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis.

Elderly patients
Elderly patients may be at an increased risk of volume depletion. Patients 65 years and older treated with ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared

to younger patients. Ertugliflozin is expected to have diminished efficacy in elderly patients with renal impairment (see sections 4.2 and 4.8).

Cardiac failure
Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with ertugliflozin in NYHA class III-IV.

Urine laboratory assessments
Due to its mechanism of action, patients taking Steglatro will test positive for glucose in their urine. Alternative methods should be used to monitor glycaemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) assay
Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Alternative methods should be used to monitor glycaemic control.

Lactose
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics
Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with ertugliflozin (see sections 4.2, 4.4, and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on the pharmacokinetics of ertugliflozin
Metabolism by UGT1A9 and UGT2B7 is the primary clearance mechanism for ertugliflozin.

Interaction studies conducted in healthy subjects, using a single dose design, suggest that the pharmacokinetics of ertugliflozin are not altered by sitagliptin, metformin, glimepiride, or simvastatin.

Multiple-dose administration of rifampin (a UGT and CYP inducer) decreases ertugliflozin AUC and C_{max} by 39% and 15%, respectively. This decrease in exposure is not considered clinically relevant and therefore, no dose adjustment is recommended. A clinically relevant effect with other inducers (e.g., carbamazepine, phenytoin, phenobarbital) is not expected.

The impact of UGT inhibitors on the pharmacokinetics of ertugliflozin has not been studied clinically, but potential increase in ertugliflozin exposure due to UGT inhibition is not considered to be clinically relevant.

Effects of ertugliflozin on the pharmacokinetics of other medicinal products
Interaction studies conducted in healthy volunteers suggest that ertugliflozin had no clinically relevant effect on the pharmacokinetics of sitagliptin, metformin, and glimepiride.

Coadministration of simvastatin with ertugliflozin resulted in a 24% and 19% increase in AUC and C_{max} of simvastatin, respectively, and 30% and 16% increase in AUC and C_{max} of simvastatin acid, respectively. The mechanism for the small increases in simvastatin and simvastatin acid is unknown and is not perpetrated through OATP inhibition by ertugliflozin. These increases are not considered to be clinically meaningful.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of ertugliflozin in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation (see section 5.3). Therefore, Steglatro should not be used during pregnancy.

Breast-feeding
There is no information regarding the presence of ertugliflozin in human milk, the effects on the breast-fed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats and caused effects in the offspring of lactating rats. Pharmacologically-mediated effects were observed in juvenile rats (see section 5.3). Since human kidney maturation occurs in utero and during the first
2 years of life when exposure from breast-feeding may occur, a risk to newborns/infants cannot be excluded. Steglatro should not be used during breast-feeding.

Fertility
The effect of ertugliflozin on fertility in humans has not been studied. No effects on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Ertugliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when Steglatro is used in combination with insulin or an insulin secretagogue and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness (see sections 4.2, 4.4, and 4.8).

4.8 Undesirable effects

Summary of the safety profile

Pool of placebo-controlled trials evaluating Steglatro 5 mg and 15 mg
The primary assessment of safety was conducted in a pool of three 26-week, placebo-controlled trials. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials (see section 5.1). These data reflect exposure of 1,029 patients to ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg
(N=510), or placebo (N=515) once daily.

The most commonly reported adverse reactions across the clinical program were vulvovaginal mycotic infection and other female genital mycotic infections. Serious diabetic ketoacidosis occurred rarely.
See “Description of selected adverse reactions” for frequencies and see section 4.4.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System Organ Class Frequency	**Adverse Reaction**
Infections and infestations	
Very common	Vulvovaginal mycotic infection and other female genital mycotic infections*,†
Common	Balanitis candida and other male genital mycotic infections*,†
Metabolism and nutrition disorders	
Common	Hypoglycaemia*,†
Rare	Diabetic ketoacidosis*,†
Vascular disorders	
Common	Volume depletion*,†
Renal and urinary disorders	
Common	Increased urination‡
Uncommon	Dysuria, Blood creatinine increased/Glomerular filtration rate decreased†
Reproductive system and breast disorders	
Common	Vulvovaginal pruritus
General disorders and administration site conditions	
Common	Thirst§
Investigations	
Common	Serum lipids changed¶, Haemoglobin increased**, BUN increased¶¶

* See Section 4.4.
† See subsections below for additional information.
‡ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.
§ Includes: thirst and polydipsia.
¶ Mean percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were LDL-C 5.8% and 8.4% versus 3.2%; total cholesterol 2.8% and 5.7% versus 1.1%; however, HDL-C 6.2% and 7.6% versus 1.9%. Median percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were triglycerides -3.9% and -1.7% versus 4.5%.
** The proportion of subjects having at least 1 increase in haemoglobin > 2.0 g/dL was higher in the ertugliflozin 5 mg and 15 mg groups (4.7% and 4.1%, respectively) compared to the placebo group (0.6%).
¶¶ The proportion of subjects having any occurrence of BUN values ≥ 50% increase and value >ULN was numerically higher in the ertugliflozin 5 mg group and higher in the 15 mg group (7.9% and 9.8%, respectively) relative to the placebo group (5.1%).

Description of selected adverse reactions

Volume depletion

Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of placebo-controlled studies, the incidence of adverse events related to volume depletion (dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) was low (< 2%) and not notably different across the ertugliflozin and placebo groups. In the subgroup analyses in the broader pool of Phase 3 studies, subjects with eGFR < 60 mL/min/1.73 m^2, subjects ≥ 65 years of age and subjects

on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative to the comparator group (see sections 4.2 and 4.4). In subjects with eGFR < 60 mL/min/1.73 m^2, the incidence was 5.1%, 2.6%, and
0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg, and the comparator group and for subjects with eGFR 45 to < 60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7%, and 0% respectively.

Hypoglycaemia
In the pool of placebo-controlled studies, the incidence of documented hypoglycaemia was increased for ertugliflozin 5 mg and 15 mg (5.0% and 4.5%) compared to placebo (2.9%). In this population, the incidence of severe hypoglycaemia was 0.4% in each group. When ertugliflozin was used as monotherapy, the incidence of hypoglycaemic events in the ertugliflozin groups was 2.6% in both groups and 0.7% in the placebo group. When used as add-on to metformin, the incidence of hypoglycaemic events was 7.2% in the ertugliflozin 5 mg group, 7.8% in the ertugliflozin 15 mg group and 4.3% in the placebo group.

When ertugliflozin was added to metformin and compared to sulphonylurea, the incidence of hypoglycaemia was higher for the sulphonylurea (27%) compared to ertugliflozin (5.6% and 8.2% for ertugliflozin 5 mg and 15 mg, respectively).

In patients with moderate renal impairment taking insulins, SU, or meglitinides as background medication, documented hypoglycaemia was 36%, 27% and 36% for ertugliflozin 5 mg, ertugliflozin
15 mg, and placebo, respectively (see sections 4.2, 4.4, and 4.5).

Diabetic ketoacidosis
Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients (see section 4.4).

Blood creatinine increased/Glomerular filtration rate decreased and renal-related events
Initial increases in mean creatinine and decreases in mean eGFR in patients treated with ertugliflozin were generally transient during continuous treatment. Patients with moderate renal impairment at
baseline had larger mean changes that did not return to baseline at Week 26; these changes reversed after treatment discontinuation.

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 2.5%, 1.3%, and 0.6% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively.

Genital mycotic infections
In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal
mycotic infection, vulvovaginitis) occurred in 9.1%, 12%, and 3.0% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively (see section 4.4).

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively.

In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

In the event of an overdose, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of ertugliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Sodium glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK04.

Mechanism of action
SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is a potent, selective, and reversible inhibitor of SGLT2.

By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamic effects

Urinary glucose excretion and urinary volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose
administration of ertugliflozin. Dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE) in patients with type 2 diabetes mellitus, providing 87% and 96% of maximal inhibition, respectively.

Clinical efficacy and safety
The efficacy and safety of ertugliflozin have been studied in 7 multi-centre, randomised, double-blind, placebo- or active comparator-controlled, Phase 3 clinical studies involving 4,863 patients with type 2 diabetes, including a study of 468 patients with moderate renal impairment. The racial distribution was
76.8% White, 13.3% Asian, 5.0% Black and 4.8% other. Hispanic or Latino patients comprised 24.2%

of the population. Patients had an average age of 57.8 years (range 21 years to 87 years), with 25.8% of patients ≥ 65 years of age and 4.5% ≥ 75 years of age.

Ertugliflozin has been studied as monotherapy and in combination with metformin and/or a dipeptidyl peptidase 4 (DPP-4) inhibitor. Ertugliflozin has also been studied in combination with current diabetes treatments, including insulin and a sulphonylurea, in patients with type 2 diabetes with moderate renal impairment.

Monotherapy
A total of 461 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin monotherapy. These patients, who were not receiving any background anti-
hyperglycaemic treatment, were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily (see Table 2).

Table 2: Results at Week 26 from a placebo-controlled monotherapy study of Steglatro*

	Steglatro 5 mg	**Steglatro 15 mg**	**Placebo**
HbA1c (%)	**N = 156**	**N = 151**	**N = 153**
Baseline (mean)	8.2	8.4	8.1
Change from baseline (LS mean†)	-0.8	-1.0	0.2
Difference from placebo (LS mean†, 95% CI)	-1.0‡ (-1.2, -0.8)	-1.2‡ (-1.4, -0.9)	
Patients [N (%)] with HbA1c < 7%	44 (28.2)§	54 (35.8)§	20 (13.1)
Body Weight (kg)	**N = 156**	**N = 152**	**N = 153**
Baseline (mean)	94.0	90.6	94.2
Change from baseline (LS mean†)	-3.2	-3.6	-1.4
Difference from placebo (LS mean†, 95% CI)	-1.8‡ (-2.6, -0.9)	-2.2‡ (-3.0, -1.3)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication, baseline eGFR and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin
A total of 621 patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥ 1,500 mg/day) participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin in combination with metformin.

Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin therapy (see Table 3).

Table 3: Results at Week 26 from a placebo-controlled study for Steglatro used in combination with metformin*

	Steglatro 5 mg	Steglatro 15 mg	Placebo
HbA1c (%)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	8.1	8.1	8.2
Change from baseline (LS mean†)	-0.7	-0.9	-0.0
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.5)	-0.9‡ (-1.1, -0.7)	
Patients [N (%)] with HbA1c < 7%	73 (35.3)§	82 (40.0)§	33 (15.8)
Body Weight (kg)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	84.9	85.3	84.5
Change from baseline (LS mean†)	-3.0	-2.9	-1.3
Difference from placebo (LS mean†, 95% CI)	-1.7‡ (-2.2, -1.1)	-1.6‡ (-2.2, -1.0)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomisation stratum (men, premenopausal
women, women who are perimenopausal or < 3 years postmenopausal, women who are ≥ 3 years postmenopausal) and the interaction of time by treatment.

‡ p≤ 0.001 compared to placebo.

§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Active-controlled study of ertugliflozin versus glimepiride as add-on combination therapy with metformin

A total of 1,326 patients with type 2 diabetes inadequately controlled on metformin monotherapy participated in a randomised, double-blind, multi-centre, 52-week, active comparator-controlled study
to evaluate the efficacy and safety of ertugliflozin in combination with metformin. These patients, who
were receiving metformin monotherapy (≥ 1,500 mg/day), were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or glimepiride administered once daily in addition to continuation of background metformin therapy. Glimepiride was initiated at 1 mg/day and titrated up to a maximum dose of 6 or
8 mg/day (depending on maximum approved dose in each country) or a maximum tolerated dose or down-titrated to avoid or manage hypoglycaemia. The mean daily dose of glimepiride was 3.0 mg (see Table 4).

Table 4: Results at Week 52 from an active-controlled study comparing Steglatro to glimepiride as add-on therapy in patients inadequately controlled on metformin*

	Steglatro 5 mg	Steglatro 15 mg	Glimepiride
HbA1c (%)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	7.8	7.8	7.8
Change from baseline (LS mean†)	-0.6	-0.6	-0.7
Difference from glimepiride (LS mean†, 95% CI)	0.2 (0.1, 0.3)	0.1‡ (-0.0, 0.2)	
Patients [N (%)] with HbA1c < 7%	154 (34.4)	167 (38.0)	190 (43.5)

Body Weight (kg)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	87.9	85.6	86.8
Change from baseline (LS mean[†])	-3.0	-3.4	0.9
Difference from glimepiride (LS mean[†], 95% CI)	-3.9 (-4.4, -3.4)	-4.3[§] (-4.8, -3.8)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication (monotherapy or dual therapy),

baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

‡ Non-inferiority is declared when the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.

§ p< 0.001 compared to glimepiride.

Factorial study with ertugliflozin and sitagliptin as add-on combination therapy with metformin

A total of 1,233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre,
26-week, active-controlled study to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥ 1,500 mg/day) were randomised to one of five active-treatment arms: ertugliflozin 5 mg or 15 mg, sitagliptin 100 mg, or sitagliptin 100 mg in combination with 5 mg or 15 mg ertugliflozin administered once daily in addition to continuation of background metformin therapy (see Table 5).

Table 5: Results at Week 26 from a factorial study with Steglatro and sitagliptin as add-on combination therapy with metformin compared to individual components alone*

	Steglatro 5 mg	**Steglatro 15 mg**	**Sitagliptin 100 mg**	**Steglatro 5 mg + Sitagliptin 100 mg**	**Steglatro 15 mg + Sitagliptin 100 mg**
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.6	8.6	8.5	8.6	8.6
Change from baseline (LS mean†)	-1.0	-1.1	-1.1	-1.5	-1.5
Difference from Sitagliptin (LS mean†, 95% CI)				-0.4‡ (-0.6, -0.3)	-0.5‡ (-0.6, -0.3)
Difference from Steglatro 5 mg (LS mean†, 95% CI)				-0.5‡ (-0.6, -0.3)	
Difference from Steglatro 15 mg (LS mean†, 95% CI)					-0.4‡ (-0.6, -0.3)
Patients [N (%)] with HbA1c < 7%	66 (26.4)	79 (31.9)	81 (32.8)	127§ (52.3)	120§ (49.2)
Body Weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from Sitagliptin (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, baseline eGFR and the interaction of time by treatment.

‡ p< 0.001 compared to control group.

§ p< 0.001 compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin and sitagliptin

A total of 463 patients with type 2 diabetes inadequately controlled on metformin (≥ 1,500 mg/day) and sitagliptin 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and sitagliptin therapy (see Table 6).

Table 6: Results at Week 26 from an add-on study of Steglatro in combination with metformin and sitagliptin*

	Steglatro 5 mg	Steglatro 15 mg	Placebo
HbA1c (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.1	8.0	8.0
Change from baseline (LS mean†)	-0.8	-0.9	-0.1
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.5)	-0.8‡ (-0.9, -0.6)	
Patients [N (%)] with HbA1c < 7%	50 (32.1)‡	61 (39.9)‡	26 (17.0)
Body Weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication.
‡ p< 0.001 compared to placebo.

Combination therapy of ertugliflozin and sitagliptin
A total of 291 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, placebo-controlled 26-week study to evaluate the efficacy and safety of ertugliflozin in combination with sitagliptin. These patients, who were not receiving any background anti-hyperglycaemic treatment, were randomised to ertugliflozin 5 mg or ertugliflozin
15 mg in combination with sitagliptin (100 mg) or to placebo once daily (see Table 7).

Table 7: Results at Week-26 from a combination therapy study of ertugliflozin and sitagliptin*

	Ertugliflozin 5 mg + Sitagliptin	Ertugliflozin 15 mg + Sitagliptin	Placebo
HbA1c (%)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	8.9	9.0	9.0
Change from baseline (LS mean†)	-1.6	-1.7	-0.4
Difference from placebo (LS mean† and 95% CI)	-1.2‡ (-1.5, -0.8)	-1.2‡ (-1.6, -0.9)	
Patients [N (%)] with HbA1c <7%	35 (35.7)§	30 (31.3)§	8 (8.3)
Body Weight (kg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	90.8	91.3	95.0
Change from baseline (LS mean†)	-2.9	-3.0	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-3.0, -1.0)	-2.1‡ (-3.1, -1.1)	

* N includes all patients who received at least one dose of study medication and had at least one measurement of the outcome variable.
† Least squares means adjusted based on a longitudinal model including terms for treatment, time, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Moderate renal impairment

The efficacy of ertugliflozin was also assessed separately in a dedicated study of diabetic patients with moderate renal impairment (468 patients with eGFR ≥ 30 to < 60 ml/min/1.73 m^2).

The LS mean (95% CI) changes from baseline in HbA1c were -0.26 (-0.42, -0.11), -0.29 (-0.44, -0.14), and -0.41 (-0.56, -0.27) in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg

groups, respectively. The HbA1c reductions in the ertugliflozin arms were not significantly different from placebo. The pre-specified analysis of glycaemic efficacy was confounded by use of a prohibited concomitant antihyperglycaemic medication. In a subsequent analysis excluding those subjects who used the prohibited medication, ertugliflozin 5 mg and 15 mg were associated with placebo-corrected reductions in HbA1c of -0.14 (-0.36, 0.08) and -0.33 (-0.55, -0.11)

Fasting plasma glucose
In three placebo-controlled studies, ertugliflozin resulted in statistically significant reductions in FPG. For ertugliflozin 5 mg and 15 mg, respectively, the placebo-corrected reductions in FPG were 1.92 and
2.44 mmol/l as monotherapy, 1.48 and 2.12 mmol/l as add-on to metformin, and 1.40 and 1.74 mmol/l as add-on to metformin and sitagliptin.

The combination of ertugliflozin and sitagliptin resulted in significantly greater reductions in FPG compared to sitagliptin or ertugliflozin alone or placebo. The combination of ertugliflozin 5 or 15 mg and sitagliptin resulted in incremental FPG reductions of 0.46 to 0.65 mmol/l compared to the ertugliflozin alone or 1.02 to 1.28 mmol/l compared to sitagliptin alone. The placebo-corrected reductions of ertugliflozin 5 or 15 mg in combination with sitagliptin were 2.16 and 2.56 mmol/l.

Efficacy in patients with baseline HbA1c ≥ 8%
In the monotherapy study conducted on a background of diet and exercise in patients with baseline HbA1c from 7-10.5%, the subgroup of patients in the study with a baseline HbA1c ≥ 8% had placebo-corrected reductions in HbA1c of 1.11% and 1.52% with ertugliflozin 5 or 15 mg, respectively.

In the study of ertugliflozin added-on to metformin in patients with baseline HbA1c from 7.0-10.5%, the placebo-corrected reductions in HbA1c for the subgroup of patients in the study with baseline HbA1c ≥ 9% were 1.31% and 1.43% with ertugliflozin 5 and 15 mg, respectively.

In the study of patients inadequately controlled on metformin with baseline HbA1c from 7.5-11.0%, among the subgroup of patients with a baseline HbA1c ≥ 10%, the combination of ertugliflozin 5 mg or 15 mg with sitagliptin resulted in reductions of HbA1c of 2.35% and 2.66% compared to 2.10%,
1.30%, and 1.82% for ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin alone, respectively.

Post-prandial glucose
In the monotherapy study, ertugliflozin 5 and 15 mg resulted in statistically significant placebo- corrected reductions in 2-hour PPG of 3.83 and 3.74 mmol/l.

Blood pressure
In three 26-week, placebo-controlled studies, ertugliflozin reduced systolic blood pressure (SBP). For ertugliflozin 5 mg and 15 mg, the statistically significant placebo-corrected reductions in SBP ranged from 2.9 mmHg to 3.7 mmHg and 1.7 mmHg to 4.5 mmHg, respectively.

In a 52-week, active-controlled study versus glimepiride, reductions from baseline in SBP were 2.2 mmHg and 3.8 mmHg for ertugliflozin 5 mg and 15 mg respectively, while subjects treated with glimepiride had an increase in SBP from baseline of 1.0 mmHg.

Subgroup analysis
In patients with type 2 diabetes treated with ertugliflozin, clinically meaningful reductions in HbA1c were observed in subgroups defined by age, sex, race, ethnicity, geographic region, baseline BMI,
baseline HbA1c, and duration of type 2 diabetes mellitus.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ertugliflozin in one or more subsets of the paediatric population in Type II diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

General introduction
The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes. The steady state mean plasma AUC and C_{max} were 398 ng·hr/ml and 81 ng/ml, respectively, with 5 mg ertugliflozin once daily treatment, and 1,193 ng·hr/ml and 268 ng/ml, respectively, with 15 mg ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median T_{max}) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose-proportional manner following single doses from
0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability
of ertugliflozin following administration of a 15-mg dose is approximately 100%.

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, ertugliflozin was administered without regard to meals.

Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

Distribution
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 86 l. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Ertugliflozin is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3) *in vitro.*

Biotransformation
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Elimination
The mean systemic plasma clearance following an intravenous 100 µg dose was 11 l/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be

17 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 41% and 50% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 34% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Special populations

Renal impairment
In a Phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were ≤ 1.7-fold, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (see section 4.4). The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Hepatic impairment
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

Paediatric population
No studies with ertugliflozin have been performed in paediatric patients.

Effects of age, body weight, gender, and race
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

Drug interactions

In vitro *assessment of ertugliflozin*
In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit or inactivate CYPs 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin and ertugliflozin glucuronides did not inhibit the activity of UGTs 1A6, 1A9 or 2B7 *in vitro*. Ertugliflozin was a weak inhibitor of UGTs 1A1 and 1A4 *in vitro* at higher concentrations that are not clinically relevant. Ertugliflozin glucuronides had no effect on these isoforms. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered drugs eliminated by these enzymes.

Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 transporters or transporting polypeptides OATP1B1 and OATP1B3 at clinically relevant concentrations *in vitro*. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, genotoxicity, and carcinogenic potential.

General toxicity

Repeat-dose oral toxicity studies were conducted in mice, rats, and dogs for up to 13, 26, and 39 weeks, respectively. Signs of toxicity that were considered adverse were generally observed at exposures greater than or equal to 77 times the human unbound exposure (AUC) at the maximum recommended human dose (MRHD) of 15 mg/day. Most toxicity was consistent with pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, and urinary changes such as polyuria, glucosuria, and calciuria. Microscopic changes related to glucosuria and/or calciuria observed only in rodents included dilatation of renal tubules, hypertrophy of zona glomerulosa in adrenal glands (rats), and increased trabecular bone (rats). Except for emesis, there were no adverse toxicity findings in dogs at 379 times the human unbound exposure (AUC) at the MRHD of 15 mg/day.

Carcinogenesis

In the 2-year mouse carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 5, 15, and 40 mg/kg/day. There were no ertugliflozin-related neoplastic findings at doses up to 40 mg/kg/day (approximately 41 times human unbound exposure at the MRHD of 15 mg/day based on AUC). In the 2-year rat carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 1.5, 5, and 15 mg/kg/day. Ertugliflozin-related neoplastic findings included an increased incidence of benign adrenal medullary pheochromocytoma in male rats at 15 mg/kg/day. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis and was not considered relevant to human risk. The no-observed-effect level (NOEL) for neoplasia was 5 mg/kg/day (approximately 16 times human unbound exposure at the MRHD of 15 mg/day).

Mutagenesis

Ertugliflozin was not mutagenic or clastogenic with or without metabolic activation in the microbial reverse mutation, *in vitro* cytogenetic (human lymphocytes), and *in vivo* rat micronucleus assays.

Reproductive toxicology

In the rat fertility and embryonic development study, male and female rats were administered ertugliflozin at 5, 25, and 250 mg/kg/day. No effects on fertility were observed at 250 mg/kg/day (approximately 386 times human unbound exposure at the MRHD of 15 mg/day based on AUC comparisons). Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were 239 and 1,069 times, respectively, the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. At a maternally toxic dose in rats (250 mg/kg/day), lower foetal viability and a higher incidence of a visceral malformation were observed at maternal exposure that was 510 times the maximum clinical dose of 15 mg/day.

In the pre- and postnatal development study, decreased postnatal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at ≥ 100 mg/kg/day (estimated 239 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC). Sexual maturation was delayed in both sexes at 250 mg/kg/day (estimated 620 times the MRHD at 15 mg/day, based on AUC).

When ertugliflozin was administered to juvenile rats from postnatal day (PND) 21 to PND 90, a period of renal development corresponding to the late second and third trimesters of human pregnancy, increased kidney weights, dilatation of the renal pelvis and tubules, and renal tubular

mineralization were seen at an exposure 13 times the maximum clinical dose of 15 mg/day, based on AUC. Effects
on bone (shorter femur length, increased trabecular bone in the femur) as well as effects of delayed puberty were observed at an exposure 817 times the MRHD of 15 mg/day based on AUC. The effects on kidney and bone did not fully reverse after the 1-month recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
(E460) Lactose monohydrate
Sodium starch glycolate (Type
A) Magnesium stearate
(E470b)

Film coating
Hypromellose 2910/6
(E464) Lactose
monohydrate Macrogol
3350 (E1521) Triacetin
(E1518)
Titanium dioxide
(E171) Iron oxide red
(E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/PVC/PA/Alu blisters**.**
Packs of 14, 28, 30, 84, and 90 film-coated tablets in non-perforated blisters.
Packs of 30x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Steglatro 5 mg film-coated tablets
EU/1/18/1267/001
EU/1/18/1267/002
EU/1/18/1267/003
EU/1/18/1267/004
EU/1/18/1267/005
EU/1/18/1267/006

Steglatro 15 mg film-coated tablets
EU/1/18/1267/007
EU/1/18/1267/008
EU/1/18/1267/009
EU/1/18/1267/010
EU/1/18/1267/011
EU/1/18/1267/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

EMA/90284/2018
EMEA/H/C/004315

Steglatro (*ertugliflozin*)

An overview of Steglatro and why it is authorised in the EU

What is Steglatro and what is it used for?

Steglatro is a medicine used to control blood glucose (sugar) levels in adults with type 2 diabetes together with diet and exercise.

Steglatro can be used in combination with other diabetes medicines or on its own in patients who cannot take metformin.

Steglatro contains the active substance ertugliflozin.

How is Steglatro used?

Steglatro is available as tablets (5 and 15mg). The patient should start with one 5 mg tablet once a day in the morning. If the patients' glucose level is still too high the dose can be increased to 15 mg once a day. For more information about using Steglatro, see the package leaflet or contact your doctor or pharmacist.

Steglatro can only be obtained with a prescription.

How does Steglatro work?

Type 2 diabetes is a disease in which the body does not make enough insulin to control the level of glucose in the blood or when the body is unable to use insulin effectively. The result is a high level of glucose in the blood.

The active substance in Steglatro, ertugliflozin, helps to lower blood glucose by making the patient pass out glucose in the urine. It does this by blocking a protein in the kidneys (called SGLT2) that normally takes glucose back into the blood from the kidneys.

What benefits of Steglatro have been shown in studies?

Several studies in around 4,800 patients with type 2 diabetes have shown that ertugliflozin helps lower glucose levels on its own and in combination with other diabetes medicine.

The studies looked mainly at effects on levels of HbA1c (a measure of blood glucose) after 6 months or one year of treatment. At the start of the studies, patients' HbA1c was above 7 percentage points. The results were as follows:

- A study of ertugliflozin on its own, showed that levels of HbA1c (a measure of blood glucose) fell by between 0.8 points and 1 point in patients who took the medicine compared with a rise of 0.2 points in patients receiving placebo (a dummy treatment).
- A second study found that in patients taking a combination of ertugliflozin and metformin, HbA1c levels fell by around 0.8 points, compared with reductions of 0.03 when placebo was added to metformin.
- A third study found that a combination of ertugliflozin at a 15 mg dose with metformin was about as effective as a combination of metformin with another diabetes medicine, glimepiride. HbA1c levels fell by 0.6 points with ertugliflozin and 0.7 points with glimepiride. A lower dose of ertugliflozin 5 mg was less effective.
- A fourth study found that, in patients taking metformin, adding ertugliflozin was as effective as adding sitagliptin, another diabetes medicine, with HbA1c levels falling by around 1 point with both treatments. HbA1c levels fell by a further 0.5 points when both medicines were added to metformin.
- A fifth study found that adding ertugliflozin to a combination of sitagliptin and metformin was more effective than placebo. HbA1c levels fell by between 0.8 and 0.9 points when ertugliflozin was added, compared with a fall of 0.1 with placebo.
- A sixth study found that adding the combination of ertugliflozin and sitagliptin to diet and exercise was much more effective than placebo, with HbA1c levels falling by between 1.6 and 1.7 points with the combination of ertugliflozin and sitagliptin compared with a fall of 0.4 points with placebo.
- A seventh study showed that ertugliflozin was not more effective than placebo in patients with moderate kidney impairment. The data from this study showed that the effect of ertugliflozin reduces when the kidneys do not work properly.

Finally, in addition to lowering glucose levels, studies showed that ertugliflozin can help patients reduce bodyweight.

What are the risks associated with Steglatro?

The most common side effects with Steglatro (which may affect more than 1 in 10 people) are fungal infections of the vagina and other infections of the female reproductive system. Rare cases of diabetic ketoacidosis, a serious condition where the patient has very high blood acid levels, may occur in up to
1 in 1,000 patients. For the full list of side effects and restrictions with Steglatro, see the package leaflet.

Why is Steglatro authorised in the EU?

Studies showed that Steglatro helps lower glucose levels on its own and in combination with other diabetes medicines. In addition, Steglatro can help some patients lose weight.

Steglatro is not as effective in patients with moderate kidney impairment and should therefore not be started in such patients.

The European Medicines Agency concluded that Steglatro's benefits are greater than its risks and it can be authorised for use in the EU.

What measures are being taken to ensure the safe and effective use of Steglatro?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Steglatro have been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Steglatro is continuously monitored. Side effects reported with Steglatro are carefully evaluated and any necessary action taken to protect patients.

Other information about Steglatro

Steglatro received a marketing authorisation valid throughout the EU on 21 March 2018. Further information on Steglatro can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. This overview was last updated in 04-2018.

Appendix D: Identification, selection and synthesis of clinical evidence

D.1. Identification and selection of relevant studies

Summary of Approach to Identifying Clinical Evidence

Two systematic literature reviews (SLRs) were conducted to identify clinical studies relevant to this submission. The first SLR was designed to identify randomised controlled trials (RCTs) on the efficacy and safety of ertugliflozin and other pharmacological interventions for the treatment of adult patients with uncontrolled T2DM. The searches for this SLR were originally conducted on the 19th of December 2016 and updated on the 11th August 2017. A second update was conducted on 8th May 2018.

The second SLR was designed to identify interventional non-RCTs investigating the efficacy and safety of ertugliflozin for the treatment of uncontrolled T2DM, in order to identify any interventional non-RCT data that might add evidence for the technology being appraised. Searches for this SLR were conducted in August 2017 and May 2018.

SLR of RCT Evidence

Search Databases

Original SLR

The following databases were searched separately on the Ovid platform to identify relevant published studies (all searches conducted on 19th of December 2016):

- MEDLINE
- MEDLINE In-Process
- Embase (1988 to November 2016)
- Cochrane (Cochrane Central Register of Controlled trials, Cochrane Database of Systematic Review, Cochrane Methodology Register)

These databases were selected in line with NICE Single Technology Appraisal (STA) guidelines. The Ovid platform was used to conduct searches for all literature databases abovementioned: Embase, MEDLINE and Cochrane (via Evidence-Based Medicine (EBM) Reviews). The Ovid platform is a search platform that provides standardized access to a wide range of medical literature databases and is an accepted tool for use in a SLR.

In addition, desk research was performed to access relevant grey literature (e.g., NICE technology assessments, clinical treatment guidelines; from 2010 to current); conference abstracts were also reviewed, which were picked up in the Embase search as well as in

separate individual searches of the society websites. Recent abstracts (2012 – current) from the ADA, the EASD and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were specifically searched for relevant material. EPAR and U.S. Food and Drug Administration (FDA) label documents and clinicaltrials.gov were also searched for missing variables or to confirm assumptions.

First SLR Update

In line with the databases searched in the original SLR, the following electronic databases were searched on 11th August 2017:

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print (1946 to present)
- Embase (1974 to 2017 August 10)
- The Cochrane Library, specifically the following:
    - Cochrane Database of Systematic Reviews (CDSR; up to Issue 8 of 12, August 2017)
    - Cochrane Methodology Register (CMR; up to Issue 3 of 4, July 2017)
    - Cochrane Central Register of Controlled Trials (CENTRAL; up to Issue 7 of 12, July 2017)
    - Database of Abstracts of Reviews and Effects (DARE; up to Issue 2 of 4, April 2015)
    - Health Technology Assessment (HTA) Database (up to Issue 4 of 4, October 2016)
    - NHS Economic Evaluation Database (NHS-EED; up to Issue 2 of 4, April 2015)

Second SLR Update (8th May 2018)

The following electronic databases were searched again:

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print (1946 to May 02, 2018)
- Embase (1974 to 2018 May 07)
- The Cochrane Library, specifically the following:
- Cochrane Database of Systematic Reviews (CDSR; up to Issue 5 of 12, May 2018)
- Cochrane Methodology Register (CMR; up to Issue 2 of 4, April 2018)
- Cochrane Central Register of Controlled Trials (CENTRAL; up to Issue 4 of 12, April 2018)

- Database of Abstracts of Reviews and Effects (DARE; up to Issue 2 of 4, April 2015)
- Health Technology Assessment (HTA) Database (up to Issue 4 of 4, October 2016)
- NHS Economic Evaluation Database (NHS-EED; up to Issue 2 of 4, April 2015)

In line with the original SLR, MEDLINE and Embase were searched separately via the Ovid SP platform. CDSR, CMR, CENTRAL, DARE, the HTA Database and NHS-EED were searched via Ovid SP in the original SLR but, in the SLR update, were searched simultaneously via the Cochrane Library Wiley Online platform.

As well as conducting electronic database searches, in the SLR update a manual search of congress abstracts reporting RCTs of ERTU presented at the following conferences in the last 3 years (2015–2018) was performed:

- American Diabetes Association (ADA) – Scientific Sessions
- European Association for the Study of Diabetes (EASD) – Annual Meeting
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – Annual European and Annual International meetings

The 4-year date limit for manual conference searches was based on an assumption that research presented at these conferences more than 4 years ago would have since been indexed in Ovid Embase and also possibly published in the form of peer-reviewed journal articles.

Finally, it was planned that the reference lists of any SLRs and network meta-analyses (NMAs) identified as relevant at the title and abstract screening stage of the SLR would be hand-searched to identify further relevant publications for inclusion in the SLR.

Search Terms

Original SLR and First and Second SLR Update – Electronic Database Searches

Search terms used in the Ovid MEDLINE databases in both the original SLR and the SLR update are presented in Table D.1, while search terms used in Ovid Embase are presented in Table D.2. Search terms used in the Cochrane Library databases in the original SLR (searched via Ovid SP) are presented in Table D.3, while search terms used in these databases in the SLR update (searched via the Cochrane Library Wiley Online platform) are presented in Table D.4.

In both the original SLR and the SLR update, when the searches were run search results from each database were downloaded and deduplicated against one another in a reference management program. In the SLR update, remaining records within the reference management program were then deduplicated against the search results from the original

SLR, with a view to retaining only those records identified in the update searches that were not captured in the original searches. Retained records were transferred into a bespoke Microsoft Excel-based platform for eligibility screening, while all other records were discarded.

Table D.1: Search terms used in the MEDLINE databases (searched via Ovid SP)

#	Search terms	Original SLR – # hits (19th December 2016)	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
1	non insulin dependent diabetes mellitus/	112889	113097	113371
2	non insulin dependent diabetes.ti,ab.	8713	9074	8554
3	(diabetes mellitus and (type 2 or type ii or type two)).ti,ab.	36296	44851	46177
4	type ii diabetes.ti,ab.	6686	7284	7364
5	NIDDM.ti,ab.	6996	7120	6880
6	((adult onset or adult-onset) and diabetes).ti,ab.	963	1005	1007
7	Type 2 diabetes.ti,ab.	83360	99357	101669
8	1 or 2 or 3 or 4 or 5 or 6 or 7	141693	158788	160327
9	Sodium-Glucose Transporter 2/	855	1062	1217
10	(SGLT2 or SGLT-2).mp.	879	1664	1966
11	empagliflozin.mp.	230	629	751
12	Canagliflozin/	224	300	354
13	canagliflozin.mp.	259	561	694
14	dapagliflozin.mp.	269	560	649
15	ertugliflozin.mp.	5	11	27
16	Glucagon-Like Peptide 1/	6765	6653	6744
17	Liraglutide/	938	1110	1184
18	exenatide.mp.	2345	2710	2725
19	lixisenatide.mp.	118	284	316
20	albiglutide.mp.	66	140	146
21	dulaglutide.mp.	73	179	200
22	semaglutide.mp.	11	94	142
23	Dipeptidyl Peptidase 4/ or Dipeptidyl-Peptidase IV Inhibitors/	5340	5532	5654
24	pioglitazone.mp.	4631	5154	5176
25	Sitagliptin Phosphate/	992	1091	1116
26	sitagliptin.mp.	1334	1933	1984
27	alogliptin.mp.	273	389	412
28	saxagliptin.mp.	378	571	607
29	linagliptin.mp.	323	530	560
30	glimepiride.mp.	1048	1225	1244
31	Glipizide/	735	740	707
32	glipizide.mp.	1064	1146	1117
33	glibenclamide/	6232	6176	5986
34	glibenclamide.mp.	7573	7977	7873
35	Gliquidone.mp.	151	154	150
36	Gliclazide/	815	833	825
37	Gliclazide.mp.	1114	1241	1248
38	liraglutide.mp.	1211	1950	2061
39	Clinical trial/	527444	529526	510132
40	Randomized controlled trial/	469536	475491	460339
41	Randomization/	95156	95089	94117
42	Single blind procedure.mp.	15	16	16
43	Double blind procedure.mp.	202	227	211
44	Crossover procedure.mp.	42	48	46
45	Placebo.mp.	182744	200633	194989

#	Search terms	Original SLR – # hits (19th December 2016)	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
46	Randomi?ed controlled trial$.tw,ab.	111865	135474	138003
47	Rct.ti,ab.	12366	15513	16034
48	Random allocation.ti,ab.	1321	1458	1436
49	Randomly allocated.ti,ab.	19515	23966	24170
50	Allocated randomly.ti,ab.	1835	2047	2051
51	(allocated adj2 random).ti,ab.	727	807	773
52	Single blind$.ti,ab.	13386	15833	15704
53	Double blind$.ti,ab.	128914	142720	138111
54	((treble or triple) adj blind$).ti,ab.	408	608	644
55	Placebo$.ti,ab.	182795	200656	194993
56	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	966830	1015142	994778
57	Case study/	1876385	1915145	1876988
58	Case report.ti,ab.	212870	266899	270242
59	Abstract report/ or letter/	944265	984555	986050
60	(book or book series or editorial or letter or note or trade journal).ti,ab.	150506	181504	188139
61	57 or 58 or 59 or 60	2778028	2920837	2901417
62	56 not 61	942233	989854	969861
63	8 and 62	17333	19476	18830
64	Sulfonylurea Compounds/	5745	5836	5748
65	(GLP1 or GLP-1).mp.	7464	8915	9241
66	(DPP4 or DPP-4).mp.	2352	3320	3520
67	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 64 or 65 or 66	35342	40259	40896
68	63 and 67	3436	4239	4206
69	limit 68 to english language	3029	4091	4063
70	limit 69 to dc=20161201-20170811	-	228	-
71	2017-08-04:2018-05-08.(dt).	-	-	959788
72	69 and 70	-	-	215

Abbreviations: SLR, systematic literature review

Table D.2: Search terms used Embase (searched via Ovid SP)

A

#	Search terms	Original SLR – # hits (19th December 2016)	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
1	non insulin dependent diabetes mellitus/	185851	200001	211436
2	non insulin dependent diabetes.ti,ab.	4869	9648	9735
3	diabetes mellitus.mp. and (type 2 or type ii or type two).ti,ab.	155323	165213	175645
4	insulin independent diabetes.mp.	63	157	157
5	type ii diabetes.ti,ab.	8506	10770	11322
6	NIDDM.mp.	4483	8120	8178
7	((adult onset or adult-onset) and diabetes).mp.	1084	1581	1652
8	Type 2 diabetes.ti,ab.	133090	144930	154711
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	214945	243186	256997
10	Randomized controlled trial/	420027	466758	501444
11	Randomization/	75432	74936	78000
12	Single blind procedure/	26639	28943	31288
13	Double blind procedure/	112454	141857	149577
14	Crossover procedure/	49871	52908	55410
15	Placebo/	268897	311869	324796

#	Search terms	Original SLR – # hits (19th December 2016)	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
16	Randomi?ed controlled trial$.tw.	147858	165218	180665
17	Rct.tw.	22292	25292	28337
18	Random allocation.tw.	1320	1722	1826
19	Randomly allocated.tw.	22706	28316	29812
20	Allocated randomly.tw.	1560	2283	2338
21	(allocated adj2 random).tw.	343	867	882
22	Single blind$.tw.	15366	19919	21080
23	Double blind$.tw.	128282	181557	189103
24	((treble or triple) adj blind$).tw.	584	728	795
25	Placebo$.tw.	200123	260097	273736
26	clinical trial/	854951	943111	969154
27	Or/10-26	1096547	1498353	1573132
28	Case study/	90538	49058	54243
29	Case report.tw.	253095	345641	362697
30	Abstract report/ or letter/	652527	1030114	1059268
31	(book or book series or editorial or letter or note or trade journal).pt.	1798243	2215343	2299136
32	28 or 29 or 30 or 31	2130790	2690829	2796261
33	empagliflozin plus linagliptin/ or empagliflozin/ or empagliflozin plus metformin/	1032	1466	1862
34	empagliflozin.mp.	1046	1539	1956
35	canagliflozin plus metformin/ or canagliflozin/	1148	1419	1729
36	canagliflozin.mp.	1164	1464	1784
37	dapagliflozin plus metformin/ or dapagliflozin/ or dapagliflozin plus saxagliptin/	1453	1751	2063
38	dapagliflozin.mp.	1496	1834	2160
39	ertugliflozin/	72	110	148
40	ertugliflozin.mp.	73	111	150
41	glucagon like peptide 1/	16506	15056	15862
42	(GLP1 or GLP-1).mp.	13457	14929	16066
43	liraglutide/ or insulin degludec plus liraglutide/	5238	5828	6396
44	exendin 4/	8138	8435	8831
45	lixisenatide/	708	842	988
46	albiglutide/	545	608	670
47	dulaglutide/	469	576	683
48	semaglutide/	128	267	435
49	dipeptidyl peptidase IV inhibitor/ or dipeptidyl peptidase IV/	11444	11737	12499
50	(DPP4 or DPP-4).mp.	4835	5361	5863
51	pioglitazone plus sitagliptin/ or metformin plus sitagliptin/ or sitagliptin/	6205	6598	7015
52	sitagliptin.mp.	6268	6757	7183
53	alogliptin plus metformin/ or alogliptin/ or alogliptin plus pioglitazone/	1240	1344	1433
54	metformin plus saxagliptin/ or dapagliflozin plus saxagliptin/ or saxagliptin/	2210	2374	2542
55	linagliptin/ or empagliflozin plus linagliptin/ or linagliptin plus metformin/	1563	1746	1893
56	pioglitazone/	16003	16462	16954
57	glimepiride plus metformin/ or glimepiride/ or glimepiride plus pioglitazone/	5817	6113	6300
58	glipizide plus metformin/ or glipizide/	4304	5528	5614
59	glibenclamide/	17632	22947	23406
60	Gliquidone/	369	643	656
61	Gliclazide/	4439	5416	5549
62	liraglutide.mp.	5284	6011	6596
63	exenatide.mp.	3002	3212	3412
64	lixisenatide.mp.	727	899	1067
65	albiglutide.mp.	553	635	698
66	dulaglutide.mp.	473	600	710

#	Search terms	Original SLR – # hits (19th December 2016)	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
67	semaglutide.mp.	129	281	458
68	pioglitazone.mp.	16305	16953	17476
69	alogliptin.mp.	1258	1390	1479
70	saxagliptin.mp.	2236	2438	2610
71	linagliptin.mp.	1601	1814	1967
72	glimepiride.mp.	5919	6253	6452
73	glipizide.mp.	4354	5640	5730
74	glibenclamide.mp.	18356	24129	24599
75	Gliquidone.mp.	378	659	672
76	Gliclazide.mp.	4491	5515	5654
77	sulfonylurea/	12067	12642	13196
78	sodium glucose cotransporter 2 inhibitor/ or sodium glucose cotransporter 2/	2392	2586	3203
79	(SGLT2 or SGLT-2).mp.	2368	2935	3522
80	27 not 32	1020569	1402035	1474205
81	80 and 9	28045	34538	36660
82	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79	75775	88031	92843
83	81 and 82	9945	12107	12869
84	limit 83 to english language	9407	11534	12282
85	limit 84 to dc=20161201-20170811	-	1093	-
86	limit 84 to dc=20170811-20180508	-	-	979

Abbreviations: SLR, systematic literature review

Table D.3: Search terms for use in CDSR, CMR, CENTRAL, DARE, the HTA Database and NHS-EED (searched via Ovid SP) for the original SLR

#	Search terms	Original SLR – # hits (19th December 2016)
1	non insulin dependent diabetes mellitus.mp.	6943
2	(diabetes mellitus and (type 2 or type ii or type two)).mp.	126811
3	"insulin independent diabetes".mp.	143
4	((insulin independent or insulin-independent) and diabetes).mp.	856
5	type ii diabetes.mp.	6714
6	NIDDM.mp.	7004
7	((adult onset or adult-onset) and diabetes).mp.	1019
8	Type 2 diabetes.mp	84008
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	144285
10	clinical trial.mp.	658419
11	Randomized controlled trial.mp.	478919
12	Randomization.mp	21226
13	Single blind procedure.mp.	15
14	Double blind procedure.mp.	202
15	Crossover procedure.mp.	42
16	Placebo.mp.	182744
17	Randomi?ed controlled trial$.tw.	111865
18	Rct.tw.	12366
19	Randomly allocated.tw.	19515
20	Allocated randomly.mp. or random allocation.tw.	3153
21	(allocated adj2 random).tw.	727
22	((treble or triple) adj blind$).mp.	408

#	Search terms	Original SLR – # hits (19th December 2016)
23	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	976877
24	Case study.ti.	24097
25	Case report.ti.	163222
26	Abstract report.mp. or letter.ti.	43955
27	(book or book series or editorial or letter or note or trade journal).ti.	94039
28	24 or 25 or 26 or 27	281207
29	23 not 28	974879
30	29 and 9	18394
31	(sodium glucose cotransporter 2 inhibitor or sodium glucose cotransporter 2).mp.	332
32	(SGLT2 or SGLT-2).mp.	879
33	empagliflozin.mp.	230
34	canagliflozin.mp.	259
35	dapagliflozin.mp.	269
36	ertugliflozin.mp.	5
37	(glucagon like peptide 1 or GLP1 or GLP-1).mp.	10544
38	liraglutide.mp.	1211
39	exenatide.mp.	2345
40	lixisenatide.mp.	118
41	albiglutide.mp.	66
42	semaglutide.mp.	11
43	dulaglutide.mp.	73
44	(dipeptidyl peptidase IV inhibitor or dipeptidyl peptidase IV).mp.	4626
45	(DPP4 or DPP-4).mp.	2352
46	sitagliptin.mp.	1334
47	alogliptin.mp.	273
48	saxagliptin.mp.	378
49	linagliptin.mp.	323
50	(thiazolidinedione or glitazone).mp.	2696
51	pioglitazone.mp.	4631
52	glimepiride.mp.	1048
53	glipizide.mp.	1064
54	glibenclamide.mp.	7573
55	Gliquidone.mp.	151
56	Gliclazide.mp.	1114
57	sulfonylurea.mp.	9221
58	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57	37932
59	30 and 58	3809
60	limit 59 to english language	3648

Abbreviations: SLR, systematic literature review

Table D.4: Search terms for use in CDSR, CMR, CENTRAL, DARE, the HTA Database and NHS-EED (searched via the Cochrane Library Wiley Online platform) for the SLR update

#	Search terms	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
1	[mh "non insulin dependent diabetes mellitus"] or "non insulin dependent diabetes mellitus":ti,ab,kw	18616	20337

#	Search terms	SLR update – # hits (11th August 2017)	SLR second update – # hits (8th May 2018)
2	("diabetes mellitus" and ("type 2" or "type ii" or "type two")):ti,ab,kw	19471	21343
3	"insulin independent diabetes":ti,ab,kw	3	3
4	(("insulin independent" or insulin-independent) and diabetes):ti,ab,kw	69	72
5	"type ii diabetes":ti,ab,kw	791	833
6	NIDDM:ti,ab,kw	995	996
7	(("adult onset" or adult-onset) and diabetes):ti,ab,kw	54	54
8	"Type 2 diabetes":ti,ab,kw	15911	17760
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	21813	23899
10	"clinical trial" or [mh "clinical trial"]	535564	549161
11	"randomized controlled trial*" or "randomised controlled trial*" or [mh "randomized controlled trial"]	603057	646934
12	randomization or [mh "randomization"]	49915	53477
13	"single blind procedure" or [mh "single blind procedure"]	15741	17506
14	"double blind procedure" or [mh "double blind procedure"]	55510	51730
15	"crossover procedure" or [mh "crossover procedure"]	21168	20310
16	placebo or [mh "placebo"]	198888	210489
17	RCT:ti,ab,kw	13549	15809
18	"randomly allocated":ti,ab,kw	23109	25341
19	"random allocation":ti,ab,kw or "allocated randomly"	25477	25716
20	(allocated near/2 random):ti,ab,kw	812	830
21	((treble or triple) next blind*)	1265	1393
22	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	806179	863864
23	[mh ^"Sodium-Glucose Transporter 2"] or ("sodium glucose cotransporter 2 inhibitor" or "sodium glucose cotransporter 2" or SGLT2 or SGLT-2):ti,ab,kw	521	661
24	[mh "empagliflozin"] or empagliflozin:ti,ab,kw	257	333
25	[mh "canagliflozin"] or canagliflozin:ti,ab,kw	201	237
26	[mh "dapagliflozin"] or dapagliflozin:ti,ab,kw	272	346
27	[mh "ertugliflozin"] or ertugliflozin:ti,ab,kw	15	30
28	[mh ^"Glucagon-Like Peptide 1"] or ("glucagon like peptide 1" or GLP1 or GLP-1):ti,ab,kw	2102	2410
29	[mh "liraglutide"] or liraglutide:ti,ab,kw	732	869
30	[mh "exenatide"] or exenatide:ti,ab,kw	525	610
31	[mh "lixisenatide"] or lixisenatide:ti,ab,kw	98	128
32	[mh "albiglutide"] or albiglutide:ti,ab,kw	58	68
33	[mh "semaglutide"] or semaglutide:ti,ab,kw	38	67
34	[mh "dulaglutide"] or dulaglutide:ti,ab,kw	97	122
35	[mh ^"Dipeptidyl Peptidase 4"] or [mh ^"Dipeptidyl-Peptidase IV Inhibitors"] or ("dipeptidyl peptidase IV inhibitor" or "dipeptidyl peptidase IV" or DPP4 or DPP-4):ti,ab,kw	1121	1285
36	[mh "sitagliptin"] or sitagliptin:ti,ab,kw	779	898
37	[mh "alogliptin"] or alogliptin:ti,ab,kw	115	139
38	[mh "saxagliptin"] or saxagliptin:ti,ab,kw	223	265
39	[mh "linagliptin"] or linagliptin:ti,ab,kw	231	276
40	[mh "thiazolidinedione"] or thiazolidinedione:ti,ab,kw	487	506
41	[mh "glitazone"] or glitazone:ti,ab,kw	100	107
42	[mh "pioglitazone"] or pioglitazone:ti,ab,kw	1427	1510
43	[mh "glimepiride"] or glimepiride:ti,ab,kw	654	701
44	[mh "glipizide"] or glipizide:ti,ab,kw	341	340
45	[mh "glibenclamide"] or glibenclamide:ti,ab,kw	1022	1027
46	[mh "Gliquidone"] or Gliquidone:ti,ab,kw	23	23
47	[mh "Gliclazide"] or Gliclazide:ti,ab,kw	391	404
48	[mh "sulfonylurea"] or sulfonylurea:ti,ab,kw	1890	1973
49	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48	8037	8942
50	#9 and #22 and #49, Publication year from 2016 to 2017	989	-
51	#9 and #22 and #49 Publication Year from 2017 to 2018	-	742

Original SLR and SLR Update – Manual Congress Searches

The manual congress searches were carried out as described in Table D.5. Both RCTs and interventional non-RCTs of ERTU were considered eligible for inclusion, with any novel abstracts identified on ERTU RCTs feeding into the PRISMA flow diagram for the SLR update, and novel abstracts on interventional non-RCTs of ERTU feeding into the PRISMA flow diagram for the non-RCTs SLR.

Table D.5: Search strategy for manual congress searches

Conference	Abstract book source	Search strategy	Results - RCTs	Results – non-RCTs
ADA Scientific Sessions • Years: 2015, 2016 & 2017	PDF abstract books	Ctrl+F in each abstract book for "ertugliflozin"	2015: Total hits: 1 Included: 0 2016: Total hits: 0 Included: 0 2017: Total hits: 5 Included: 1	2015: Total hits: 1 Included: 0 2016: Total hits: 0 Included: 0 2017: Total hits: 5 Included: 4
EASD Annual Meeting • Years: 2015, 2016 & 2017	Abstracts and posters: www.easdvirtualmeeting.org/resourcegroups#~filters/resourcetype=1&tag=*&event=10&in=*&order=primary_ref	**Filtered by event:** each one selected and searched in turn: • Lisbon 2017 • Munich 2016 • Stockholm 2015 **Search:** "ertugliflozin" "Show industry content" was selected.	2015: Total hits: 2 Included: 0 2016: Total hits: 6 Included: 2 2017: Total hits: 6 Included: 1	2015: Total hits: 2 Included: 0 2016: Total hits: 6 Included: 3 2017: Total hits: 6 Included: 5
ISPOR Annual European Meeting • Years: 2015, 2016 & 2017	ISPOR presentations database: www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	**Disease/disorder:** "diabetes" **Meeting:** Selected and searched each in turn: • ISPOR 20th Annual European Congress – Glasgow, Scotland – 2017 • ISPOR 19th Annual European Congress – Vienna, Austria – 2016 • ISPOR 18th Annual European Congress – Milan, Italy – 2015 **Keyword:** "ertugliflozin" in "titles"	2015: Total hits: 0 Included: 0 2016: Total hits: 0 Included: 0 2017: Total hits: 0 Included: 0	2015: Total hits: 0 Included: 0 2016: Total hits: 0 Included: 0 2017: Total hits: 0 Included: 0
ISPOR Annual International Meeting • Year: 2015,	ISPOR presentations database: www.ispor.org/RESEARCH_STUDY_DIGEST/research_ind	**Disease/disorder:** "diabetes" **Meeting:** Selected and searched each in turn:	2015: Total hits: 0 Included: 0 2016: Total hits: 0	2015: Total hits: 0 Included: 0 2016: Total hits: 0

Conference	Abstract book source	Search strategy	Results - RCTs	Results – non-RCTs
2016, 2017 & 2018	ex.asp	• ISPOR 23rd Annual International Meeting – Baltimore, MD, USA – 2018 • ISPOR 22nd Annual International Meeting – Boston, MA, USA – 2017 • ISPOR 21st Annual International Meeting – Washington DC, USA – 2016 • ISPOR 20th Annual International Meeting – Philadelphia, PA, USA – 2015 **Keyword:** "ertugliflozin" in "titles"	Included: 0 2017: Total hits: 0 Included: 0 2018: Total hits: 0 Included: 0	Included: 0 2017: Total hits: 0 Included: 0 2018: Total hits: 0 Included: 0

Abbreviations: ADA, American diabetes association; EASD, European association for the study of diabetes; ISPOR, international society for pharmacoeconomics and outcomes research

Study Selection

Articles were included in the original SLR and the SLR update if they met the eligibility criteria presented in Table D.6.

It should be noted that although ertugliflozin is defined as the intervention of interest in this submission, interventions other than ertugliflozin were listed as relevant for the purposes of the SLR. This was to ensure that studies that did not contain ertugliflozin in at least one of the study arms were still eligible for inclusion in the SLR, thus allowing the creation of an intervention "network" for the purposes of the NMA.

It should also be noted that the eligibility criteria for the SLR were broader than required for the purposes of this submission with regard to the patient population, intervention(s) and comparator(s). This was to ensure that the SLR was fit for purpose to inform other regulatory submissions for ertugliflozin. For the purpose of this submission, only triple therapy is the relevant patient population.

Table D.6: Eligibility criteria for the RCT evidence SLR

Domain	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years) with uncontrolled* T2DM having previously received one of the following interventions: • **Monoterapy:** Diet and exercise, no background pharmacological therapy • **Dual therapy:** Metformin alone • **Triple therapy *(relevant for the purposes of this submission)*:** Metformin plus a DPP-4 inhibitor	Any of the following: • Non-humans • Patients do not have uncontrolled* T2D having previously received a relevant intervention • Studies are on children (<18 years old)
Intervention(s)	**Monotherapy*:*** • Sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin 100 mg and 300 mg, dapagliflozin 5 mg and 10 mg, empagliflozin 10 mg and 25 mg, ertugliflozin 5 mg and 15 mg) • **Dual therapy:** • Metformin + SGLT-2 inhibitor (canagliflozin 100 mg and 300 mg, dapagliflozin 5 mg and 10 mg, empagliflozin 10 mg and 25 mg, ertugliflozin 5 mg and 15 mg) • **Triple therapy *(relevant for the purposes of this submission)*:** • Metformin + DPP-4 inhibitor + SGLT-2 inhibitor	Studies not investigating a relevant intervention at a relevant dose for a relevant patient population
Comparator(s)	A single agent or combination of agents listed under "intervention(s)" for the matching population, which could include different doses of the same drug, or the background intervention for the matching population plus placebo (for example, for monotherapy diet and exercise plus placebo would be a suitable comparator)	No comparator, or comparator is not placebo with the matching background intervention /a second intervention of interest
Outcomes	Any of the following: • Glycaemic control (HbA1c) • Weight/body mass index • Changes in cardiovascular risk factors (e.g. estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, high density lipoproteins, low density lipoproteins, cholesterol, triglycerides) • Complications of diabetes, including cardiovascular, renal and eye • Adverse effects of treatment (e.g. hypoglycaemia [both non-severe and requiring medical attention], hematocrit, urinary tract infections, genital tract infections and malignancies) • Mortality • Health-related quality of life	Studies not presenting a relevant outcome
Study design	RCTs with study duration of 24–26 weeks and/or study results reported at 24–26 weeks	RCTs of duration outside of the range of 24–26 weeks, or that do not report results at 24–26 weeks

Domain	Inclusion Criteria	Exclusion Criteria
		Any other study designs, including: • Controlled (but not randomised) clinical trials • Interventional non-RCTs, including single-arm clinical trials • Observational studies • Case control studies • Editorials, notes, comments or letters • Opinions • SLRs and NMAs • Narrative or non-systematic literature reviews
Other considerations	• English language • Human subjects • Publication year: in the original SLR, any publication year; in the SLR update, any publication year providing that the publication was not captured in the original SLR	• Non-English language full-texts • Articles not on human subjects • Publication year: NA

Abbreviations: T2DM, type 2 diabtes mellitus; RCT, randomised clinical trial; mg, milligram; SLR, systematic literature review; NMA, network meta-analysis
NA, not applicable; RCT, randomised controlled trial; T2D, type 2 diabetes
*"Uncontrolled" refers to a baseline (at time of intervention initiation, not including any wash-out periods or run-ins) HbA1c greater than 7%.

For both the original SLR and the SLR update, the citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail by the two independent reviewers. At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, it was planned that data would be extracted by a single reviewer into a pre-specified data extraction grid and verified by a second individual.

It was planned that the quality of included RCTs would be assessed using the criteria provided by the York Centre for Reviews and Dissemination. Quality assessments were completed by one individual in the first instance, and checked by a second reviewer.

Results

Triple therapy

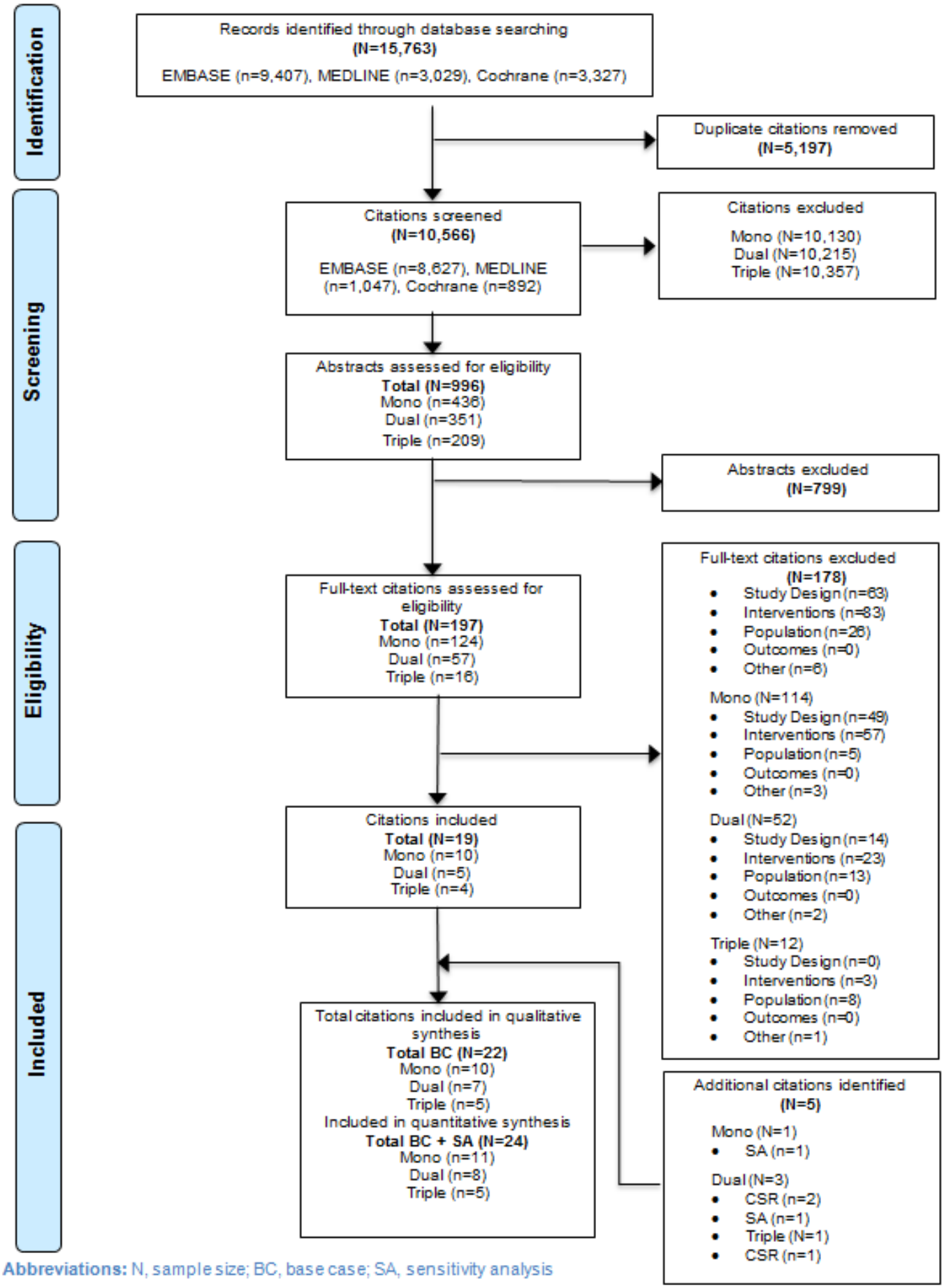
The PRISMA flow diagram for the original SLR is presented in Figure D.1, while the PRISMA flow diagram for the first and second SLR updates are presented in Figure D.2 and D.3, respectively. As mentioned above, the criteria for study selection were broader than required

for the purposes of this submission (only triple therapy) with regard to the patient population and comparator(s). As a result, the PRISMA flow diagram shows all studies identified for the broader SLR (mono, dual and triple therapy).

A total of 8 publications were relevant for the purpose of this submission in triple therapy across the original SLR and both updates (reporting on 5 studies). Only one ertugliflozin RCT (VERTIS SITA2) was identified and included in the SLR and NMA.

A list of all publications and studies relevant for the purposes of this submission and included across both the original SLR and the SLR updates is provided in Table D.7. A list of publications included in the original SLR and the updates but on populations irrelevant for the purposes of this submission (i.e. relevant to "mono or dual therapy" in the eligibility criteria table) is provided in Table D.8. A list of publications excluded from the original SLR, the first and second SLR update for triple therapy is provided in Table D.9.

Figure D.1: PRISMA flow diagram for the original SLR – TRIPLE THERAPY



Abbreviations: N, sample size; BC, base case; SA, sensitivity analysis

Figure D.2: PRISMA flow diagram for the first SLR update – TRIPLE THERAPY

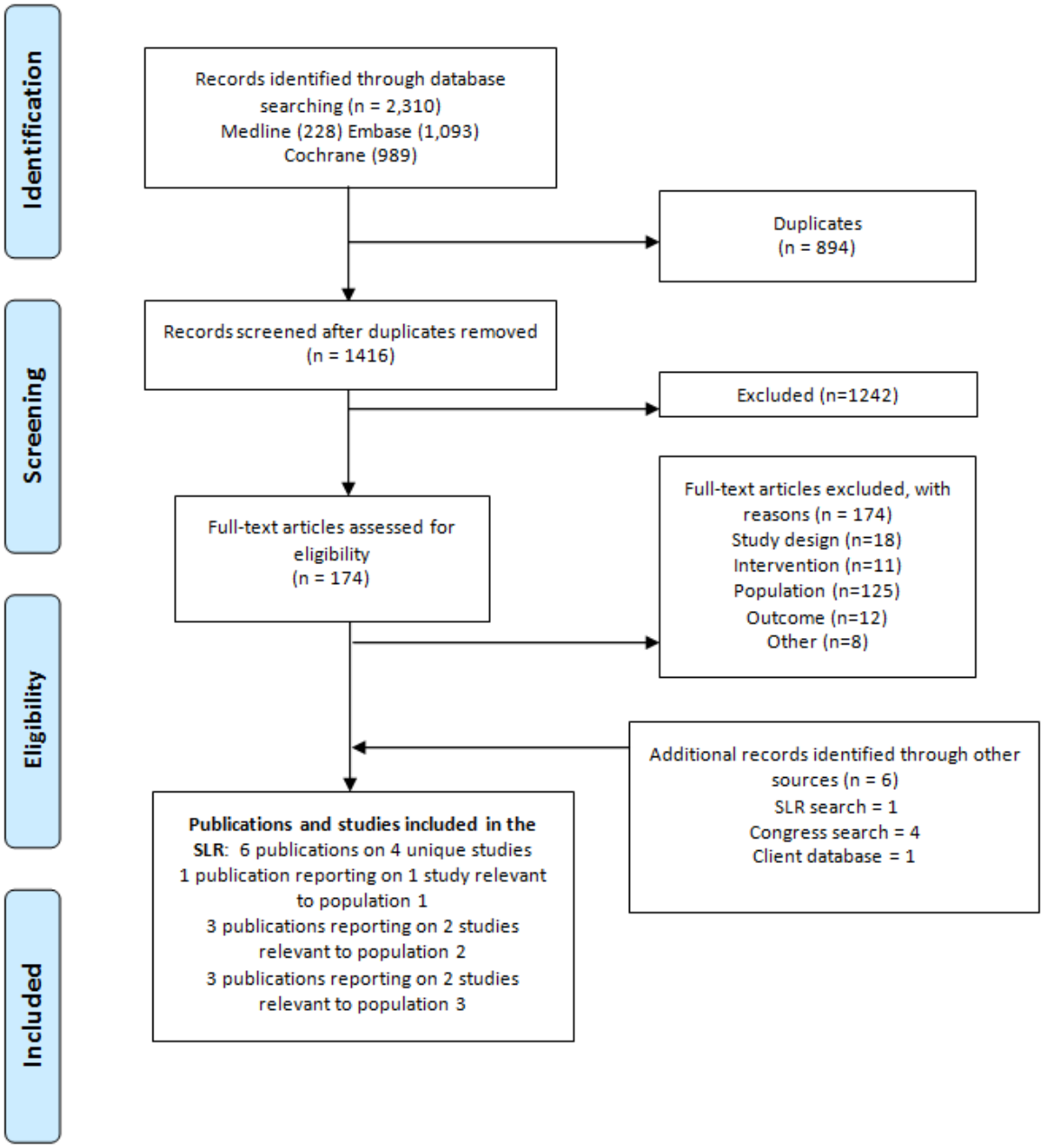


Figure D.3: PRISMA flow diagram for the second SLR update – TRIPLE THERAPY

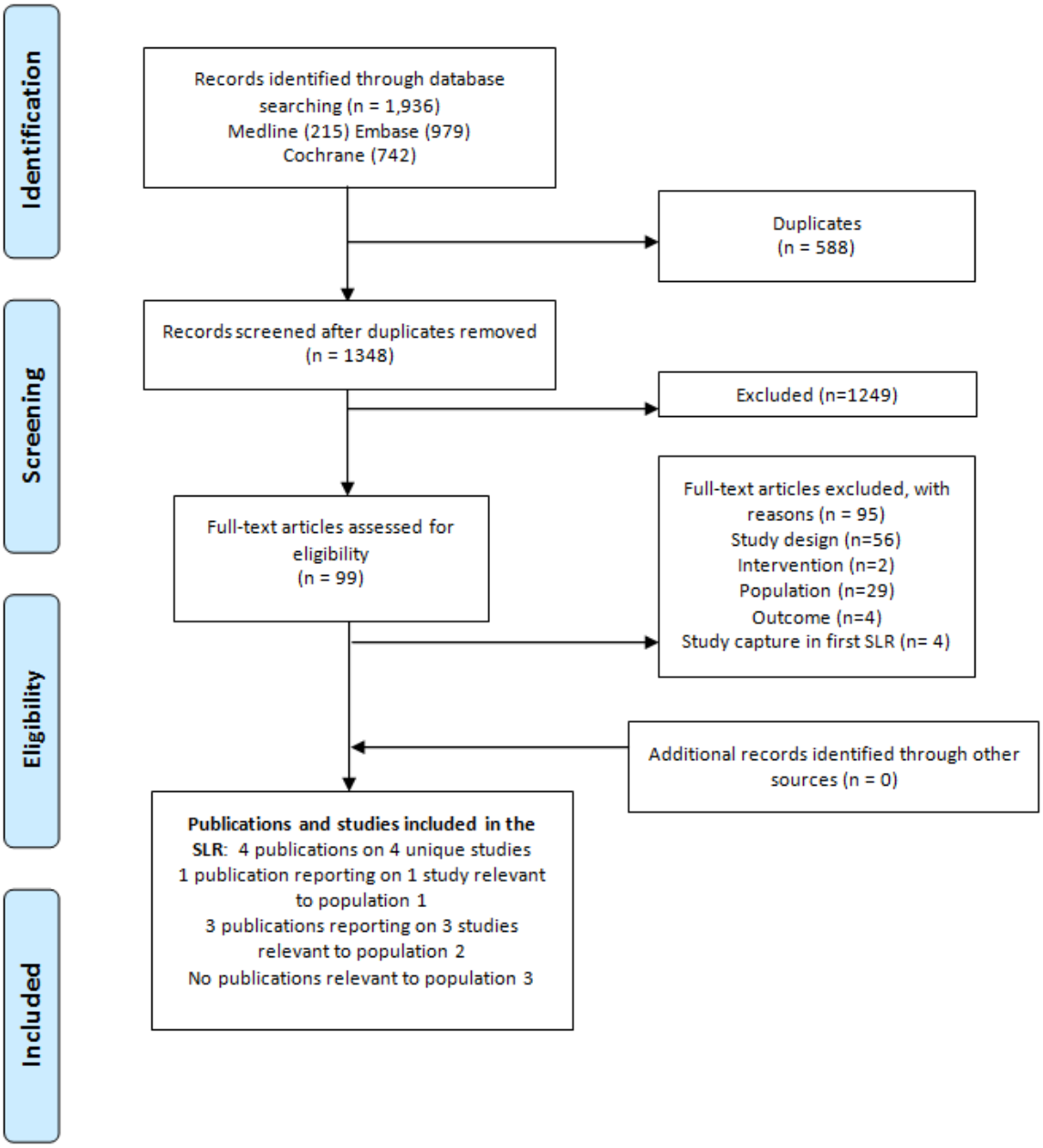


Table D.7: Studies and publications included in the original SLR and the SLR updates and relevant for the purposes of the triple therapy indication

Study name	Publication source (original SLR/SLR update)	Reference
VERTIS SITA2 CSR 006	Original SLR	Merck & Co Inc, Pfizer Inc. Clinical Study Report 006: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in the Treatment of Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin (P006). 2016.
	First SLR update	Lauring B, Eldor R, Liu J, Dagogo-Jack S, Amorin G, Johnson J, Hille D, Huyck S, Golm G, Terra S, Mancuso J. Efficacy and safety of ertugliflozin in subjects with type 2 diabetes mellitus inadequately controlled on the dual combination of metformin and sitagliptin: the VERTIS SITA2 trial. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S93.
	First SLR update	Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, Liao Y, Huyck S, Golm G, Terra SG, Mancuso JP. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. Diabetes, Obesity and Metabolism. 2017 Sep 17. [Epub ahead of print].
Jabbour 2014	Original SLR	Jabbour S, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24 week, multicenter, randomized, double-blind, placebo controlled study. Diabetes Care. 2014;37(3):740-750.
Mathieu 2015	Original SLR	Mathieu C, et al. Randomized, Double-Blind, phase 3 trial of triple therapy with dapagliflozin Add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care. 2015;38(11):2009-2017.
Rodbard 2016	Original SLR	Rodbard H, et al. Efficacy and safety of titrated canagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin and sitagliptin. Diabetes, Obesity and Metabolism. 2016;18(8):812-819.
Softeland 2017	Original SLR	Softeland E, et al. Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. Diabetes Care. 2017;40(2):201-209.
	First SLR update	Safety and efficacy of the combination of empagliflozin and linagliptin compared to linagliptin alone over 24 weeks in patients with type 2 diabetes. Available from https://clinicaltrials.gov/ct2/show/NCT01734785. Last accessed: 2nd November 2017.

Abbreviations: SLR, systematic literature review

Table D.8 Studies and publications included in the original SLR and the first and second SLR updates, but irrelevant for the purposes of this submission ("triple therapy")

Study name	Publication source (original SLR/SLR update)	Publication

Bayley 2012	Original SLR	Bailey, C., et al., Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes, Obesity and Metabolism, 2012. 14(10): p. 951-959.
Ferrannini 2010	Original SLR	Ferrannini, E., et al., Dapagliflozin monotherapy in Type 2 diabetic patients with inadequate glycemic control by Diet and exercise a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes care, 2010. 33(10): p. 2217-2224
Hadjadj 2016	Original SLR	Hadjadj, S., et al., Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care, 2016: p. dc160522
Inagaki 2014	Original SLR	Inagaki, N., et al., Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. Expert opinion on pharmacotherapy, 2014. 15(11): p. 1501-1515
Ji 2014	Original SLR	Ji, L., et al., Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clinical therapeutics, 2014. 36(1): p. 84-100. e9
Lewin 2015	Original SLR	Lewin, A., et al., Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care, 2015. 38(3): p. 394-402
Roden 2013	Original SLR	Roden, M., et al., Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes & Endocrinology, 2013. 1(3): p. 208-219
Rosenstock 2016	Original SLR	Rosenstock, J., et al., Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naïve type 2 diabetes. Diabetes Care, 2016: p. dc151736
Stenlöf 2013	Original SLR	Stenlöf, K., et al., Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes, Obesity and Metabolism, 2013. 15(4): p. 372-382
Terra 2017	Original SLR	Terra, S.G., et al., Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes, Obesity and Metabolism, 2017. 19(5): p. 721-728
Bailey 2010	Original SLR	Bailey, C.J., et al., Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. The Lancet, 2010. 375(9733): p. 2223-2233
Merck CSR P005	Original SLR	Merck & Co Inc and Pfizer Inc, Clinical study report: A Phase III, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin Compared with Ertugliflozin Alone and Sitagliptin Alone, in the Treatment of Subjects with T2DM With Inadequate Glycemic Control on Metformin Monotherapy (P005). 2016
Merck CSR P007	Original SLR	Merck & Co Inc and Pfizer Inc, Clinical study report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy (P007). 2016
DeFronzo 2015	Original SLR	DeFronzo, R.A., et al., Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care, 2015. 38(3): p. 384-393
Haring 2014	Original SLR	Häring, H.-U., et al., Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care, 2014. 37(6): p. 1650-1659

Lavalle-González 2013	Original SLR	Lavalle-González, F., 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. 56(12): p. 2582-2592.
Yang 2015	Original SLR	Yang, W., et al., Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. Journal of diabetes, 2015
VERTIS MONO	SLR first update	Terra S, Davies MJ, Frias J, Derosa G, Darekar A, Focht K, Golm G, Johnson J, Saur D, Dagogo-Jack S. Ertugliflozin effectively improves glycaemic control as monotherapy in patients with type 2 diabetes: the VERTIS MONO trial. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S346-S346.
	SLR second update	Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes, Obesity and Metabolism. 2018 Jun;20(6):1453-60.
VERTIS MET	SLR first update	Rosenstock J, Frias J, Pall D, Charbonnel B, Pascu R, Saur D, Darekar A, Shi H, Huyck SB, Lauring B, Terra SG. Effect of ertugliflozin on glycemic control, body weight, blood pressure (BP), and bone mineral density (BMD) in Type 2 Diabetes Mellitus inadequately controlled with metformin monotherapy: VERTIS MET Trial. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A311.
	SLR first update	Charbonnel B, Darekar A, Lauring B, Saur D, Shi H, Frias J, Rosenstock J, Pall D, Pascu R, Terra S, Huyck S. Efficacy and Safety of Ertugliflozin in Patients with T2DM Inadequately Controlled with Metformin Monotherapy: VERTIS MET trial. Conference: European Association for the Study of Diabetes – 53rd Annual Meeting. 2017 Sep 11:A878.
	SLR second update	Rosenstock J, Frias J, Páll D, Charbonnel B, Pascu R, Saur D, Darekar A, Huyck S, Shi H, Lauring B, Terra SG. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes, Obesity and Metabolism. 2018 Mar;20(3):520-9.
VERTIS FACTORIAL	SLR first update	Pratley R, Eldor R, Golm G. Safety and efficacy of ertugliflozin plus sitagliptin versus either treatment alone in subjects with type 2 diabetes inadequately controlled with metformin: the VERTIS FACTORIAL trial. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. 2016 Sep 12:A728.
	SLR second update	Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, Sunga S, Johnson J, Terra SG, Mancuso JP, Engel SS. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. Diabetes, Obesity and Metabolism. 2018 May;20(5):1111-20.
VERTIS SU	SLR second update	Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, Huyck S, Terra SG, Mancuso JP, Engel SS, Lauring B. Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: The VERTIS SU Randomized Study. Diabetes Therapy. 2018;9(1):193-207

Table D.9: Electronic database records excluded at the full-text review stage of the original SLR and the SLR updates – triple therapy

Reference	Rationale for exclusion
Original SLR	
Bailey T, Takacs R, Tinahones FJ, Rao PV, Tsoukas GM, Christensen SB, Kaltoft MS, Maislos M. Switching from sitagliptin to liraglutide in subjects with type 2 diabetes: analysis of composite endpoints from the LIRA-SWITCH randomised trial. InDiabetologia 2016 Aug 1 (Vol. 59, pp. S1-S1). 233 SPRING ST, NEW YORK, NY 10013 USA: SPRINGER	Intervention
Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, Ye J, Scott R, Johnson S, Stewart M, Rosenstock J. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. The lancet Diabetes & endocrinology. 2014 Apr 1;2(4):289-97.	Intervention
Seino Y, Inagaki N, Haneda M, Kaku K, Sasaki T, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin added to various oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus. Journal of diabetes investigation. 2015 Jul;6(4):443-53.	Intervention
Bailey RA, Damaraju CV, Martin SC, Meininger GE, Rupnow MF, Blonde L. Attainment of diabetes-related quality measures with canagliflozin versus sitagliptin. The American journal of managed care. 2014 Jan;20(1 Suppl):s16-24.	Other
Blonde L, Sheehan JJ, Barrett YC, Garcia-Sanchez R. Quality Measure Attainment After Add-on Therapy of Both Saxagliptin and Dapagliflozin to Metformin versus Single Add-on of Saxagliptin or Dapagliflozin. JCOM. 2016 Sep;23(9).	Population
Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hospital practice. 2013 Apr 1;41(2):72-84.	Population
Chien MN, Lee CC, Chen WC, Liu SC, Leung CH, Wang CH. Effect of sitagliptin as add-on therapy in elderly type 2 diabetes patients with inadequate glycemic control in Taiwan. International Journal of Gerontology. 2011 Jun 1;5(2):103-6.	Population
DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, Broedl UC. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes care. 2015 Jan 12:dc142364.	Population
Grandy S, Sternhufvud C, Ryden A, Sugg J, Rohwedder K. Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks. Diabetes, Obesity and Metabolism. 2016 Mar;18(3):306-9.	Population
Linjawi S, Sothiratnam R, Sari R, Andersen H, Hiort LC, Rao P. The study of once-and twice-daily biphasic insulin aspart 30 (BIAsp 30) with sitagliptin, and twice-daily BIAsp 30 without sitagliptin, in patients with type 2 diabetes uncontrolled on sitagliptin and metformin—The Sit2Mix trial. Primary care diabetes. 2015 Oct 1;9(5):370-6.	Population
Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, Iqbal N. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes care. 2014 Oct 28:DC_141142.	Population
Tinahones FJ, Gallwitz B, Nordaby M, Götz S, Maldonado-Lutomirsky M, Woerle HJ, Broedl UC. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes, Obesity and Metabolism. 2017 Feb;19(2):266-74.	Population
SLR updates	
De Boer SA, Heerspink HJ, Juárez Orozco LE, van Roon AM,	Duplicate

Reference	Rationale for exclusion
Kamphuisen PW, Smit AJ, Slart RH, Lefrandt JD, Mulder DJ. Effect of linagliptin on pulse wave velocity in early type 2 diabetes: A randomized, double-blind, controlled 26-week trial (RELEASE). Diabetes, Obesity and Metabolism. 2017;19(8):1147-54.	
Deng XL, Ma R, Zhu HX, Zhu J. Short article: A randomized-controlled study of sitagliptin for treating diabetes mellitus complicated by nonalcoholic fatty liver disease. European Journal of Gastroenterology & Hepatology. 2017 Mar 1;29(3):297-301.	Duplicate
Bailey TS, Takács R, Tinahones FJ, Rao PV, Tsoukas GM, Thomsen AB, Kaltoft MS, Maislos M. Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial. Diabetes, Obesity and Metabolism. 2016 Dec 1;18(12):1191-8.	Duplicate
Scalzo RL, Moreau KL, Ozemek C, Herlache L, McMillin S, Gilligan S, Huebschmann AG, Bauer TA, Dorosz J, Reusch JE, Regensteiner JG. Exenatide improves diastolic function and attenuates arterial stiffness but does not alter exercise capacity in individuals with type 2 diabetes. Journal of Diabetes and its Complications. 2017 Feb 28;31(2):449-55.	Duplicate
Softeland, E.;Meier, J. J.;Vangen, B.;Toorawa, R.;Maldonado-Lutomirsky, M. ;Broedl, U. C. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: A 24-week randomized, double-blind, parallel-group trial. Diabetes Care. 2017 Feb 1;40(2);201-9.	Duplicate
Tai H, Wang MY, Zhao YP, Li LB, Dong QY, Liu XG, Kuang JS. The effect of alogliptin on pulmonary function in obese patients with type 2 diabetes inadequately controlled by metformin monotherapy. Medicine. 2016 Aug;95(33):e4541.	Duplicate
Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, Golm G, Johnson J, Saur D, Lauring B, Dagogo-Jack S. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes, Obesity and Metabolism. 2017 May 1;19(5):721-8.	Duplicate
Wang W, Yang J, Yang G, Gong Y, Patel S, Zhang C, Izumoto T, Ning G. Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: A multinational 24-week, randomized clinical trial. Journal of Diabetes. 2016 Mar 1;8(2):229-37.	Duplicate
Ametov AS. The role of dipeptidyl peptidase-4 inhibitors in fat metabolism in patients with type 2 diabetes. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A627.	Not English language or publication type or study design of interest
Aroda, VR, Frfas JP, Tabak O, Tadayon S, Zacho J, Capehorn M. Semaglutide reduces HbA1C and body weight across multiple background oad treatment categories. Conference: 99th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2017 Apr;38(3S1):A620	Not English language or publication type or study design of interest
Aroda VR, Unger J, Cariou B, Birch S, Tadayon S, Jodar E. Semaglutide consistently reduces both fasting and postprandial glucose levels across sustain 1-5 clinical trials. Conference: 99th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2017 Apr;38(3S1):A622	Not English language or publication type or study design of interest
de Boer SA, Heerspink HJ, Lefrandt JD, Hovinga–de Boer MC, van Roon AM, Orozco LE, Glaudemans AW, Kamphuisen PW, Slart RH, Mulder DJ. Effect of linagliptin on arterial 18 f-fluorodeoxyglucose positron emission tomography uptake. Journal of the American College of Cardiology. 2017 Feb 20;69(8):1097-8.	Not English language or publication type or study design of interest
Briggs AH, Bhatt DL, Scirica BM, Raz I, Johnston KM, Szabo SM, Bergenheim K, Mukherjee J, Hirshberg B, Mosenzon O. Health-related quality-of-life implications of cardiovascular events in individuals with type 2 diabetes mellitus: A subanalysis from the Saxagliptin Assessment of	Not English language or publication type or study design of interest

Reference	Rationale for exclusion
Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-TIMI 53 trial. Diabetes Research and Clinical Practice. 2017 Jan 23;130:24-33.	
Ferrannini, E. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. Therapeutic Research. 2016;37(4):380-1.	Not English language or publication type or study design of interest
Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus. Circulation. 2016 Sep 6;134(10):752-72.	Not English language or publication type or study design of interest
Jones, B. Liraglutide and cardiovascular outcomes in type 2 diabetes. Annals of Clinical Biochemistry. 2016 Nov;53(6):712.	Not English language or publication type or study design of interest
Kheniser K, Kashyap SR. Canagliflozin versus placebo for post-bariatric surgery patients with persistent type II diabetes: A randomized controlled trial (CARAT). Diabetes, Obesity and Metabolism. 2017 Apr 1;19(4):609-10.	Not English language or publication type or study design of interest
Li X, Li A, Wu L, Wang F, Geng J, Liu J, Bai X. Effect of the monotherapy of sitagliptin on glycemic control of patients with type 2 diabetes in different duration. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2017 Jul 13. [Epub ahead of print].	Not English language or publication type or study design of interest
Østergaard L, Frandsen CS, Dejgaard TF, Madsbad S. Fixed-ratio combination therapy with GLP-1 receptor agonist liraglutide and insulin degludec in people with type 2 diabetes. Expert Review of Clinical Pharmacology. 2017 Apr;10(6):621-32.	Not English language or publication type or study design of interest
Polidori D, Sanghvi A, Seeley RJ, Hall KD. How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake. Obesity. 2016 Nov 1;24(11):2289-95.	Not English language or publication type or study design of interest
Reed SD, Li Y, Leal J, Graham F, Alfredsson J, Gray AM, Buse JB, Green JB, Kaufman KD, Riefflin A, Suryawanshi S. Emerging sitagliptin benefit for all-cause hospitalizations: Evidence from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A360.	Not English language or publication type or study design of interest
Shekelle, P. In patients with type 2 diabetes and CV disease, empagliflozin reduced a composite of CV events at 3.1 years. Annals of Internal Medicine. 2016 Jan 19;164(2);JC2.	Not English language or publication type or study design of interest
Watanabe C, Akuta N, Suzuki Y, Kobayashi M, Sezaki H, Hayashi K, Mori Y, Kumada H. Effects of the sglt2 inhibitor on histological improvement of nonalcoholic fatty liver disease based on serial liver biopsies. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A510.	Not English language or publication type or study design of interest
Ahren B, Comas LM, Kumar H, Sargin M, Karsbol JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide vs sitagliptin as add-on to metformin and/or thiazolidinediones after 56 weeks in subjects with Type 2 diabetes (SUSTAIN 2). Diabetic Medicine. 2017 Mar 1;34(S1):145.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. The Lancet Diabetes & Endocrinology. 2017 May 31;5(5):341-54.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bergmark BA, Cannon CP, White WB, Jarolim P, Liu Y, Bonaca MP, Zannad F, Morrow DA. Baseline adiponectin concentration and clinical outcomes among patients with diabetes and recent acute coronary	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant

Reference	Rationale for exclusion
syndrome in the EXAMINE trial. Diabetes, Obesity and Metabolism. 2017 Mar 1;19(7):962-969.	intervention
Bethel MA, Engel SS, Garg J, Stevens SR, Lokhnygina Y, Josse RG, Green JB, Peterson ED, Holman RR. Time to insulin in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A316.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bethel MA, Engel SS, Green JB, Huang Z, Josse RG, Kaufman KD, Standl E, Suryawanshi S, Van de Werf F, McGuire DK, Peterson ED. Assessing the safety of sitagliptin in older participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Care. 2017 Apr 1;40(4):494-501.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal N. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. The Journal of Clinical Endocrinology. 2016 Jan 1;101(1):44-51.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bizino MB, Jazet IM, Lamb HJ, Smit JW. Double-Blind, Placebo-Controlled, Randomised Trial to Assess the Effect of Liraglutide on Ectopic Fat Accumulation in Type 2 Diabetes Mellitus Patients. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A63-A64.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bizino MB, Jazet IM, Smit JW, Lamb HJ. Double-Blind, Placebo-Controlled, Randomised Trial to Assess the Effect of Liraglutide on Left Ventricular Diastolic Dysfunction in Type 2 Diabetes Mellitus Patients. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A63.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Buse JB, Bethel MA, Green JB, Stevens SR, Lokhnygina Y, Aschner P, Grado CR, Tankova T, Wainstein J, Josse R, Lachin JM. Pancreatic safety of sitagliptin in the TECOS study. Diabetes Care. 2017 Feb 1;40(2):164-70.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Cahn A, Mosenzon O, Bhatt DL, Leibowitz G, Yanuv I, Rozenberg A, Iqbal N, Hirshberg B, Stahre C, Im K, Kanevsky E. Hypoglycaemia manifestations and recurrent events: Lessons from the SAVOR-TIMI 53 outcome study. Diabetes, Obesity and Metabolism. 2017;19(7):1045-1050.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Campbell-Scherer D. Semaglutide is non-inferior to placebo for cardiovascular outcomes in patients with type 2 diabetes. Evidence-Based Medicine. 2017 Apr 1;22(2):57-8.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Cavender MA, White WB, Jarolim P, Bakris GL, Cushman WC, Kupfer S, Gao Q, Mehta CR, Zannad F, Cannon CP, Morrow DA. Serial Measurement of High Sensitivity Troponin I and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus in the EXAMINE Trial. Circulation. 2017; 135(20):1911-1921.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Cherney DZ, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2017 Aug 1;5(8):610-21.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Cordiner R, Fisher M, Drummond R. SUSTAIN-6: cardiovascular safety of a once-weekly GLP-1 receptor agonist. Practical Diabetes. 2016 Oct 1;8(33):266-8a.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, Engel SS, Lopes RD, McGuire DK, Riefflin A, Rodbard HW. Effect of	Did not include adult patients with uncontrolled type 2 diabetes having

Reference	Rationale for exclusion
sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. Diabetes Care. 2016 Dec 1;39(12):2304-10.	previously received a relevant intervention
Davidson JA, Schernthaner G, Hieronymus L, Jodon H, Vijapurkar U, Meininger G, Canovatchel W. Canagliflozin is Superior to Sitagliptin in Reducing Both A1C and Body Weight in Patients with Type 2 Diabetes Mellitus. Conference: 97th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2015;36:no pagination.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
De Boer SA, Heerspink HJ, Juárez Orozco LE, van Roon AM, Kamphuisen PW, Smit AJ, Slart RH, Lefrandt JD, Mulder DJ. Effect of linagliptin on pulse wave velocity in early type 2 diabetes: A randomized, double-blind, controlled 26-week trial (RELEASE). Diabetes, Obesity and Metabolism. 2017;19(8):1147-54.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
De la Peña A, Loghin C, Cui X, Zhang X, Kapitza C, Kelly RP. Once-weekly dulaglutide 1.5 mg restores insulin secretion in response to intravenous glucose infusion. Diabetes, Obesity and Metabolism. 2017 Apr 1;19(4):517-23.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Defronzo RA, Martinez R, Al-Jabori H, Adams J, Triplitt C, Cersosimo E. Liraglutide fails to offset the rise in hepatic glucose production (HGP) seen with SGLT2i treatment. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A283.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Deng XL, Ma R, Zhu HX, Zhu J. Short article: A randomized-controlled study of sitagliptin for treating diabetes mellitus complicated by nonalcoholic fatty liver disease. European Journal of Gastroenterology & Hepatology. 2017 Mar 1;29(3):297-301.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Dou J, Ma J, Liu J, Wang C, Johnsson E, Yao Y, Zhao J, Pan C. Efficacy and safety of saxagliptin plus metformin as initial therapy in patients with type 2 diabetes. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A327.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Engel SS, Suryawanshi S, Stevens SR, Josse RG, Cornel JH, Jakuboniene N, Riefflin A, Tankova T, Wainstein J, Peterson ED, Holman RR. Safety of sitagliptin in patients with type 2 diabetes and chronic kidney disease: outcomes from TECOS. Diabetes, Obesity and Metabolism. 2017 Apr 1;19(11):1587-93.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Erondu N, Hollander PA, Bays H, Rosenstock J, Frustaci M, Fung A, Vercruysse F. Coadministration of canagliflozin and phentermine for weight management in overweight and obese adults. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S40.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Eynatten M, Bergenstal RM, Calabro P, Maldonado-Lutomirsky M, Mattheus M, Lachin JM, Wanner C. Effect of empagliflozin on nephropathy in subgroups by age: results from EMPA-REG OUTCOME. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S483.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Fitchett D, Inzucchi SE, Wanner C, Mattheus M, George JG, Woerle HJ, Zinman B. Reduction in hospitalisation for heart failure with empagliflozin is consistent across categories of baseline HbA1c and change in HbA1c: results from the EMPA-REG OUTCOME trial. European Journal of Heart Failure. 2017 May 1;19(S1):121.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Fitchett D, Mcknight J, Lee J, George JT, Mattheus M, Woerle HJ, Inzucchi SE. Empagliflozin (EMPA) Reduces Heart Failure Irrespective of Control of Blood Pressure (BP), Low Density Lipoprotein Cholesterol (LDL-C), and HbA1c. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A312-A313.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure	Did not include adult patients with uncontrolled type 2 diabetes having

Reference	Rationale for exclusion
outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Italian Journal of Medicine. 2016;10(S2):45.	previously received a relevant intervention
Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. European Heart Journal. 2016 Jan 26;37(19):1526-34.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riddle MC, Rydén L, Xavier D, Atisso CM. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial of dulaglutide's cardiovascular effects. Diabetes, Obesity and Metabolism. 2017 Jun 1. [Epub ahead of print].	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Gilbert MP, Marre M, Holst JJ, Garber A, Baeres FM, Thomsen H, Pratley RE. Comparison of the long-term effects of liraglutide and glimepiride monotherapy on bone mineral density in patients with type 2 diabetes. Endocrine Practice. 2015 Nov 17;22(4):406-11.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Heerspink HJL, Desai M, Jardine M, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independent of glycaemic effects. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(1):S28.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
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Smits MM, Tonneijck L, Muskiet MH, Hoekstra T, Kramer MH, Diamant M, van Raalte DH. The effects of GLP-1 based therapies on postprandial haemodynamics: Two randomised, placebo-controlled trials in overweight	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant

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Suzuki S, Oura T, Takeuchi M, Boye KS. Evaluation of the impact of once weekly dulaglutide on patient-reported outcomes in Japanese patients with type 2 diabetes: comparisons with liraglutide, insulin glargine, and placebo in two randomized studies. Health and Quality of Life Outcomes. 2017 Jun 12;15(1):123.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Tanaka A, Shimabukuro M, Okada Y, Taguchi I, Yamaoka-Tojo M, Tomiyama H, Teragawa H, Sugiyama S, Yoshida H, Sato Y, Kawaguchi A. Rationale and design of a multicenter placebo-controlled double-blind randomized trial to evaluate the effect of empagliflozin on endothelial function: the EMBLEM trial. Cardiovascular diabetology. 2017 Apr 12;16(1):48.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Tanaka R, Yamashiro K, Nobukazu M, Kazuyuki N, Yosiaki S, Yuji U, Yasuyuki O, Nobutaka H, Takao U. Efficacy of alogliptin (dpp-4 inhibitor) for the secondary prevention after ischemic stroke or tia with type 2 diabetes mellitus. European Stroke Journal. 2017;2(S1):321.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Teli V, Gupta V. A real-life prospective study to evaluate effect of sodium-glucose cotransporter-2 inhibitor (canagliflozin) therapy on cardiovascular and renal markers in patients with type 2 diabetes mellitus. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A321.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Tinahones FJ, Gallwitz B, Nordaby M, Götz S, Maldonado-Lutomirsky M, Woerle HJ, Broedl UC. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes, Obesity and Metabolism. 2017 Feb 1;19(2):266-74.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Tonneijck L, Smits MM, Muskiet MH, Hoekstra T, Kramer MH, Danser AJ, Diamant M, Joles JA, Raalte DH. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. Diabetologia. 2016 Jul 1;59(7):1412-21.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention

Reference	Rationale for exclusion
Toural E, Ridderstrale M, Fitchett D, Giljanovic KS, Woerle HJ, Mattheus M, Zinman B, Inzucchi SE. Effect of empagliflozin on cardiovascular death in subgroups by age: results from EMPA-REG OUTCOME. Diabetologica. 2016;59(1S1):S539-S540.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Tran S, Kramer CK, Zinman B, Choi H, Retnakaran R. Effect of Liraglutide on Time to Post-challenge Peak Glucose in Patients with Type 2 Diabetes (T2DM). Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A288.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Valderas JP, Carrasco C, Maiz C, Crovari F, Boza C. GLP-1 receptor agonist therapy induces a greater reduction in glycaemic variability compared to gastric bypass in type 2 diabetic patients. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S331.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Vellanki P, Alexanian S, Baldwin D, Rasouli N, Anzola IA, Ramos C, Urrutia MA, Jones J, Modzelewski K, Ensminger E, Bakhtiari HF. Efficacy and Safety of Linagliptin in General Surgical Patients with Type 2 Diabetes: Linagliptin Surgery Trial. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A336.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Vidal J, Giorgino F, Stager W, Nikonova EV, Vlajnic A, Perfetti R, Meier J. Postprandial glycaemic outcomes of a fixed-ratio combination of insulin glargine and lixisenatide in the LixiLan-L trial. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S382-S383.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Vilsboll T, Bain SC, Consoli A, Davies MJ, Bergan EQ, Hansen O, Lingvay I. Semaglutide provides sustained reductions in body weight over two years in subjects with type 2 diabetes. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A299-A300.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Wang W, Li P, Yang J, Gu L. Efficacy and safety of once-weekly dulaglutide monotherapy compared to glimepiride in Chinese patients with type 2 diabetes mellitus. Diabetes/Metabolism: Research & Reviews. 2015 Dec 1;31:10-1.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Wanner C, Inzucchi S, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Reduced progression of kidney disease with empagliflozin: results from EMPA-REG OUTCOME. Diabetic Medicine. 2017 Mar 1;34:80-81.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016 Jul 28;375(4):323-34.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Diabetes & Endocrinology. 2016 Mar 31;4(3):211-20.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
White WB, Cushman W, Kupfer S, Bakris G, Bergenstal R, Heller S, Mehta C, Nissen S, Zannad F, Liu Y, Cannon C. Average clinician measured blood pressure predict cardiovascular outcomes in patients with type 2 diabetes following acute coronary syndromes in the examine trial. Journal of the American College of Cardiology. 2017;69(11):1676.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Wit HM, Vervoort GM, Jansen HJ, Galan BE, Tack CJ. Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes'(ELEGANT) randomized controlled trial. Journal of internal medicine. 2016 Mar 1;279(3):283-92.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention

Reference	Rationale for exclusion
Wysham C, Bonadonna RC, Aroda VR, Puig Domingo M, Kapitza C, Stager W, Yu C, Niemoeller E, Souhami E, Bergenstal RM. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial. Diabetes, Obesity and Metabolism. 2017 Jun 8;19(10):1408-1415.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Wysham CH, Vieke D, Vetter M, He Y, Iqbal N, Hardy E, Ryden A, Rosenstock J. Patient-reported treatment satisfaction with exenatide once weekly suspension for autoinjection (EQW-SAI) vs exenatide twice daily (EBID) in patients with inadequately controlled type 2 diabetes mellitus (T2DM). Conference: 97th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2015;36:no pagination.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Yoon KH, Hardy E, Han J. Exenatide versus insulin lispro added to basal insulin in a subgroup of korean patients with type 2 diabetes mellitus. Diabetes & Metabolism Journal. 2017 Feb 1;41(1):69-74.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, Mattheus M, Woerle HJ, Broedl UC, Johansen OE, Albers GW. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. Stroke. 2017 Feb 8;48(5):1218-1225.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Zinman B, Marso SP, Christiansen E, Calanna S, Rasmussen S, Buse JB. Severe hypoglycemia, cardiovascular outcomes, and death: the LEADER experience. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017;66:A95.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Zinman B, Mathieu C, Kaspers S, Mattheus M, Woerle HJ, Fitchett D. Empagliflozin (EMPA) reduces mortality in analyses adjusted for control of blood pressure (BP), low density lipoprotein cholesterol (LDL-C), and HbA1c over time. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017;66:A313.	Did not include adult patients with uncontrolled type 2 diabetes having previously received a relevant intervention
Bailey TS, Takács R, Madueño FT, Thomsen AB, Kaltoft MS, Maislos M. Efficacy and Safety of Switching from Sitagliptin to Liraglutide in Subjects with Type 2 Diabetes: A Randomized, Double-Blind, Double-Dummy, Active-Controlled 26-Week Trial. Novel Treatment for Diabetes-Focusing on GLP-1 and SGLT2. Conference: 98th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2016;37(2S1):no pagination.	Did not investigate an intervention of interest
Frias JP, Hardy E, Ahmed A, Ohman P, Jabbour SA, Wang H, Guja C. Exenatide Once Weekly (QW) plus Dapagliflozin, Exenatide QW, or Dapagliflozin Added to Metformin Monotherapy in Subgroups of Patients with Type 2 Diabetes in the DURATION-8 Study. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A296.	Did not investigate an intervention of interest
Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study. Diabetes, Obesity and Metabolism. 2017 Mar 1;19:979–988.	Did not investigate an intervention of interest
Ekholm E, Hansen L, Johnsson E, Iqbal N, Carlsson B, Chen H, Hirshberg B. Combined treatment with saxagliptin plus dapagliflozin reduces insulin levels by increased insulin clearance and improves β-cell function. Endocrine Practice. 2016 Nov 16;23(3):258-65.	Did not investigate an intervention of interest
Nauck MA, di Domenico M, Patel S, Kobe M, Toorawa R, Woerle HJ. Linagliptin and pioglitazone combination therapy versus monotherapy with linagliptin or pioglitazone: A randomised, double-blind, parallel-group, multinational clinical trial. Diabetes and Vascular Disease Research. 2016 Jul;13(4):286-98.	Did not include a comparator of interest
Del Prato S, Fleck P, Wilson C, Chaudhari P. Comparison of alogliptin	Did not include a comparator of

Reference	Rationale for exclusion
and glipizide for composite endpoint of glycated haemoglobin reduction, no hypoglycaemia and no weight gain in type 2 diabetes mellitus. Diabetes, Obesity and Metabolism. 2016 Jun 1;18(6):623-7.	interest
Baron MA, Denham D, Prabhakar P, Azeem R, Kjems L, Rosenstock J. Efficacy and tolerability of ITCA 650 versus sitagliptin in uncontrolled type 2 diabetes patients on metformin monotherapy: results of the FREEDOM-2 study. Conference: European Association for the Study of Diabetes – 52nd Annual Meeting. Diabetologia. 2016 Aug 1;59(S1):S77-8.	Did not include a comparator of interest
Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, Jabbour SA. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2016 Dec 31;4(12):1004-16.	Did not include a comparator of interest
Handelsman Y, Mathieu C, Del Prato S, Johnsson E, Kurlyandskaya R, Iqbal N, Rosenstock J. Triple vs. dual therapy with saxagliptin plus dapagliflozin vs. sitagliptin added to metformin-failure uncontrolled type 2 diabetes. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017;66:A35-A36.	Did not include a comparator of interest
Rosenstock J, Bailey CJ, Mathieu C. Chen H, Garcia-Sanchez R, Saraiva GL. Composite endpoint analysis of dapagliflozin versus saxagliptin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin. Endocrine Practice. 2017;23(1):38a-39a.	Did not include a comparator of interest
Rosenstock J, Prabhakar P, Kjems L, Huang H, Baron M. ITCA 650 Significantly Reduces the Need to Advance Antidiabetes Therapy Compared with Sitagliptin. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017;66:A295.	Did not include a comparator of interest
Zang L, Liu Y, Geng J, Luo Y, Bian F, Lv X, Yang J, Liu J, Peng Y, Li Y, Sun Y. Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial. Diabetes, Obesity and Metabolism. 2016 Aug 1;18(8):803-11.	Did not include a comparator of interest
Davies MJ, Merton KW, Vijapurkar U, Balis DA, Desai M. Canagliflozin improves risk factors of metabolic syndrome in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2017 Jan 27;10:47-55.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Gupta S, Shaikh S, Joshi P, Bhure S, Suvarna V. Long-term efficacy and safety of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes in Indian subgroup: Results from a 76-week extension trial of phase iii, double-blind, randomized study. Indian Journal of Endocrinology and Metabolism. 2017 Mar 21;(2):286-292.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Jabbour SA, Frias JP, Guja C, Hardy E, Ahmed A, Ohman P. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly, or dapagliflozin added to metformin monotherapy on cardiovascular risk markers in patients with type 2 diabetes in the DURATION-8 study. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A307.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Jax T, Stirban A, Terjung A, Esmaeili H, Berk A, Thiemann S, Chilton R, Eynatten M, Marx N. A randomised, active-and placebo-controlled, three-period crossover trial to investigate short-term effects of the dipeptidyl peptidase-4 inhibitor linagliptin on macro-and microvascular endothelial function in type 2 diabetes. Cardiovascular Diabetology. 2017 Jan 21;16(1):13.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Mita T, Katakami N, Yoshii H, Onuma T, Kaneto H, Osonoi T, Shiraiwa T, Kosugi K, Umayahara Y, Yamamoto T, Yokoyama H. Alogliptin, a dipeptidyl peptidase 4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the Study of Preventive	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks

Reference	Rationale for exclusion
Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A). Diabetes Care. 2016 Jan 1;39(1):139-48.	
Neal B, Perkovic V, Matthews DR, Mahaffey KW, Fulcher G, Meininger G, Erondu N, Desai M, Shaw W, Vercruysse F, Yee J. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study–Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes, Obesity and Metabolism. 2017 Mar 1;19(3):387-93.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Patel S, Lewin AJ, DeFronzo R, Liu D, Kaste R, Woerle HJ, Broedl UC. Combination of empagliflozin/linagliptin for 52 Weeks as add-on to metformin in subjects with type 2 diabetes. Conference: 97th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2015;36: o pagination.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Sach-Friedl S, Augustin T, Magnes C, Ekardt E, Eberl A, Narath S, Brunner M, Korsatko S, Svehlikova E, Treiber G, Pieber T. Effect of SGLT2i, DPP-4i, and the combination of SGLT2i+ DPP-4i on glucagon, endogenous glucose production (EGP), and lipolysis in patients with type 2 diabetes (T2DM). Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A312.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Vella, A.;Freeman, J. L. R.;Dvergsten, C.;Dunn, I. ;Valcarce, C. TTP399: A liver-selective and therapeutically viable glucokinase activator: Results from a 6-month phase 2 study. Conference: 99th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2017;38(3S1):no pagination.	Study not of 24-26 weeks' duration or did not report study results at 24-26 weeks
Ji L, Han P, Wang X, Liu J, Zheng S, Jou YM, O'Neill EA, Golm GT, Engel SS, Kaufman KD, Shankar RR. Randomized clinical trial of the safety and efficacy of sitagliptin and metformin co-administered to Chinese patients with type 2 diabetes mellitus. Journal of Diabetes Investigation. 2016 Sep 1;7(5):727-36.	Did not report a relevant outcome
Seufert JR, Patel S, Pfarr E, Del Parigi A, Lee C. HbA1c Changes with Empagliflozin/Linagliptin Are Independent of Baseline Age in Subjects with Type 2 Diabetes. Conference: 98th Annual Meeting of the Endocrine Society. Endocrine Reviews. 2016;37(2S1):no pagination.	Did not report a relevant outcome

SLR of interventional Non-RCTs of Ertugliflozin

Search Databases

The following electronic databases were searched on 9th August 2017:

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print (1946 to present)
- Embase (1974 to 2017 August 08)
- Cochrane Central Register of Controlled Trials (CENTRAL; up to Issue 7 of 12, July 2017)
- Cochrane Database of Systematic Review (CDSR; up to Issue 8 of 12, August 2017)
- Database of Abstracts of Reviews of Effects (DARE; up to Issue 2 of 4, April 2015)

The following electronic databases were searched again on 9th May 2018 for the SLR update

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print (1946 to May 02, 2018)
- Embase (1974 to 2018 May 08)
- Cochrane Central Register of Controlled Trials (CENTRAL; up to Issue 4 of 12, April 2018)
- Cochrane Database of Systematic Review (CDSR; up to Issue 5 of 12, May 2018)
- Database of Abstracts of Reviews of Effects (DARE; up to Issue 2 of 4, April 2015)

MEDLINE and Embase were searched separately via the Ovid SP platform. CDSR, CENTRAL and DARE were searched simultaneously via the Cochrane Library Wiley Online platform.

As well as conducting electronic database searches, a manual hand-search of abstracts presented at key congresses over the last 4 years (2015–2018) was undertaken. The same conferences were searched using the same search strategy as described in the methodology sections for the SLR of RCT evidence; please refer to the "SLR of RCT Evidence" sections of this submission for further information.

Finally, it was planned that the reference lists of any SLRs and NMAs identified as relevant at the title and abstract screening stage of the SLR would be hand-searched to identify any further relevant publications for inclusion in the SLR.

Search Terms

SLR Update - Electronic Database Searches

Search terms for use in MEDLINE and Embase (searched separately via Ovid SP) are presented in Table D.10 and Table D.11, respectively. Search terms for use in CENTRAL, CDSR and DARE (searched simultaneously via the Cochrane Library Wiley Online platform) are presented in Table D.12.

When the searches were run, search results from each database were downloaded and deduplicated against one another in EndNote. Retained records were transferred into a bespoke Microsoft Excel-based platform for eligibility screening.

Table D.10: Search terms used in MEDLINE (searched via Ovid SP)

#	Search terms	Hits (9th August 2017)	Hits (9th May 2018)
1	ertugliflozin/	0	0
2	(ertugliflozin$ or MK 8835 or MK8835 or "PF 04971729" or PF04971729 or PF 4971729 or PF4971729).mp.	13	29
3	1 or 2	13	29
4	2017-08-04:2018-05-08.(dt).	-	958247
5	3 and 4	-	16

Table D.11: Search terms used in EMBASE (searched via Ovid SP)

#	Search terms	Hits (9th August 2017)	Hits (9th May 2018)
1	ertugliflozin/	109	148
2	(ertugliflozin$ or MK 8835 or MK8835 or "PF 04971729" or PF04971729 or PF 4971729 or PF4971729).mp.	120	160
3	1 or 2	120	160
4	limit 3 to dc=20170811-20180508	-	47

Table D.12: Search terms used in CDSR, CENTRAL and DARE (searched simultaneously via the Cochrane Library Wiley Online platform)

#	Search terms	Hits (9th August 2017)	Hits (9th May 2018)
1	[mh "ertugliflozin"]	0	0
2	(ertugliflozin* or "MK 8835" or MK8835 or "PF 04971729" or PF04971729 or "PF 4971729" or PF4971729):ti,ab,kw	20	35
3	#1 or #2	20	-
4	#3 in Cochrane Reviews (Reviews Only), Other Reviews and Trials	20	-
5	#1 or #2 Publication Year from 2017 to 2018	-	20
"Cochrane Reviews (Reviews Only)" corresponds to CDSR; "Other Reviews" corresponds to DARE; and "Trials" corresponds to CENTRAL.			

SLR Update – Manual Congress Searches

Please refer to the manual congress searches described previously for the RCT evidence SLR.

Study Selection

Articles were included in the SLR if they met the eligibility criteria presented in Table D.13**Error! Reference source not found.**. The same approach to record screening, data extraction and quality assessment in terms of the number of individuals involved at each stage and their responsibilities was undertaken as described for the SLR of RCT evidence, with the exception that it was planned that the quality of included non-RCTs would be assessed using the Downs and Black checklist [50].

Table D.13: Eligibility criteria for the SLR of interventional non-RCTs of ertugliflozin

Domain	Inclusion Criteria	Exclusion Criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years) with uncontrolled* T2D	Any of the following: • Non-humans • Patients do not have uncontrolled* T2D • Studies are on children (<18 years old)
Intervention(s)	Ertugliflozin as monotherapy for T2D, or in combination with metformin and/or sulfonylurea and/or insulin	Studies not investigating ertugliflozin as monotherapy for T2D or in combination with an intervention other than metformin, sulfonylurea or insulin
Comparator(s)	Any or none	NA
Outcomes	Any of the following: • Glycaemic control (HbA1c) • Weight/body mass index • Changes in cardiovascular risk factors (e.g. estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, high density lipoproteins, low density lipoproteins, cholesterol, triglycerides) • Complications of diabetes, including cardiovascular, renal and eye • Adverse effects of treatment (e.g. hypoglycaemia [both non-severe and requiring medical attention], hematocrit, urinary tract infections, genital tract infections and malignancies) • Mortality • Health-related quality of life	Studies not presenting a relevant outcome
Study design	The following study designs: • Interventional non-RCTs, including controlled (but not randomised) clinical trials and single-arm clinical trials	Any other study designs, including: • RCTs • Observational studies • SLRs and (network) meta-analyses (although the references lists of these will be hand-searched for relevant primary studies) • Case studies and case reports • Editorials, notes, comments or letters • Narrative or non-systematic literature reviews
Other considerations	• English language • Human subjects • Study duration: No limit • Publication year: No limit	• Non-English language full-texts • Articles not on human subjects • Study duration: NA • Publication year: NA

Abbreviations: T2DM, type 2 diabetes mellitus; ERTU, ertugliflozin; MET, metformin; RCT, randomised clinical trial; SLR, systematic literature review
NA, not applicable; RCT, randomised controlled trial; T2D, type 2 diabetes
*"Uncontrolled" refers to a baseline (at time of intervention initiation, not including any wash-out periods or run-ins) HbA1c greater than 7%.

Results

The PRISMA flow diagram for the SLR is presented in Figure D.4 and for the SLR update in figure D..; no relevant publications were identified for inclusion. A list of publications excluded from the first SLR

at the full-text review stage is provided in Table D.14 wherease for the second SLR update in table D.15.

Figure D.4 PRISMA flow diagram for the SLR of interventional non-RCTs of ertugliflozin

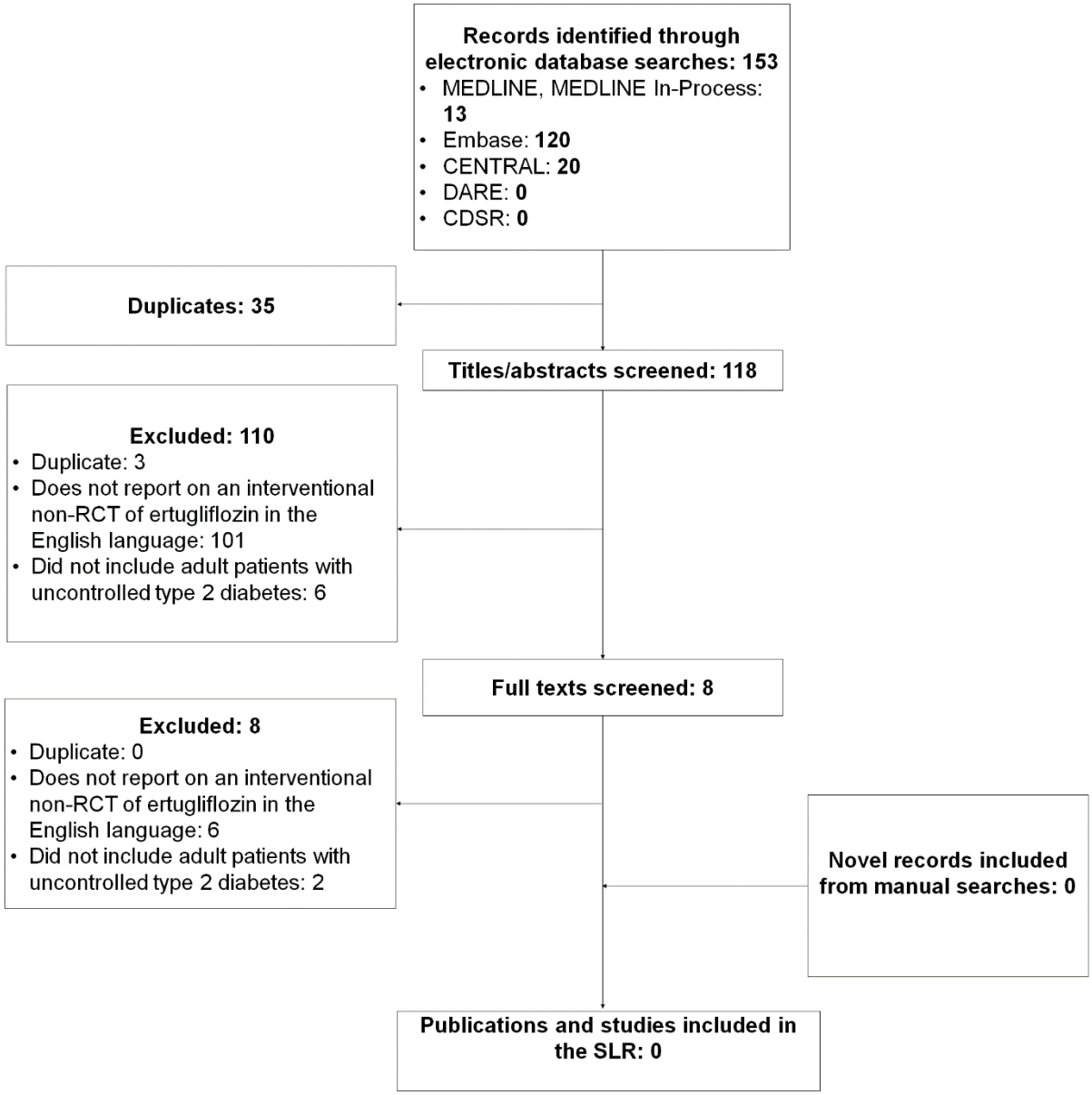


Figure D.5 PRISMA flow diagram for the SLR of interventional non-RCTs of ertugliflozin

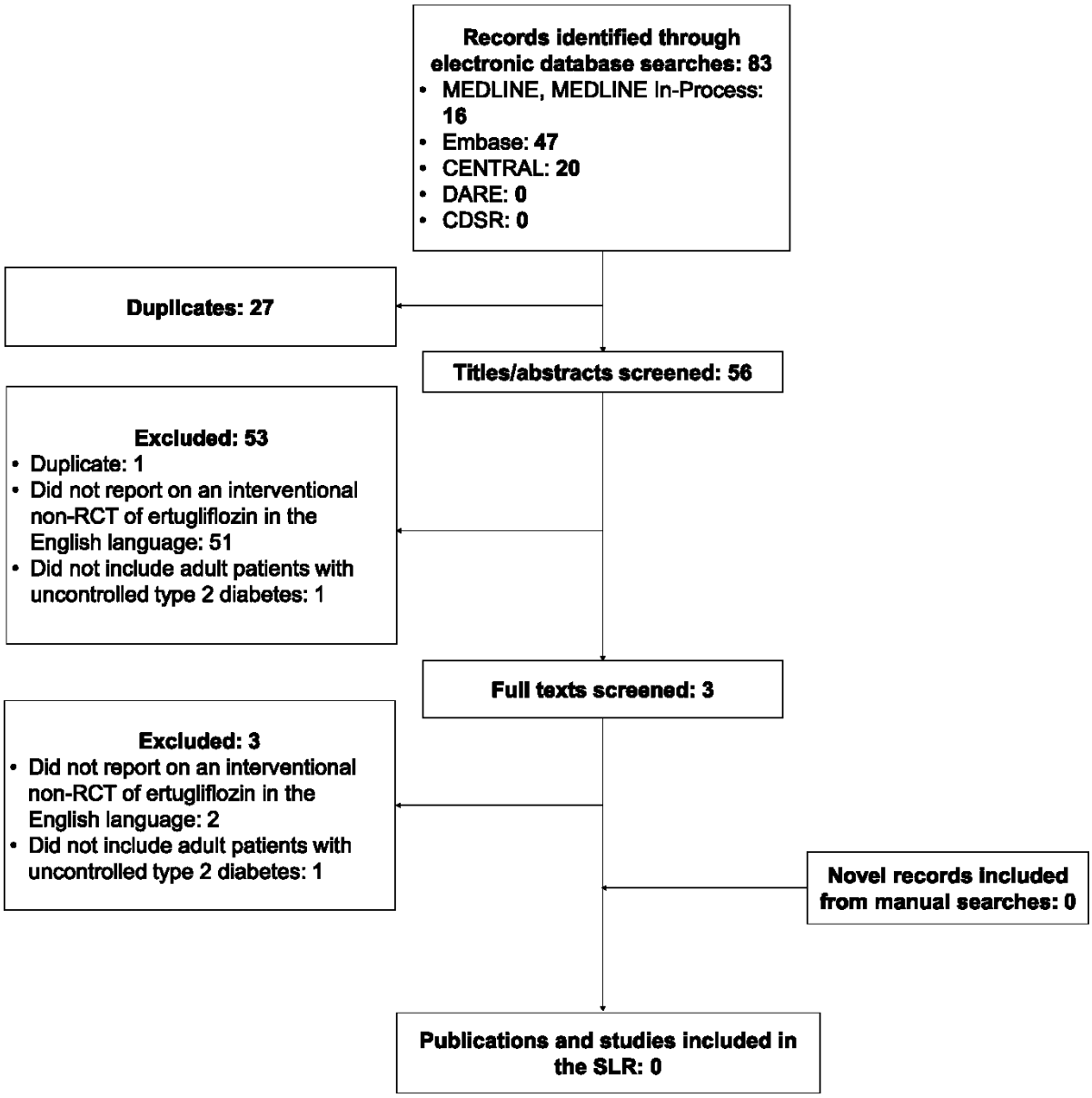


Table D.13: Electronic database records excluded at the full-text review stage of the SLR of interventional non-RCTs of ertugliflozin

Reference	Rationale for exclusion
Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes, Obesity and Metabolism. 2015 Aug 1;17(8):805-8.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Kocyigit D, Murat Gurses K, Ulvi Yalcin M, Tokgozoglu L. Anti-hyperglycemic agents for the treatment of type 2 diabetes mellitus: role in cardioprotection during the last decade. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2017 Mar 1;17(1):19-31.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Liu J, Eldor R, Dagogo-Jack S, Amorin G, Johnson J, Liao Y, Huyck S, Golm G, Terra SG, Mancuso JP, Engel SS. Safety and efficacy of ertugliflozin after 52 weeks in subjects with T2DM inadequately controlled on metformin and sitagliptin: results from the extension phase of the VERTIS SITA2 Trial. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A35.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Study of safety and efficacy of PF-04971729 in patients with type 2 diabetes and hypertension. Accessed at https://clinicaltrials.gov/ct2/show/NCT01096667. Last accessed: 2nd November 2017.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Pratley RE, Raji A, Eldor R, Sunga S, Qiu Y, Johnson J, Huyck S, Golm G, Terra SG, Mancuso JP, Engel SS. Safety and efficacy of ertugliflozin plus sitagliptin vs. either treatment alone after 52 weeks in subjects with T2DM inadequately controlled on metformin: VERTIS FACTORIAL trial extension. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A34.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Rosenstock J, Frias J, Pall D, Charbonnel B, Pascu R, Saur D, Darekar A, Shi H, Huyck SB, Lauring B, Terra SG. Effect of ertugliflozin on glycemic control, body weight, blood pressure (BP), and bone mineral density (BMD) in T2DM inadequately controlled with metformin monotherapy: VERTIS MET Trial. Conference: American Diabetes Association - 77th Scientific Sessions. Diabetes. 2017 Jun 1;66:A311.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Sahasrabudhe V, Terra SG, Fountaine RJ, Hickman A, Saur D, Matschke K, Shi H, O'Gorman M, Chakravarthy MV, Cutler DL. The effect of renal impairment on the pharmacokinetics and pharmacodynamics of ertugliflozin in subjects with type 2 diabetes mellitus. Conference: European Association for the Study of Diabetes – 51st Annual Meeting. Diabetologia. 2015;1:S359	Did not include adult patients with uncontrolled type 2 diabetes
Sahasrabudhe V, Terra SG, Hickman A, Saur D, Shi H, O'gorman M, Zhou Z, Cutler DL. The effect of renal impairment on the pharmacokinetics and pharmacodynamics of ertugliflozin in subjects with type 2 diabetes mellitus. The Journal of Clinical Pharmacology. 2017 Nov 1;57(11):1432-43.	Did not include adult patients with uncontrolled type 2 diabetes

Abbreviations: SLR, systematic literature review

Table D.15. Electronic database records excluded at the full-text review stage of the second SLR update of interventional non-RCTs of ertugliflozin

Reference	Reason for Exclusion
Aronson R, Frias J, Goldman A, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes, Obesity & Metabolism 2018;08:08.	Does not report on an interventional non-RCT of ertugliflozin in the English language

Reference	Reason for Exclusion
Fediuk DJ, Sweeney K, Zhou S, et al. Population pharmacokinetic (POPPK) model for ertugliflozin in healthy subjects and type 2 diabetes mellitus (T2DM) patients. Journal of Pharmacokinetics and Pharmacodynamics 2017;44 (1 Supplement 1):S25.	Does not report on an interventional non-RCT of ertugliflozin in the English language
Sahasrabudhe V, Terra SG, Hickman A, et al. The Effect of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Ertugliflozin in Subjects With Type 2 Diabetes Mellitus. Journal of Clinical Pharmacology 2017;57:1432-1443.	Did not include adult patients with uncontrolled type 2 diabetes

Summary of trials used for indirect or mixed treatment comparisons

Table D.16 provides a summary of the arms, sample size and length of the selected studies for the triple therapy of interest (5). In addition, the table provides a summary of the previous treatment of the subjects, including whether they had been on previous AHA.
Table D.17 presents the RCTs included through the SLR whereas Table D.18 shows the outcomes reported for each intervention.

Triple therapy

Limited variability was observed in baseline characteristics of included studies. All studies reported HbA1c at baseline, which varied from a low of 7.9% to a high of 8.5%. All studies report age and gender, which varied slightly between studies. Baseline weight (kgs) and FPG was reported across studies. There were missing baseline measurements for BMI and SBP. Regarding outcomes, all studies reported HbA1c change, weight change, HbA1c in target and NSHE. Jabbour 2014 did not report SBP and Bailey 2016 did not report GTIs at the 24-26 week time point. Though the available data was limited, included studies for triple therapy were similar (or at least as similar as included studies among monotherapy and dual therapy) in terms of age, percent female, starting HbA1c BMI, SBP and FPG.

Table D.16: Baseline characteristics of all included studies across of line of therapies

Study	Arms	N	Age (years)	Duration of disease (years)	% Female	HbA1c (%)	Weight (kg)	BMI (kg/m2)	SBP (mmHg)	DBP (mmHg)	FPG (mg/dL)
Triple Therapy studies included											
Dagogo et al., 2018 [9]	MET + SITA + PBO	153	58.3	9.4	35%	8.0	86.4	30.3	130	NR	170
	MET + SITA + ERTU5	156	59.2	9.9	48%	8.1	87.6	31.2	132	NR	168
	MET + SITA + ERTU15	153	59.7	9.2	46%	8.0	86.6	30.9	132	NR	172
	Total/Avg	462	59.1	9.5	43%	8.0	86.9	30.8	131	NR	170
Jabbour et al., 2014 [11]	MET + SITA + PBO	113	56.6	6.5	41%	7.9	94.2	NR	NR	NR	165
	MET + SITA + DAPA10	113	56.8	6.7	41%	7.8	94.0	NR	NR	NR	167
	Total/Avg	226	56.7	6.6	41%	7.9	94.1	NR	NR	NR	166
Mathieu et al., 2015 [13]	MET + SAXA + PBO	129	55.0	8.0	53%	8.2	88.2	32.2	NR	NR	177
	MET + SAXA + DAPA10	146	55.2	7.2	56%	8.2	85.8	31.2	NR	NR	179
	Total/Avg	275	55.1	7.6	54%	8.2	87.0	31.7	NR	NR	178
Rodbard et al., 2016 [15]	MET + SITA + PBO	94	57.5	10.1	48%	8.4	90.0	31.7	NR	NR	180
	MET + SITA + CANA	99	57.4	9.8	38%	8.5	94.1	32.3	NR	NR	186
	Total/Avg	193	57.5	10.0	43%	8.5	92.1	32.0	NR	NR	183
Softeland et al., 2017 [17]	MET + LINA + PBO	108	55.9	NR	44%	8.0	82.3	29.6	130	NR	164
	MET + LINA + EMPA10	109	54.3	NR	39%	8.0	88.4	31.2	130	NR	167
	MET + LINA + EMPA25	110	55.4	NR	35%	8.0	84.4	29.9	131	NR	169
	Total/Avg	217	55.1	NA	42%	8.0	85.4	30.4	130	NR	166

Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin; NR, not reported; NA, not available

Table D.17: RCTs in T2DM identified through SLR and included in the NMA for monotherapy and combination therapy

Trial Identifier	Previous treatment	Intervention (n)	Study duration (weeks)
Triple therapy – SGLT-2i on a background of MET + DPP-4i			
Jabbour et al., 2014 [11]	MET ≥1500 and 10 week dose-stabilization of SITA100. 52% of subjects were on MET + SITA100 prior to study commencement	MET + SITA + PBO (113) MET + SITA + DAPA10 (113)	24
Dagogo et al., 2018 [9]	MET ≥1500 for ≥12 weeks, entered in to 16 week run in phase with LINA5 prior to randomization	MET + SITA + PBO (153) MET + SITA + ERTU5 (156) MET + SITA + ERTU15 (153)	26
Mathieu et al., 2015 [13]	MET ≥1500 for ≥8 weeks or MET ≥1500 and DPP-4i inhibitor ≥8 weeks	MET + SAXA100 + PBO (129) MET + SAXA100 + DAPA10 (145)	24
Rodbard et al., 2016 [15]	MET ≥1500 and SITA100 for ≥12 weeks	MET + SITA + PBO (94) MET + SITA + CANA (99)	26
Softeland et al., 2017 [17]	MET ≥1500 for ≥12 weeks	MET + LINA5 + PBO (108) MET + LINA5 + EMPA10 (109) MET + LINA5 + EMPA25 (110)	24

Abbreviations: SGLT-2i, sodium glucose co-transporter 2 inhibitor; DPP-4i, dipeptydil peptidase-4 inhibitor; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin

Methods and outcomes of studies included in indirect or mixed treatment comparison

Table D.16 displays the outcomes reported in the included studies for each intervention and by line of therapy according to those specified in the scope (see section B.1.1 of Document B).

Table D.18: Outcomes reported by included studies informing the NMA in triple therapy

Reference	Arms	N	HbA1c change (%)	Weight change (kg)	SBP (mm/hg)	DBP (mm/hg)	HbA1c in target (%)	NSHE (%)	SHE (%)	UTIs (%)	GTIs (%)	AEs (%)
Triple therapy – background therapy MET												
Dagogo 2018 [9]	SITA+ERTU5	156	-0.78	-3.4	-3.8	/	32%	4%	0.0%	3%	3%	42%
	SITA+ERTU15	153	-0.86	-3.0	-4.8	/	40%	2%	0.0%	5%	2%	44%
	SITA+PBO	153	-0.09	-1.3	-0.9	/	17%	3%	0.6%	2%	0%	48%
Jabbour 2014 [11]	SITA+PBO	113	0.00	-0.4	NR	/	12%	4%	0.0%	10%	17%	NR
	SITA+DAPA10	113	-0.40	-2.5	NR	/	22%	5%	0.7%	8%	1%	NR
Mathieu 2015 [13]	SAXA+PBO	129	-0.10	-0.4^	2.0**	/	13%	0%	NR	6%	1%	59%
	SAXA+DAPA10	146	-0.82	-1.9^	-1.9**	/	37%	0%	NR	5%	5%	56%
Rodbard 2016 [15]	SITA+PBO	94	-0.01	-1.6^	0.1^	/	12%	2%	0.0%	2%	1%	40%
	SITA+CANA	99	-0.91	-3.4^	-5.8^	/	32%	4%	0.0%	2%	6%	44%
Softeland 2017 [17]	LINA+PBO	108	0.14	-0.3^	-1.7	/	17%	1%	0.0%	7%	2%	68%
	LINA+EMPA10	109	-0.65	-3.1^	-3.0	/	37%	0%	0.0%	7%	2%	55%
	LINA+EMPA25	110	-0.56	-2.5^	-4.3	/	33%	3%	0.0%	4%	5%	52%

Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; NSHE, non-severe hypoglycaemic event; SHE, severe hypoglycaemic event; UTI, urinary tract infection; GTI, genital tract infections; AE, adverse event; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin; NR, not reported
*Included in sensitivity analysis only, ^ Data sourced from clinicaltrials.gov ** SE not able to be imputed, therefore the study is unable to be included in the network

Methods of analysis of studies included in the indirect or mixed treatment comparison

Network meta-analysis methodology

Feasibility assessment

Prior to analysis, a full assessment of the feasibility of the NMA was performed. The key steps of the feasibility were [51]:

1. The assessment of the existence of a network of interlinked studies (for each outcome of interest in each population group) to allow the comparisons of interest
2. The assessment of any differences in study and patient characteristics across comparisons that are likely or known modifiers of the relative treatment effects of the interventions of interest.

Based on review of published studies and previous HTA submissions, the list of patient and disease characteristics at baseline that may play a role as effect modifiers included:

- Patient gender
- Patient age
- Baseline Weight/BMI
- Baseline HbA1c
- Baseline SBP

The distribution of the abovementioned effect modifiers was examined using graphs, presented in Appendix O.

Modelling approach and assumptions

The analysis was conducted in a Bayesian framework [52]. Some of the advantages of using Bayesian methods over classical frequentist methods are listed in section 16.8.1 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [53]. The appropriate statistical models were used based on the nature of the outcomes:

- Dichotomous outcomes (e.g. AEs): logit link with binomial likelihood distribution;
- Continuous outcomes (e.g. change from baseline): identity link and a normal likelihood;

The analysis was conducted using WinBUGS software package [54], with the selection on models based on suggestions per the NICE Decision Support Unit [55]. The methodology also followed guidance from the ISPOR Task Force on Indirect Treatment Comparisons [56-58].

Meta-regression was considered to adjust for differences in key study level effect modifiers (i.e. baseline HbA1c) [27]. However, due to data limitations that prevented convergence of networks, it was not possible to control for differences in effect modifiers via meta-regression.

Assessment of convergence

Convergence was assessed by visual inspection of the trace and density plots and the autocorrelation as well as reviewing the credible intervals. A burn-in of at least 50,000 simulations was discarded and three chains were used. Thinning of the chains by 5 with a burn-in of 100,000 and a further 200,000 simulations were required to achieve convergence in some cases. All results presented are based on a further sample of at least 100,000 simulations or until convergence was achieved. Lastly, we observed the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation. This should be no more than 5% of the posterior standard deviation of the parameters of interest [59].

Assessment of model fit and model selection

Both results from the fixed and random effect models are presented in Document B. However, one model was chosen to make inference in the base case and presented in the results Section 2.9 of Document B. The Deviance Information Criterion (DIC) was reported and the total residual deviance to choose the appropriate model for the data as well. The DIC provides a measure of model fit that penalizes model complexity – lower values of the DIC suggest a more parsimonious model; however, differences of less than 3 are not considered to be important [60]. A FEM was selected unless there was a significant difference in the DIC (>3) for the REM based on recent best practice recommendations.[52]

To check formally whether a model's fit is satisfactory, an absolute measure of fit was considered: the total residual deviance. The value of total residual deviance was compared to the number of independent data points to check if the model fit could be improved. As a rule of the thumb, each data point should have contributed about 1 to the posterior mean deviance, which indicates that a model that is good predictor

Missing data

Data on missing standard errors (SEs) associated with the change in continuous outcomes from baseline were imputed using methods described in section 16.1.3.2. of the "Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0" [61]. The following equation was used:

$$SE_{change} = \frac{\sqrt{SD^2_{baseline} + SD^2_{final} - in \times CorrlSD_{baseline} \times SD_{final})}}{\sqrt{sample\ size}}$$

In cases where SD_{final} was not available, $SD_{baseline}$ in place of SD_{final} was used, as described by Cochrane Handbook [61]. As the correlation was not reported in any trials, 0.5 was used in the formula above; this has been described as a conservative assumption [55]. Standard deviations (SDs) were converted to SEs using the formula: $SE = SD/\sqrt{sample\ size}$. 95% confidence intervals (CIs) were converted to standard errors using the formula.

$$SE = \frac{95\%\ CI\ upper - 95\%\ CI\ lower}{2x(1.96)}$$

The following calculation was used to calculate standard errors from p-values:

$$SE = \frac{|\overline{X}|}{\phi^{-E}\left(1 - \frac{p}{2}\right)}$$

Where,

$\overline{X} = Mean\ arm\ level\ change\ from\ baseline\ or\ mean\ between\ treatment\ difference\ in\ change\ from\ baseline$

$p = The\ p - value\ reported\ in\ the\ trial$

$\phi^{-=}$ represents the inverse normal distribution function

Continuity correction

In cases where there were 0 events reported for an event, a continuity correction was carried out where 0.5 added across all arms [53].

Inconsistency

Inconsistency was tested by performing a series of Bucher tests [62] to test for conflicts between direct and indirect evidence. Where significant inconsistency ($p<0.05$) was identified, the studies identified as causing the potential inconsistency were investigated further through sensitivity analyses to determine whether specific effect modifiers could be identified, and if required, these studies were removed in sensitivity analyses and the results reported.

Reporting results

The analyses conducted consisted of both continuous and binary outcomes. The results corresponding to binary outcomes HbA1c in target, NSHE, SHE, UTIs and GTIs were represented by the median odds ratios (OR). To be consistent, continuous values were reported using the median difference from baseline. The results display show tables of the median differences and OR for binary and continuous outcomes, respectively, with associated 95% credible intervals (95% CrI) for the selected base case scenario (whether random effects or fixed effects). In Bayesian statistics, a credible interval is an interval in the domain of a posterior probability distribution or predictive distribution used for interval estimation and can be considered as comparable to confidence intervals from the frequentist approach [63]. Significant results, defined as a credible interval not including 0 for continuous outcomes and 1 for OR, were highlighted in bold. Results for the non-selected model and DIC can be found in Appendix P.

Programming language

The analysis was conducted using WinBUGS software package [54]. WinBUGS is a Bayesian analysis software that, through the use of Monte Carlo Markov chains, calculates posterior distributions for the parameters of interest, given likelihood functions derived from data and prior probabilities. The Monte Carlo Markov Chain simulation begins with an approximate distribution and, if the model is a good enough fit to the data, the distribution converges to the true distribution. Some of the advantages of using Bayesian methods over classical frequentist methods are listed in section 16.8.1 of the “Cochrane Handbook for Systematic Reviews of Interventions”.

D.1.2 Participant flow in the relevant randomised control trials

Participant flow through Phase A (weeks 0-26) of the VERTIS SITA 2 study is summarised in Figure D.6. Participant flow through Phase A and B (weeks 0-52) of the VERTIS SITA 2 study is summarised in Figure D.7.

Figure D.6: Subject disposition for phase A of the VERTIS SITA2 study

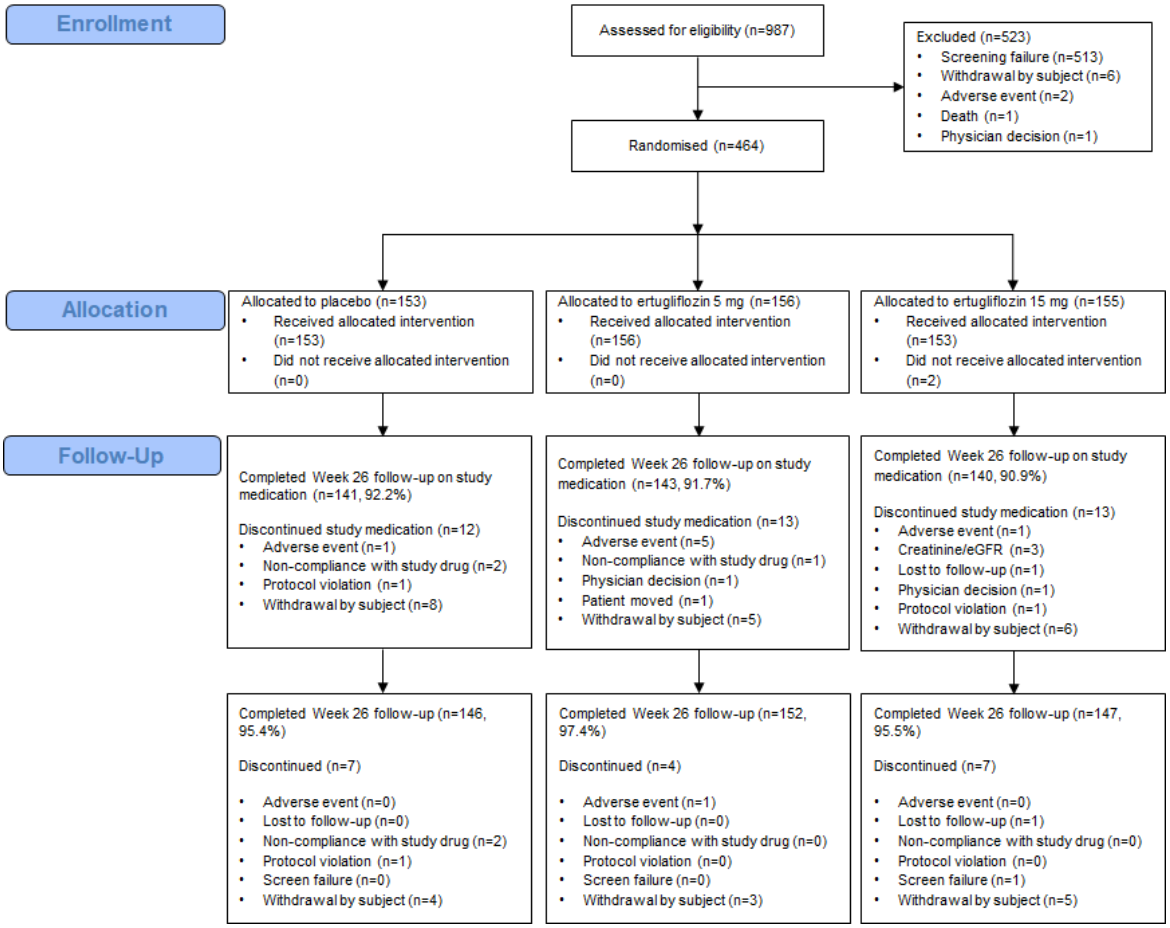
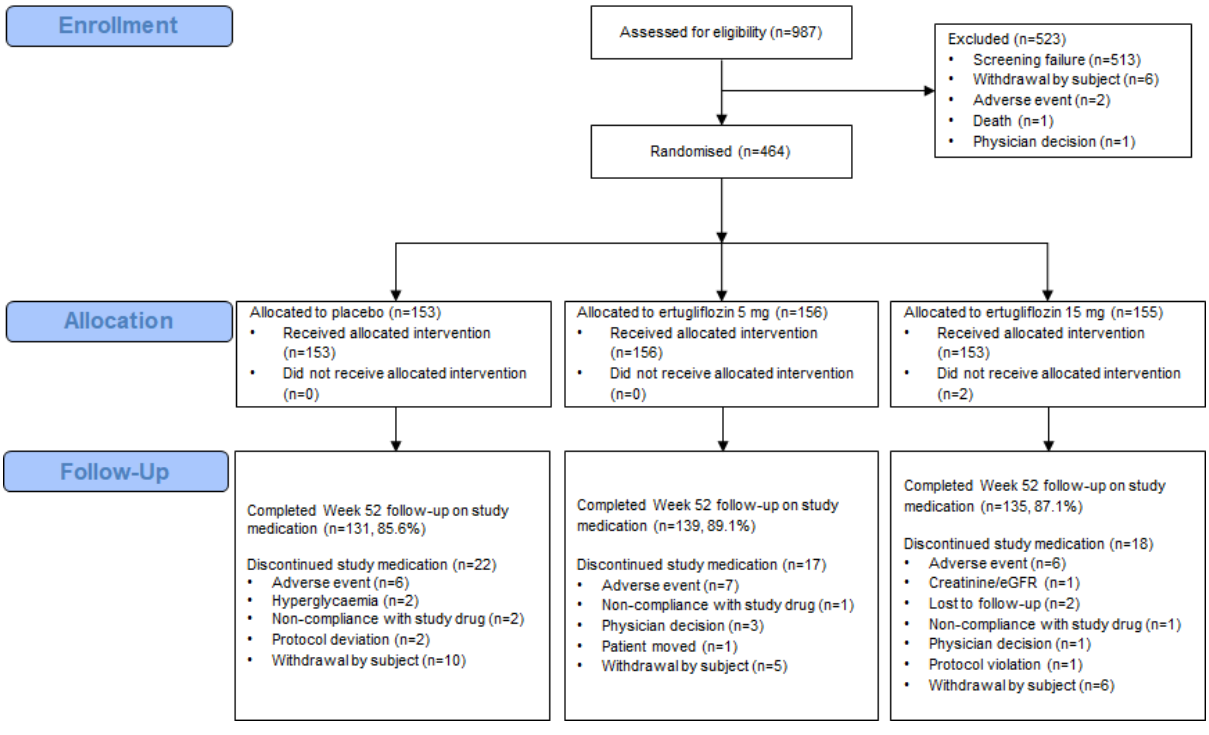


Figure D.7: Subject disposition for phase A + B of the VERTIS SITA2 study



D.1.3 Quality assessment for each trial

Table D.19 summarises the quality assessment performed for each of the RCTs identified through the SLR for the triple therapy indication relevant to this submission.

Triple therapy

There were 4 published RCTs, in addition to the Merck CSR 006, selected for review in triple therapy; all were multinational and were conducted after 2014. Three of the studies had two arms and two had three arms. There were some differences in trial design that made comparisons in this population difficult. In particular, Rodbard 2016 had dose titration of canagliflozin. In addition to metformin, study participants also had sitagliptin 100 mg (3), saxagliptin (1) or linagliptin (1) as the DPP-4i background therapy.

FAS analysis method requiring only baseline measurement of HbA1c was utilised by one study; two studies used FAS and required at least one on-treatment measurement. Rodbard 2016 reported statistical evaluation by mITT. Mathieu 2015 did not describe analysis population.

The included studies for triple therapy introduced heterogeneity into the analysis given differences in treatment approaches. Specifically, the only included canagliflozin study had titration (as such, patients were neither high nor low dose) and the SGLT-2 were used on top of different DPP-4i. Consequently, data for this population could not support investigations among all doses of SGLT-2i and could not support investigations into the potential impact of differences in underlying DPP-4i therapy (the networks had to assume no difference due to variations in DPP-4i).

Table D.17: Quality assessment of RCTs relevant to this submission

Study ID and publications	Was the randomisation method 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?	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?	Did the authors of the study publication declare any conflicts of interest?
Triple therapy – ERTU studies								
Dagogo et al., 2018 [9]	Yes - centrally randomised with a computer-generated randomisation schedule using an interactive voice and web response system	Yes - centrally randomised	Yes - all have T2DM and HbA1c 7.0-10.5%. Demographic and baseline characteristics were similar across treatment groups	Yes - patients, investigators, and the sponsor were blinded to treatment allocation. Ertugliflozin and matching placebos were packaged identically so that blinding/masking was maintained	No - similar percentages discontinued in each of the arms. Missing data were handled using the LOCF method	No - all stated objectives were reported	No - the primary population for efficacy analyses was the Full Analysis Set (FAS), which included all randomised subjects who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline)	Yes - some of the authors work for Merck & Co. Inc., who developed the drug under investigation
Triple therapy – studies not investigating ERTU								
Jabbour 2014 [11]	NR - reports the study was randomised but no description of how this was achieved	NR - whether allocation was concealed is not reported	Yes - all have T2DM and HbA1c ≥7.0-≤10.0%. Demographic and baseline characteristics including age, race, weight, duration of diabetes, FPG	Yes - study described as double blind	No - the percentages of discontinuation for the placebo and dapagliflozin arms were 89.8% and 92.4% respectively	No - all stated objectives were reported	No - the FAS was used, defined as all randomised individuals who took at least one dose of double-blind study medication, had a non-missing baseline value	Yes - some of the authors work for AstraZeneca, who co-developed the drug under investigation

Study ID and publications	Was the randomisation method 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?	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?	Did the authors of the study publication declare any conflicts of interest?
			and SBP were similar across treatment groups				and ≥1 post-baseline efficacy value for ≥1 efficacy variable	
Mathieu 2015 [13]	Yes - randomly assigned by an interactive voice response system in a centrally blocked 1:1 ratio	Yes - centrally randomised	Yes - all have T2DM and HbA1c 7.5-11.5%. Demographic and baseline characteristics including age, race, BMI, duration of diabetes, FPG, PPG and eGFR were similar across treatment groups	Yes - study described as double blind	No - the percentages of discontinuation for the placebo and dapagliflozin arms were 95.6% and 92.5% respectively	No - all stated objectives were reported	NR - no mention of analysis population	Yes - some of the authors work for AstraZeneca or Bristol-Myers Squibb, who co-developed the drug under investigation
Rodbard 2016 [15]	Yes - randomly assigned using a computer-generated randomisation schedule prepared by or under supervision of the sponsor prior to initiation of the study	Unclear – stated only that the randomisation schedule was prepared by or under supervision of the sponsor	Yes - all have T2DM and HbA1c ≥7.5-≤10.5%. Demographic and baseline characteristics including age, race, weight, duration of diabetes, FPG and BMI were similar across treatment groups	Yes - study described as double blind	Yes - a greater percentage of patients in the canagliflozin group discontinued the study compared with patients in the placebo group (89.7% vs. 76.4%). Missing data were handled using	Yes - vital signs measurements are mentioned in the methods and not reported in the results	No - modified intention-to-treat (mITT) analysis set, defined as all patients who were randomised and received ≥1 dose of double-blind study drug	Yes - some of the authors work for Janssen Research & Development, who developed the drug under investigation

Study ID and publications	Was the randomisation method 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?	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?	Did the authors of the study publication declare any conflicts of interest?
					the LOCF method for missing lipid data, but it is unclear for other outcomes			
Softeland 2017 [17]	Yes - randomly assigned by a third-party interactive voice response system stratified by HbA1c	Yes - third-party interactive voice response system	Yes - all have T2DM and HbA1c ≥8.0-≤10.5%. Demographic and baseline characteristics including age, race, weight, time since diagnosis of diabetes, FPG, SBP, DBP, eGFR and BMI were similar across treatment groups	Yes - study described as double blind	No - the percentages of discontinuation for the placebo, empagliflozin 10 mg and empagliflozin 25 mg arms were 95.5%, 92.0% and 95.5% respectively	No - all stated objectives were reported	No - efficacy was analysed in the FAS, defined as all patients who received one or more doses of study drug during the double-blind period, and who had an HbA1c measurement at baseline (prior to randomisation to double-blind treatment) and at least one on-treatment HbA1c measurement during the double-blind period	Yes - some of the authors work for Boehringer Ingelheim Ltd., who developed the drug under investigation

Appendix E: Subgroup analysis

PRE-DEFINED SUBGROUP ANALYSIS

Subgroup analysis results for change from baseline in HbA1c at week 26 by baseline HbA1c categories and gender, excluding data after initiation of glycaemic rescue therapy, are presented in Table E.1 and Figure E.1. A post-hoc subgroup analysis for gender was included (Figure E.1) because there was a higher proportion of males in the placebo group (65.4%) compared with the ertugliflozin 5 mg group (51.9%) and the 15 mg group (53.6%). LS mean reductions from baseline in HbA1c were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group across the HbA1c and gender subgroup categories. The improvements in HbA1c in the ertugliflozin groups relative to the placebo group were numerically greater in the subgroup of subjects with a baseline HbA1c level above versus at or below the median HbA1c level (7.9%). In the ertugliflozin 5 mg and 15 mg groups, mean reductions from baseline in HbA1c at week 26 were numerically greater in male than in female subjects.

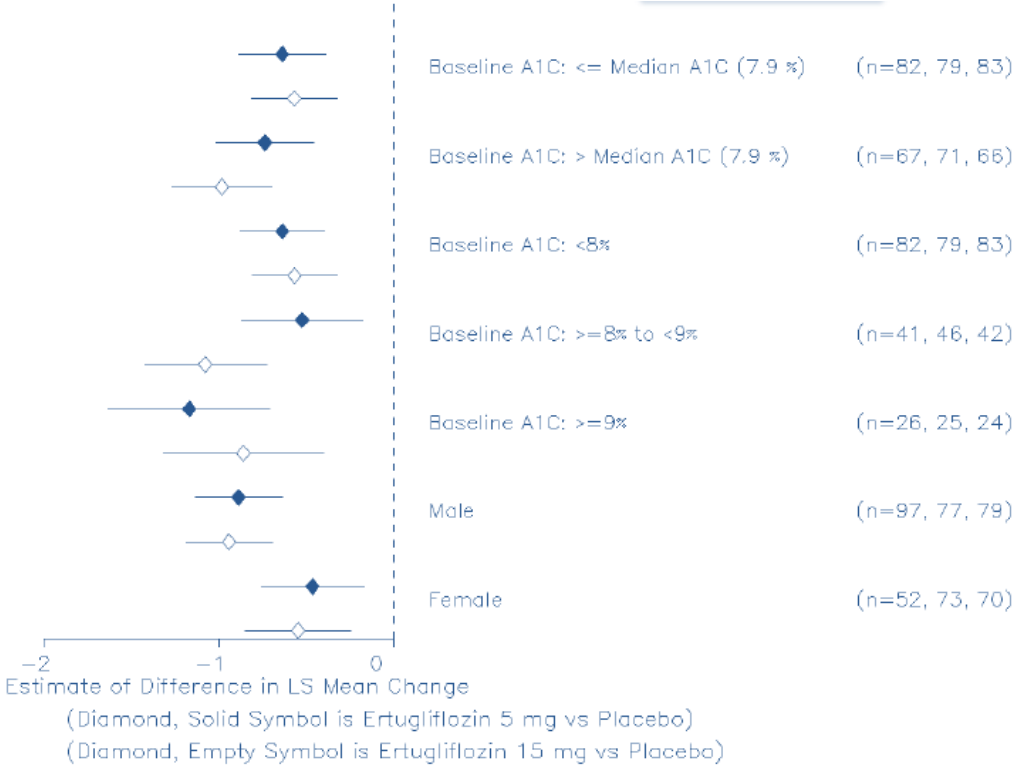
As stated in Section 2.7, results from the subgroup analyses should be considered with caution: sample sizes within subgroups are smaller than the overall trial sample size, reducing precision of the estimate, and the subgroup subject sample does not represent a randomised subset of the study population.

Table E.1 HbA1c (%) change from baseline at week 26 by subgroup (Repeated Measures Analysis of Covariance; FAS: Excluding Rescue Approach)

Subgroups		Baseline		Week 26		Differences in LS means (95% CI)
		N	Mean (SD)	N	Mean (SD)	
Gender						
Male	PBO	97	8.04 (0.91)	77	7.75 (1.08)	
	ERT 5 mg	77	8.00 (0.93)	69	7.12 (0.80)	- 0.89 (-1.14, -0.64)
	ERT 15 mg	79	8.07 (0.88)	74	7.13 (0.92)	- 0.94 (-1.19, -0.70)
Female	PBO	52	8.02 (1.01)	41	7.59 (0.77)	
	ERT 5 mg	73	8.13 (0.79)	68	7.35 (0.64)	- 0.47 (-0.77, -0.17)
	ERT 15 mg	70	7.93 (0.78)	63	7.21 (0.69)	- 0.54 (-0.85, -0.24)
≤ Median HbA1c (7.9%)						
PBO		82	7.37 (0.36)	75	7.49 (0.80)	
ERT 5 mg		79	7.43 (0.36)	74	6.95 (0.58)	-0.64 (-0.89, -0.40)
ERT 15 mg		83	7.38 (0.37)	74	6.99 (0.69)	-0.57 (-0.82, -0.32)
> Median HbA1c (7.9%)						
PBO		67	8.84 (0.78)	43	8.03 (1.17)	
ERT 5 mg		71	8.77 (0.69)	63	7.57 (0.76)	-0.74 (-1.02, -0.46)
ERT 15 mg		66	8.80 (0.54)	63	7.38 (0.91)	-0.98 (-1.27, -0.70)
Subgroup: Baseline HbA1c levels						

Subgroups	Baseline		Week 26		Differences in LS means (95% CI)
	N	Mean (SD)	N	Mean (SD)	
< 8%					
PBO	82	7.37 (0.36)	75	7.49 (0.80)	
ERT 5 mg	79	7.43 (0.36)	74	6.95 (0.58)	-0.64 (-0.88, -0.40)
ERT 15 mg	83	7.38 (0.37)	74	6.99 (0.69)	-0.57 (-0.81, -0.33)
≥ 8% to < 9%					
PBO	41	8.30 (0.23)	29	7.72 (0.96)	
ERT 5 mg	46	8.33 (0.26)	41	7.46 (0.80)	-0.53 (-0.87, -0.18)
ERT 15 mg	42	8.46 (0.27)	39	7.02 (0.53)	-1.08 (-1.43, -0.73)
≥ 9%					
PBO	26	9.69 (0.54)	14	8.69 (1.33)	
ERT 5 mg	25	9.58 (0.48)	22	7.77 (0.62)	-1.17 (-1.63, -0.71)
ERT 15 mg	24	9.38 (0.34)	24	7.97 (1.09)	-0.86 (-1.3_2, -0.40)

Figure E.1 Forest plot of HbA1c (%) change from baseline at week 26 by subgroup
(Repeated Measures Analysis of Covariance; FAS: Excluding Rescue Approach)



Abbreviations: LS=Least Squares
(n=n1, n2, n3): n1 = the number of subjects in Placebo group
n2 = the number of subjects in Ertugliflozin 5 mg group
n3 = the number of subjects in Ertugliflozin 15 mg group

POST-HOC SUBGROUP ANALYSES

The objective was to estimate the treatment difference between ertugliflozin 5 mg and ertugliflozin 15 mg versus placebo on:

- the proportion of subjects reaching target (HbA1c <7.0%),
- the change from baseline in systolic blood pressure (mmHg) at week 26,

for the overall population, and for various subgroups defined on baseline values or the use of antihypertensive drugs at baseline. All the analyses approaches used are in line with the Phase A CSR (please refer to Document B section B.3.4). The Full Analysis Set (FAS) population was the primary analysis population for most efficacy endpoints. The key data analysed and reported below are efficacy data from the 26-week Phase A CSR.

1.a Subgroup analyses and effect of baseline factors

The consistency of the treatment effect at week 26 was assessed for various subgroups. For proportion of subjects reaching target (HbA1c<7.0%), the following subgroup was used: baseline HbA1c levels (<8.0%, ≥8.0% to <9%, and ≥9%).

For the change from baseline in SBP (mmHg), the following subgroups were used:

- Baseline sitting SBP (<130 mmHg, ≥130 mmHg to <140 mmHg, and ≥140 mmHg),
- Beta-blocker drug at baseline (yes/no),
- Calcium-channel drug at baseline (yes/no),
- Diuretic drug at baseline (yes/no).

In accordance with the CSR approach, for the subgroups that had only 2 categories, if the sample size was not at least 20 in all treatment groups and within each subgroup category, then that subgroup analysis was not performed. For the 3-level subgroups, if the sample size was not at least 20 in all treatment groups within a certain category, then that category was combined with another category. All 3-level subgroups considered in this report satisfied the condition of at least 20 subjects in all of the treatment groups in each subgroup category.

For the change from baseline in SBP, the consistency of the treatment effect was assessed with a repeated measures ANCOVA (RMANCOVA) method. For the proportion of subjects reaching target (HbA1c<7.0%), a logistic regression analysis with multiple imputation procedure based on cLDA prediction modeling was performed within each subgroup level.

1.b Subgroup analyses results

Results from the subgroup analyses should be considered with caution: sample sizes within subgroups are smaller than the overall trial sample size (especially for the three antihypertensive drug subgroups), reducing precision of the estimate (wider confidence

intervals), and the subgroup subject sample does not represent a randomised subset of the study population. Also there is a regression to the mean phenomenon when analysing the change from baseline in HbA1c (and systolic blood pressure) by categories of baseline HbA1c (and systolic blood pressure): extreme values appear to get closer to the mean over time, regardless of any antihypertensive treatment.

Proportion of subjects reaching target (HbA1c<7.0%)

Table E.2 shows the results of the subgroup analysis on the proportion of subjects reaching target at week 26 using the logistic regression approach with multiple imputation in the FAS population excluding rescue approach within each subgroup level. The model-based odds of reaching target at week 26, using multiple imputation for subjects with missing week 26 data, were greater in both ertugliflozin groups compared to the placebo group for each of the three baseline HbA1c categories.

Table E.2 Analysis of subjects with HbA1c <7.0% (<53 mmol/mol) at week 26 by Subgroups Logistic Regression using Multiple Imputation; FAS, excluding rescue approach

P006a[a]			Adjusted Odds Ratio Relative to Placebo[b]	
Treatment	N	Number (%) of Subjects With HbA1c <7.0% (Raw proportions)	Point Estimate	95% CI
Subgroup : Baseline HbA1c levels				
<8.0%				
Placebo	83	19 (22.9)		
Ertugliflozin 5 mg	82	40 (48.8)	4.62	(2.23, 9.58)
Ertugliflozin 15 mg	84	40 (47.6)	4.20	(2.05, 8.59)
>=8.0% to <9.0%				
Placebo	43	6 (14.0)		
Ertugliflozin 5 mg	47	8 (17.0)	1.57	(0.48, 5.12)
Ertugliflozin 15 mg	44	18 (40.9)	5.46	(1.81, 16.45)
>=9.0%				
Placebo	26	1 (3.8)		
Ertugliflozin 5 mg	26	2 (7.7)	3.22	(0.09, 109.82)
Ertugliflozin 15 mg	24	3 (12.5)	1.77	(0.12, 27.06)

a: Database Lock Date: 07JAN2016

b: Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), covariates for baseline HbA1c and baseline eGFR (continuous).

Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Change from baseline in sitting SBP (mmHg)

Table E.3**Error! Reference source not found.** shows the results of the subgroup analysis on the change from baseline in sitting SBP at week 26 using the RMANCOVA approach. The improvements in SBP in the ertugliflozin groups relative to the placebo group were numerically greater in the subgroup of subjects with a baseline SBP ≥ 140 mmHg versus those with a baseline between 130 and 140 mmHg. Confidence intervals are wide and mostly overlapping for the different subgroup categories.

The results for the subgroup of subjects on beta-blocker drugs at baseline, calcium-channel blocker drugs at baseline and diuretic drugs at baseline are also displayed in Table E.3. The number of subjects using calcium-channel blockers or diuretics drugs at baseline is very small, and these subgroups results should be interpreted with caution. Confidence intervals are wide and mostly overlapping for the different subgroup categories.

Table E.3 Analysis of change from baseline in sitting SBP (mmHg) at week 26 by subgroups; FAS, excluding rescue approach

Study: P006a[a]	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	LS Mean (95%-CI)[d]	Difference in LS Mean (95 %-CI)[d]
Baseline Sitting Systolic Blood Pressure (mmHg)							
<130 mmHg							
Placebo	74	119.25 (8.80)	60	122.69 (11.38)	74	3.48 (0.90,6.06)	
Ertugliflozin 5 mg	67	120.94 (7.62)	59	120.03 (11.14)	67	-0.81 (-3.42,1.79)	-4.29 (-7.94; -0.65)
Ertugliflozin 15 mg	63	119.36 (7.74)	58	119.40 (10.97)	63	-0.32 (-2.95,2.32)	-3.80 (-7.47; -0.12)
130 mmHg to <140 mmHg							
Placebo	41	134.59 (2.79)	31	131.62 (10.90)	41	-3.38 (-6.92,0.17)	
Ertugliflozin 5 mg	45	134.89 (2.91)	41	130.66 (9.80)	45	-4.00 (-7.14,-0.86)	-0.62 (-5.34; 4.10)
Ertugliflozin 15 mg	45	134.63 (2.60)	39	129.99 (11.23)	45	-4.90 (-8.09,-1.70)	-1.52 (-6.29; 3.25)
140 mmHg and over							
Placebo	35	147.06 (4.73)	31	140.94 (10.55)	35	-5.47 (-9.07,-1.86)	
Ertugliflozin 5 mg	42	147.06 (5.94)	41	137.63 (14.52)	42	-9.49 (-12.65,-6.33)	-4.02 (-8.79; 0.74)

Study: P006a[a]	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	LS Mean (95%-CI)[d]	Difference in LS Mean (95 %-CI)[d]
Ertugliflozin 15 mg	43	147.09 (5.74)	41	135.07 (8.81)	43	-12.13 (-15.29,-8.97)	-6.67 (-11.43; -1.91)
Beta-Blocker Drug							
Beta-Blocker Drug							
Placebo	39	133.42 (12.88)	34	134.21 (13.78)	39	1.51 (-1.88,4.90)	
Ertugliflozin 5 mg	44	135.93 (11.28)	42	131.14 (11.79)	44	-3.99 (-7.11,-0.87)	-5.50 (-10.06; -0.93)
Ertugliflozin 15 mg	39	134.83 (12.72)	36	128.50 (12.20)	39	-5.16 (-8.47,-1.86)	-6.67 (-11.40; -1.95)
No Beta-Blocker Drug							
Placebo	111	128.71 (13.27)	88	127.81 (12.80)	111	-2.03 (-4.14,0.08)	
Ertugliflozin 5 mg	110	130.62 (12.63)	99	127.01 (14.67)	110	-3.98 (-5.98,-1.99)	-1.95 (-4.83; 0.93)
Ertugliflozin 15 mg	112	130.75 (13.06)	102	126.54 (12.51)	112	-4.94 (-6.91,-2.97)	-2.91 (-5.78; -0.04)
Calcium-Channel Blocker Drug							
Calcium-Channel Blocker Drug							
Placebo	29	134.26 (13.14)	23	131.74 (10.56)	29	-1.56 (-5.65,2.53)	
Ertugliflozin 5 mg	28	139.78 (9.43)	28	132.00 (12.03)	28	-5.17 (-8.97,-1.37)	-3.61 (-9.16; 1.94)
Ertugliflozin 15 mg	36	135.37 (14.18)	33	130.98 (11.49)	36	-3.24 (-6.70,0.21)	-1.68 (-7.02; 3.66)
No Calcium-Channel Blocker Drug							
Placebo	121	128.90 (13.17)	99	129.09 (13.90)	121	-0.92 (-2.92,1.07)	
Ertugliflozin 5 mg	126	130.44 (12.45)	113	127.30 (14.30)	126	-3.67 (-5.54,-1.80)	-2.75 (-5.46; -0.04)
Ertugliflozin 15 mg	115	130.69 (12.54)	105	125.82 (12.49)	115	-5.54 (-7.48,-3.60)	-4.61 (-7.37; -1.85)
Diuretic Drug							
Diuretics Drug							
Placebo	36	136.32 (12.44)	32	134.21 (13.55)	36	0.41 (-3.09,3.92)	
Ertugliflozin 5 mg	28	134.12 (12.19)	27	130.96 (11.98)	28	-2.66 (-6.51,1.19)	-3.07 (-8.25; 2.11)
Ertugliflozin 15 mg	30	135.96 (12.24)	28	130.66 (12.65)	30	-3.41 (-7.16,0.34)	-3.82 (-8.94; 1.30)
No Diuretics Drug							
Placebo	114	127.91 (12.96)	90	127.95 (12.94)	114	-1.53 (-3.62,0.57)	

Study: P006a[a]	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	LS Mean (95%-CI)[d]	Difference in LS Mean (95 %-CI)[d]
Ertugliflozin 5 mg	126	131.70 (12.53)	114	127.59 (14.37)	126	-4.27 (-6.13,-2.41)	-2.74 (-5.52; 0.04)
Ertugliflozin 15 mg	121	130.78 (13.09)	110	126.13 (12.25)	121	-5.39 (-7.29,-3.49)	-3.86 (-6.66; -1.06)

a: Database Lock Date: 07JAN2016

b: For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point

c: For Change from Baseline at Week 26, N is the number of subjects in the FAS (i.e., randomised subjects who took at least 1 dose of study medication and had a baseline measurement and at least one assessment after baseline).

d: Obtained from a repeated measures ANCOVA model with terms for prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), covariates for eGFR and baseline systolic blood pressure, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions. Time was fitted as a categorical term. For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once.

CI: Confidence Interval; LS: Least Squares; SD: Standard Deviation.

Appendix F: Adverse reactions

Please find below details on additional adverse reactions reported for the VERTIS CV study.

On March 5th 2018, the U.S. Food and Drug Administration (FDA) disclosed ertugliflozin interim data related to lower limb amputation from the ongoing VERTIS CV trial as part of their assessment of the medicines.

The data posted are as follows:

In the on-treatment analysis (events occurring within two weeks of the last dose of study medication), there were 61 subjects in VERTIS CV with one or more amputations.

- The exposure-adjusted incidence rates for amputation were 4.3, 6.8, and 5.0 per 1,000 patient years for the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg groups, respectively.
- The crude incidence rates were 0.6%, 0.9% and 0.7% for the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg groups, respectively.

In the all post-randomization follow-up analysis (all events regardless of whether patients were on study medication), there were 72 subjects in VERTIS CV with one or more amputations.

- The exposure-adjusted incidence rates for amputation were 4.5, 7.3, and 5.2 per 1,000 patient years for the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively.
- The crude incidence rates were 0.7%, 1.1% and 0.8% for the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg groups, respectively.

It is important to note that these data, which were available to the FDA during the agency's review of ertugliflozin, are interim and not yet final. The U.S. Package Inserts (USPI) for ertugliflozin state that an increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT-2is.

A causal association between ertugliflozin and lower limb amputation has not been definitively established. The prescribing information for ertugliflozin also states that before initiating the products, healthcare providers should consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers.

Please see section B.3.9 of Document B Company evidence submission for a summary of the ertugliflozin safety profile in mono and dual therapy.

Appendix G: Published cost-effectiveness studies

G.1 Identification of studies

A SLR was conducted to identify evidence to support the evaluation of ertugliflozin alone, in combination with metformin alone (metformin + ertugliflozin), and in combination with metformin and sitagliptin (metformin + sitagliptin + ertugliflozin) for type 2 diabetes mellitus patients. A single review was performed to identify relevant studies in T2DM that included published economic evaluations, studies reporting EQ-5D utility values and studies reporting cost and resource use data.

The following electronic databases were searched:

- MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print
- Embase
- The Cochrane Library, specifically:
    - National Health Service Economic Evaluation Database (NHS-EED)
    - Health Technology Assessment Database (HTAD)
- EconLit

MEDLINE, MEDLINE In-Process, MEDLINE EPub Ahead of Print and Embase were searched separately via the Ovid SP platform on May 3rd 2017. The Cochrane Library databases were searched through the Cochrane Library, via the Wiley Online platform on May 3rd 2017. EconLit was searched via the EBSCO platform on May 15th 2017. Congress abstracts presented at major diabetes and health economics congresses were also hand-searched to identify recent economic evidence which may not have been published as full-text journal articles at the time of the database search. Searches were performed on congresses held over the prior three years (2015–2017) as any high-quality studies reported in abstract form before that time were assumed to have been published as full-text articles.

The following congresses were searched in June 2017:

- American Diabetes Association (ADA)
- Diabetes UK
- European Association for the Study of Diabetes (EASD)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – Annual European and Annual International meetings

Searches of the following Health Technology Assessment (HTA) body websites were also conducted in June 2017 to identify relevant HTAs from the last 10 years:

- All Wales Medicines Strategy Group (AWMSG)
- National Centre for Pharmacoeconomics (NCPE)
- NICE
- Scottish Medicines Consortium (SMC)

To supplement the searches, the following databases for health state utility values and cost-effectiveness analyses were searched on June 20th 2017, to ensure no relevant publications were omitted:

- The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center
- The University of Sheffield Health Utilities Database (ScHARRHUD)
- The EQ-5D Publications Database
-

Bibliographies of identified SLRs, meta-analyses and HTA submissions were also hand-searched for any additional, relevant studies for inclusion. The search strategy used for the electronic database searches is presented in Table G.1. The search strategy used for the congress proceedings is presented in Table G.5, for the HTA body websites in Table G.6 for the online databases in Table G.7.

Articles identified from the search were first screened based on their title and abstract (Stage 1) against predefined eligibility criteria (see Table G.8Table). Full-texts of all articles that met the eligibility criteria were then obtained and were subsequently screened for inclusion using the same eligibility criteria (Stage 2). Screening was performed by two independent reviewers and discrepancies were resolved by discussion.

For the health-related quality of life stream of the review only, a publication date limit of 2015 onwards was applied to all hits at the screening stages. The multiple technology appraisal (MTA) investigating canagliflozin, dapagliflozin and empagliflozin monotherapy [47] was published in 2015 and contained a comprehensive list of sources of utility data which had been validated in the assessment group report. This date limit approach therefore enabled identification of utility data published since the MTA which may be more relevant for use in the current economic analysis. Search strategy

Table G.1: Search terms for the MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE ePub Ahead of Print databases (searched via the Ovid SP platform)

Group	#	Searches	Results
Type 2 diabetes mellitus	1	exp *diabetes mellitus, Type 2/	88122
	2	(NIDDM or non insulin dependent diabet$ or noninsulin dependent diabet$ or late onset diabet$ or maturity onset diabet$ or maturity-onset diabet$ or stable diabet$ or slow onset diabet$ or slow-onset diabet$ or adult onset diabet$).tw.	15864
	3	((diabet$ adj2 type II) or (diabet$ adj2 type 2)).tw.	112524
	4	or/1-3	145135
Economic evaluations	5	*Economics/ or exp *Economic evaluation/ or *Cost-benefit analysis/ or *Cost effectiveness analysis/ or *Cost minimization analysis/	22818
	6	(cost adj (utility or consequence or benefit or effectiveness or minimi?ation)).tw.	57549
	7	5 or 6	76286
Cost and resource use	8	"Costs and cost analysis"/	45921
	9	Cost allocation/	2019
	10	Cost control/	21345
	11	Cost savings/	10405
	12	Cost of illness/	22501
	13	Cost sharing/	2259
	14	"Deductibles and coinsurance"/	1605
	15	Medical savings accounts/	520
	16	Health care costs/ or Health care cost/	33612
	17	Direct service costs/	1140
	18	Drug costs/	14264
	19	Employer health costs/	1092
	20	Hospital costs/ or Hospital cost/	9511
	21	Health expenditures/	16533
	22	Capital expenditures/	1995
	23	*Value of life/	1763
	24	exp economics, Hospital/	22454
	25	exp economics, Medical/	14154
	26	Economics, nursing/	3985
	27	Economics, pharmaceutical/	2760
	28	exp "Fees and charges"/	29073
	29	exp Budgets/ or Financial management/	28247

	30	(low adj cost).mp.	39070
	31	(high adj cost).mp.	11077
	32	(health?care adj cost$).mp.	7598
	33	(fiscal or funding or financial or finance).tw.	119523
	34	(cost adj estimate$).mp.	1875
	35	(cost adj variable).mp.	39
	36	(unit adj cost$).mp.	2070
	37	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	236409
	38	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	78748
	39	or/8-38	615623
Utilities	40	(health utilit$ or health state$ utilit$ or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based or cost utility analys?s).tw.	5729
	41	(utilities or disutilit$).tw.	5919
	42	(preference$ adj2 elicit$).tw.	861
	43	(health$ year$ equivalent$ or hye$).tw.	868
	44	(eq-5d$ or EQ 5D or eq5d$ or euroqol$ or euro qol$).tw.	7363
	45	(sf 6$ or sf6$ or short form 6$ or shortform 6$ or shortform6$ or sf six$ or sfsix$ or short form six$ or shortform six$ or shortformsix$).tw.	2687
	46	("HUI" or "HUI2" or "HUI3" or "15D").tw.	2675
	47	("standard gamble" or "SG" or "time trade off" or "time tradeoff" or "TTO").tw.	9578
	48	HALex.tw.	30
	49	(quality of well being or quality of wellbeing or qwb).tw.	432
	50	rosser.tw.	82
	51	(QALY$ or quality adjusted life$ or quality adjusted survival$ or qald$ or qale$ or qtime$).tw.	11113
	52	("discrete choice experiment$" or "discrete choice model$" or "conjoint analys$" or "choice analys$").tw.	1667
	53	or/40-52	39175
Limits (cost and resource use studies)	54	limit 39 to yr="2007 - 2017"	315467
	55	exp united kingdom/ or (united kingdom or UK or England or Scotland or Northern Ireland or Wales or English or Scottish or Northern Irish or Welsh or British or Britain).tw,in.	1703855
	56	54 and 55	46007
Exclusion terms	57	Animals/ not humans/	4358012

	58	(comment or letter or editorial or "case reports" or "clinical trial, phase I").pt.	3278161
	59	(case stud$ or case report$).ti.	245928
	60	or/57-59	7616278
Total	61	7 or 53 or 56	145284
	62	4 and 61	2205
	63	62 not 60	2125

Databases: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present.

Table G.2: Search terms for the Embase database (searched via the Ovid SP platform)

Group	#	Searches	Results
Type 2 diabetes mellitus	1	exp *diabetes mellitus, Type 2/ or exp *non insulin dependent diabetes mellitus/	107685
	2	(NIDDM or non insulin depended diabet$ or noninsulin dependent diabet$ or late onset diabet$ or maturity onset diabet$ or maturity-onset diabet$ or stable diabet$ or slow onset diabet$ or slow-onset diabet$ or adult onset diabet$).tw.	12004
	3	((diabet$ adj2 type II) or (diabet$ adj2 type 2)).tw.	162021
	4	or/1-3	190947
Economic evaluations	5	*Health economics/ or exp *Economic evaluation/ or *Cost-benefit analysis/ or *Cost effectiveness analysis/ or *Cost minimization analysis/	62734
	6	(cost adj (utility or consequence or benefit or effectiveness or minimi?ation)).tw.	76629
	7	5 or 6	115705
Cost and resource use	8	"Costs and cost analysis"/	51398
	9	Cost allocation/	56457
	10	Cost control/	58484
	11	Cost savings/	51768
	12	Cost of illness/	16490
	13	Cost sharing/	56457
	14	"Deductibles and coinsurance"/	56457
	15	Medical savings accounts/	56457
	16	Health care costs/ or Health care cost/	157384
	17	Direct service costs/	157376
	18	Drug costs/	64346
	19	Employer health costs/	157376
	20	Hospital costs/ or Hospital cost/	17188
	21	Health expenditures/ or Health care financing/	140550

	22	Capital expenditures/	157376
	23	*Value of life/	18987
	24	exp economics, Hospital/	721906
	25	exp economics, Medical/	721906
	26	Economics, nursing/	32968
	27	Economics, pharmaceutical/	6474
	28	exp "Fees and charges"/	37738
	29	exp Budgets/ or Financial management/	127335
	30	(low adj cost).mp.	41647
	31	(high adj cost).mp.	13055
	32	(health?care adj cost$).mp.	12127
	33	(fiscal or funding or financial or finance).tw.	139478
	34	(cost adj estimate$).mp.	2611
	35	(cost adj variable).mp.	53
	36	(unit adj cost$).mp.	3378
	37	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	293208
	38	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	100812
	39	or/8-38	1233649
Utilities	40	(health utilit$ or health state$ utilit$ or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based or cost utility analys?s).tw.	8100
	41	(utilities or disutilit$).tw.	8804
	42	(preference$ adj2 elicit$).tw.	1060
	43	(health$ year$ equivalent$ or hye$).tw.	1290
	44	(eq-5d$ or EQ 5D or eq5d$ or euroqol$ or euro qol$).tw.	12445
	45	(sf 6$ or sf6$ or short form 6$ or shortform 6$ or shortform6$ or sf six$ or sfsix$ or short form six$ or shortform six$ or shortformsix$).tw.	3263
	46	("HUI" or "HUI2" or "HUI3" or "15D").tw.	3692
	47	("standard gamble" or "SG" or "time trade off" or "time tradeoff" or "TTO").tw.	12882
	48	HALex.tw.	42
	49	(quality of well being or quality of wellbeing or qwb).tw.	485
	50	rosser.tw.	95
	51	(QALY$ or quality adjusted life$ or quality adjusted survival$ or qald$ or qale$ or qtime$).tw.	17338
	52	("discrete choice experiment$" or "discrete choice model$" or "conjoint analys$" or "choice analys$").tw.	2179
	53	or/40-52	56492

Limits (cost and resource use studies)	54	limit 39 to yr="2007 - 2017"	635284
	55	exp united kingdom/ or (united kingdom or UK or England or Scotland or Northern Ireland or Wales or English or Scottish or Northern Irish or Welsh or British or Britain).tw,in,ad.	2775662
	56	54 and 55	101928
Limits (conference abstracts)	57	"Journal: Conference Abstract".pt.	0
	58	limit 57 to yr="1860 - 2014"	0
Exclusion terms	59	Animals/ not humans/	1270750
	60	(comment or letter or editorial or "case reports" or "clinical trial, phase I").pt.	1493321
	61	(case stud$ or case report$).ti.	296967
	62	or/59-61	3037772
Total	63	7 or 53 or 56	241496
	64	4 and 63	4084
	65	64 not 62	3982
	66	65 and 58	0
	67	65 not 66	3982
	68	remove duplicates from 67	3927

Database: Embase 1974 to 2017 May 02.

Table G.3: Search terms for use in the HTA Database and NHS-EED (searched simultaneously via the Cochrane Library Wiley Online platform)

Group	#	Searches	Results
Type 2 diabetes mellitus	#1	[mh "diabetes mellitus, Type 2" [mj]]	3716
	#2	(NIDDM or "non insulin dependent diabet*" or "noninsulin dependent diabet*" or "late onset diabet*" or "maturity onset diabet*" or "maturity-onset diabet*" or "stable diabet*" or "slow onset diabet*" or "slow-onset diabet*" or "adult onset diabet*"):ti,ab,kw	9589
	#3	((diabet* near/2 "type II") or (diabet* near/2 "type 2")):ti,ab,kw	20186
	#4	#1 or #2 or #3	21344
	#5	#4 in Technology Assessments and Economic Evaluations *HTA* *NHS-EED*	557 *159* *398*

Table G.4: Search terms for use in EconLit (searched via the EBSCO platform)

Group	#	Searches	Results
Type 2 diabetes mellitus	1	NIDDM or "non insulin dependent diabet*" or "noninsulin dependent diabet*" or "late onset diabet*" or "maturity onset diabet*" or "maturity-onset diabet*" or "stable diabet*" or "slow onset diabet*" or "slow-onset diabet*" or "adult onset diabet*"	3
	2	Diabet* N2 "type II"	10

	3	Diabet* N2 "type 2"	66
	4	1 or 2 or 3	79

Table G.5: Search strategy for conference abstract searching

Conference	Link	Search Strategy	Search Terms (Hits)	Relevant Hits
American Diabetes Association (ADA) ○ ADA 2017 ○ ADA 2016	Abstracts: http://diabetes.diabetesjournals.org/content/scientific-sessions-abstracts Posters (2016): https://ada.scientificposters.com/epsSearchADA.cfm	The abstracts were in pdf form so the 'ctrl + f' function was used to search each term one by one.	2017: 1. Cost (11) 2. Utility (14) 3. Utilities (14) 4. Quality of life (0) 5. Resource (11) 6. Economic (9) 2016: 1. Cost (7) 2. Utility (15) 3. Utilities (15) 4. Quality of life (0) 5. Resource (9) 6. Economic (2)	2017: 0 2016: 3
Diabetes UK Professional Conference ○ 2017	2017: http://onlinelibrary.wiley.com/doi/10.1111/dme.2017.34.issue-S1/issuetoc	On the right hand side of the screen, there is a search bar. The "In this issue" option was selected from the dropdown bar. In the bottom search bar, each term was searched one by one.	1. Cost (15) 2. Utility (0) 3. Utilities (0) 4. Quality of life (0) 5. Resource (0) 6. Economic (0)	0
European Association for the Study of Diabetes (EASD) Annual Meeting ○ EASD 2016	Abstracts and poster: http://www.easdvirtualmeeting.org/resourcegroups#~filters/resourcetype=1&tag=*&event=10&in=*&order=primary_ref	On the left hand side of the page, under the "Filter by Type" box, all 5 boxes were checked so that all abstracts, eposters etc. were searched. Under the "Filter by Event" box, the 2016 and 2015 meetings were	1. Cost (138) 2. Utility (180) 3. Utilities (180) 4. Quality of life (96) 5. Resource (73) 6. Economic (119)	0

Conference	Link	Search Strategy	Search Terms (Hits)	Relevant Hits
		selected. In the search bar at the top right, each term was searched one by one.		
International Society for Pharmacoeconomics and outcomes research ○ ISPOR International Meeting 2017 ○ ISPOR International Meeting 2016 ○ ISPOR European Meeting 2016 ○ ISPOR International Meeting 2015 ○ ISPOR European Meeting 2015	Abstracts: https://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	Each meeting was searched in turn: International 2017: select "22nd Annual International Congress – Boston, MA, USA – 2017" International 2016: select "21st Annual International Congress – Washington DC, USA – 2016" EU 2016: select "19th Annual European Congress – Vienna, Austria – 2016" International 2015: select "20th Annual International Congress – Philadelphia, PA, USA – 2015" EU 2015: "18th European Congress – Milan, Italy – 2017" For each meeting, "Diabetes" was selected under the "Disease/Disorder" dropdown menu. Keyword search: each term was searched one by one and the "abstracts" option was selected.	International 2017: 1. Cost (73) 2. Utility (5) 3. Utilities (2) 4. Quality of life (12) 5. Resource (16) 6. Economic (26) International 2016: 1. Cost (63) 2. Utility (6) 3. Utilities (5) 4. Quality of life (7) 5. Resource (6) 6. Economic (33) European 2016: 1. Cost (80) 2. Utility (16) 3. Utilities (7) 4. Quality of life (16) 5. Resource (24) 6. Economic (39) International 2015: 1. Cost (57) 2. Utility (9) 3. Utilities (5) 4. Quality of life (12) 5. Resource	International 2017: 0 International 2016: 0 European 2016: 0 International 2015: 0 European 2015: 0

Conference	Link	Search Strategy	Search Terms (Hits)	Relevant Hits
			(11) 6. Economic (32) European 2015: 1. Cost (92) 2. Utility (16) 3. Utilities (9) 4. Quality of life (22) 5. Resource (19) 6. Economic (41)	

Table G.6: Search strategy for HTA body website searching

HTA Body	Link	Search Strategy	Search Terms (Hits)	Relevant Hits
All Wales Medicines Strategy Group AWMSG	http://www.awmsg.org/	The term was searched in the search bar at the top right.	1. Diabetes (20)	3
Scottish Medicines Consortium SMC	https://www.scottishmedicines.org.uk/Home	The term was searched in the search bar.	1. Diabetes (145)	30
National Institute for Health and Care Excellence NICE	https://www.nice.org.uk/	The term was searched in the search bar. Under the "Filter results by" option on the left-hand side of the screen, the following two boxes were selected "Guidance" and "NICE Advice".	1. Type 2 Diabetes (292)	5
National Centre for Pharmacoeconomics NCPE	http://www.ncpe.ie/	The term was searched in the search bar at the top right.	1. Diabetes (15)	0

Table G.7: Search strategy for online database searching

Website	Link	Search Strategy	Search Terms (Hits)	Relevant Hits
The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center	http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx	The "articles" option was selected. The term was searched in the search bar.	1. Type 2 diabetes (198)	0
The University of Sheffield Health Utilities Database (ScHARRHUD)	http://www.scharrhud.org/	In the menu at the top of the page "search" was selected. In the first search bar, the term was searched (in Abstract [AB]).	1. Type 2 diabetes (25)	0
The EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	The advanced search was used. In the "type" dropdown, "abstract" was selected and in the "abstract" box the first term was searched. The [+] button to the right of the abstract was then selected. This added a new search line. In this search line in the "type" dropdown, "And" was selected in the operator box and "abstract" in the Type box. The second term was entered in the "abstract" box. Once the results of type 2 diabetes AND cost had been searched, "cost" was deleted from the abstract box and replaced with the remaining terms one by one.	1. Type 2 diabetes 2. Cost (32) 3. Economic (23) 4. Utility (34) 5. Utilities (16) 6. Quality of life (135) 7. Resource (12)	0

Table G.8: Eligibility criteria for the SLR

Domain	Economic evaluations		HRQoL and utilities		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
Population	Patients with type 2 diabetes mellitus with inadequate glycaemia control on either: • Diet and exercise • A first-line non-insulin blood glucose lowering therapy (which could have been administered in combination with insulin)	Individuals without type 2 diabetes, or individuals with type 2 diabetes but without inadequate glycaemia control on either diet and exercise or a first-line non-insulin blood glucose lowering therapy. Additionally, populations where outcomes are not presented separately for the patients of interest	Patients with type 2 diabetes mellitus	Individuals without type 2 diabetes, or populations where outcomes are not presented separately for the patients of interest	Patients with type 2 diabetes mellitus	Individuals without type 2 diabetes, or populations where outcomes are not presented separately for the patients of interest
Intervention(s)	Any non-insulin blood glucose lowering monotherapy, including: • Thiazolidinediones (TZDs; e.g. pioglitazone) • Sodium-glucose cotransporter 2 (SGLT-2)	Studies not investigating a pharmacological intervention of interest, or studies where the pharmacological intervention of interest is not considered separately	Any or none	-	Any or none	-

Domain	Economic evaluations		HRQoL and utilities		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) • Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin, saxagliptin, linagliptin, alogliptin) • Glucagon-like peptide-1 (GLP-1) agonists (e.g. exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide) • Sulfonylureas (e.g. glimepiride, glipizide, gliquidone, gliclazide) Alternatively, combination therapies with any of the above and/or metformin and/or					

Domain	Economic evaluations		HRQoL and utilities		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	sulfonylurea and/or insulin					
Comparator(s)	Any	-	Any or none	-	Any or none	-
Outcomes	Outcomes of relevant study designs, including: • Incremental cost-effectiveness ratios (ICERs) • Cost per clinical outcome • Total quality-adjusted life years (QALYs) • Total costs • Incremental costs and QALYs	Studies not presenting relevant outcomes	Health state utility values for the population of interest, measured using EQ-5D with the UK value set Health state utility values for the population of interest, measured using EQ-5D with the UK value set.	Health state utility values for the population of interest, measured using methods other than EQ-5D such as: • SF-6D • HUI3 • Time trade-off • Standard gamble Studies not presenting relevant outcomes for the population of interest such as HRQoL only Studies reporting data that did not match the required model inputs	Direct costs of and resource use associated with: • T2DM management • Cardiovascular complications • Renal complications • Acute events • Eye disease • Neuropathy • Foot ulcer • Amputation The data must be relevant to the UK NHS or PSS, and of relevance to an economic evaluation of ertugliflozin In addition, all data must have been collected	Studies not presenting relevant cost and resource use data for the population of interes (e.g. indirect costs; non-UK costs only), or studies presentin data collected more than 10 years ago Studies reporting data that did not match the required model inputs

Domain	Economic evaluations		HRQoL and utilities		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
					within the last 10 years for the study to be eligible for inclusion	
Study design	Any of the following analysis types: • Cost-effectiveness • Cost-utility • Cost-benefit • Cost-minimisation • Cost-consequence	Any other types of analysis	Any original research study	-	Any original research study, including budget impact models and cost-of-illness studies	-
Publication type	• Journal publications reporting original research • Congress abstracts reporting original research published in or after 2014 • HTAs	• Journal publications or congress abstracts not reporting original research • Congress abstracts from prior to 2014	• Journal publications reporting original research published in or after 2015 • Congress abstracts reporting original research published in or after 2014 • HTAs	• Journal publications published prior to 2015 • Journal publications or congress abstracts not reporting original research • Congress abstracts from prior to 2014	• Journal publications reporting original research • Congress abstracts reporting original research published in or after 2014 • HTAs	• Journal publications or congress abstracts not reporting original research • Congress abstracts from prior to 2014
	Systematic reviews and meta-analyses will be included at the title/abstract screening stage and will be used for the identification of any		Systematic reviews and meta-analyses will be included at the title/abstract screening stage and will be used for the identification of		Systematic reviews and meta-analyses will be included at the title/abstract screening stage and will be used for the	

Domain	Economic evaluations		HRQoL and utilities		Cost and resource use	
	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	additional primary studies not identified through the database searches. They will then be excluded during the full-text review stage unless they reported primary, original research themselves.		any additional primary studies not identified through the database searches. They will then be excluded during the full-text review stage unless they reported primary, original research themselves.		identification of any additional primary studies not identified through the database searches. They will then be excluded during the full-text review stage unless they reported primary, original research themselves.	
Other considerations	• UK NHS or PSS perspective or UK-based analyses only • English language • Human subjects	• Non-UK NHS or PSS perspective • Non-English language articles • Articles not on human subjects	• English language • Human subjects	• Non-English language articles • Articles not on human subjects	• Studies conducted in the UK only • English language • Human subjects	• Studies not conducted in the UK • Non-English language articles • Articles not on human subjects

Abbreviations: DPP-4: dipeptidyl peptidase-4; EQ-5D: EuroQol 5 dimensions questionnaire; GLP-1: glucagon-like peptide-1; HRQoL: health-related quality of life; HTA: health technology assessment; HUI: health utilities index; ICER: incremental cost-effectiveness ratio; NHS: National Health System; PSS: Personal and Social Services; QALY: quality adjusted life year; SGLT-2: sodium-glucose cotransporter 2; SF-6D: short form 6 dimensions questionnaire; TZD: thiazolidinediones; UK: United Kingdom.

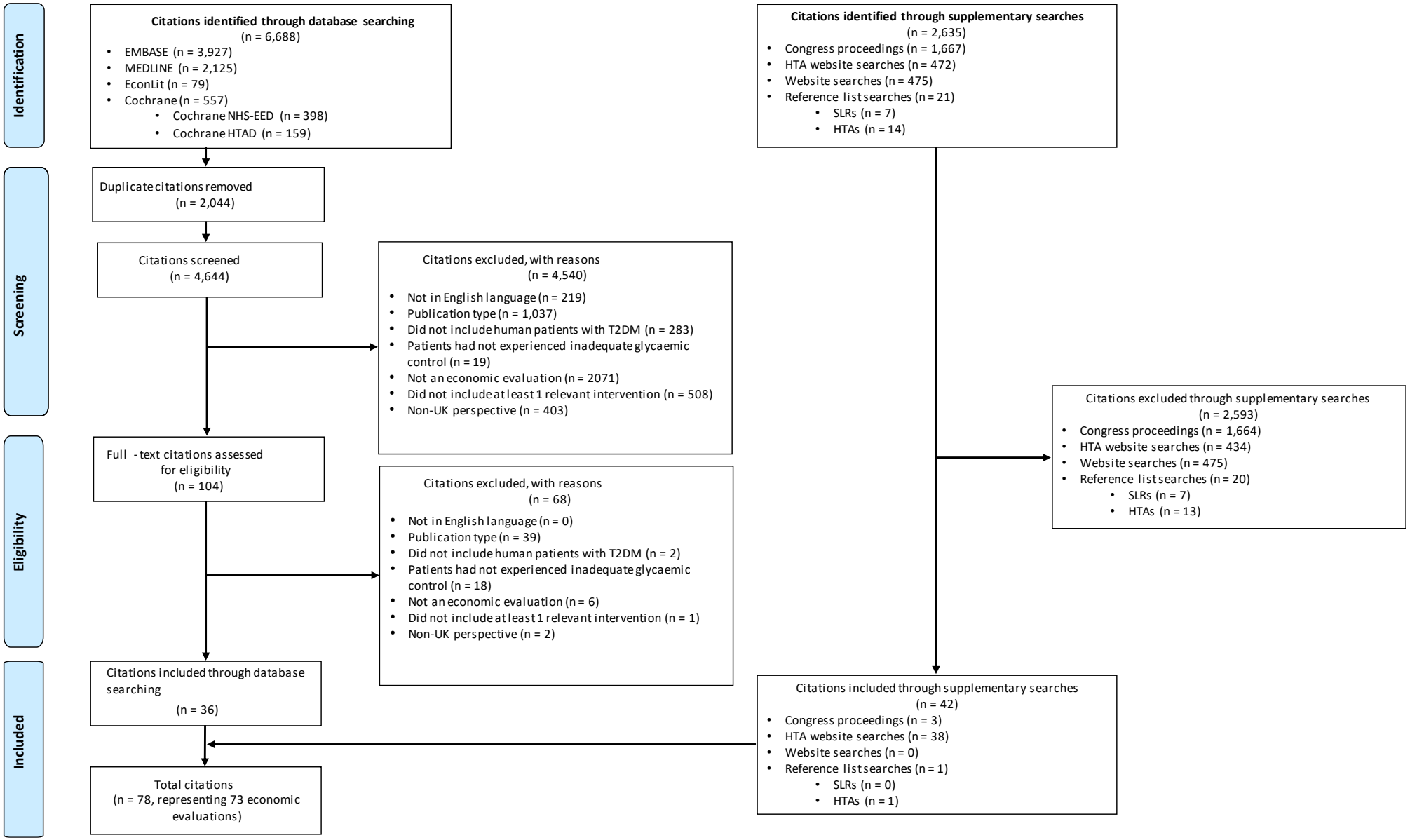
G.2 Description of identified studies

A total of 4,644 articles were identified through electronic database searching and a further 2,635 through supplementary searches. Of these, a total of 97 publications were included in the review:

- 78 publications, representing 73 unique economic evaluations,
- 8 publications, representing 6 unique utility studies
- 11 publications, representing 10 unique cost and resource use studies

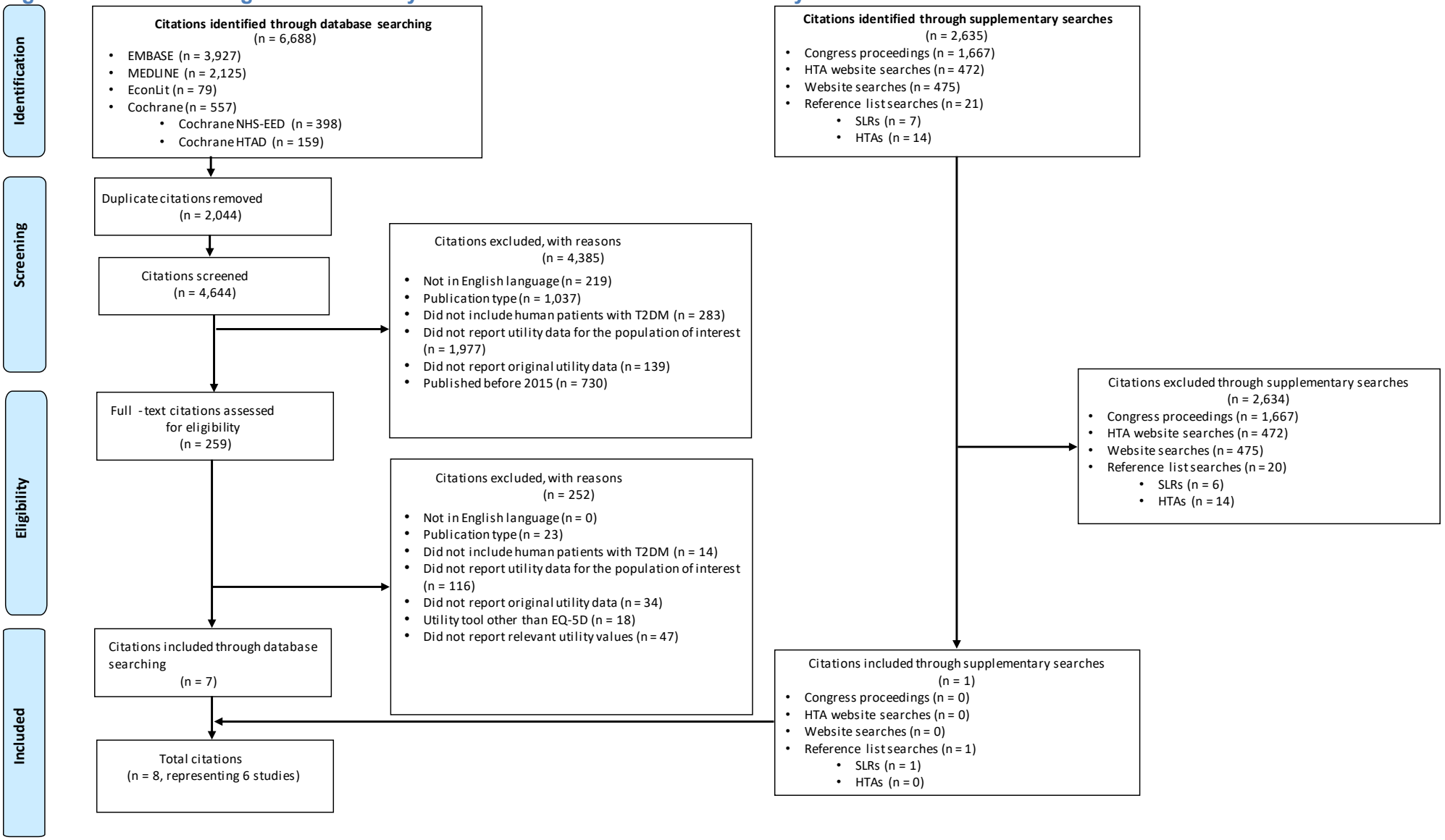
The results of the review are presented in the PRISMA diagrams provided in Figures 1–3, which correspond to the economic evaluations (Figure G.1Figure), health-state utility studies (Figure G.2) and cost and resource use studies (Figure G.3), respectively.
Further details of the included studies are presented in Appendix 0 for the economic evaluations, **Error! Reference source not found.**for the utility studies and **Error! Reference source not found.**for the cost and resource use studies. Lists of articles excluded during the screening of full-text articles (Stage 2) are presented in Tables G.9–11 which correspond to the economic evaluations (Table G.9), utility studies (Table G.10) and cost and resource use studies (Table G.11) identified, respectively.

Figure G.1: PRISMA diagram of the economic evaluations identified for the economic systematic literature review



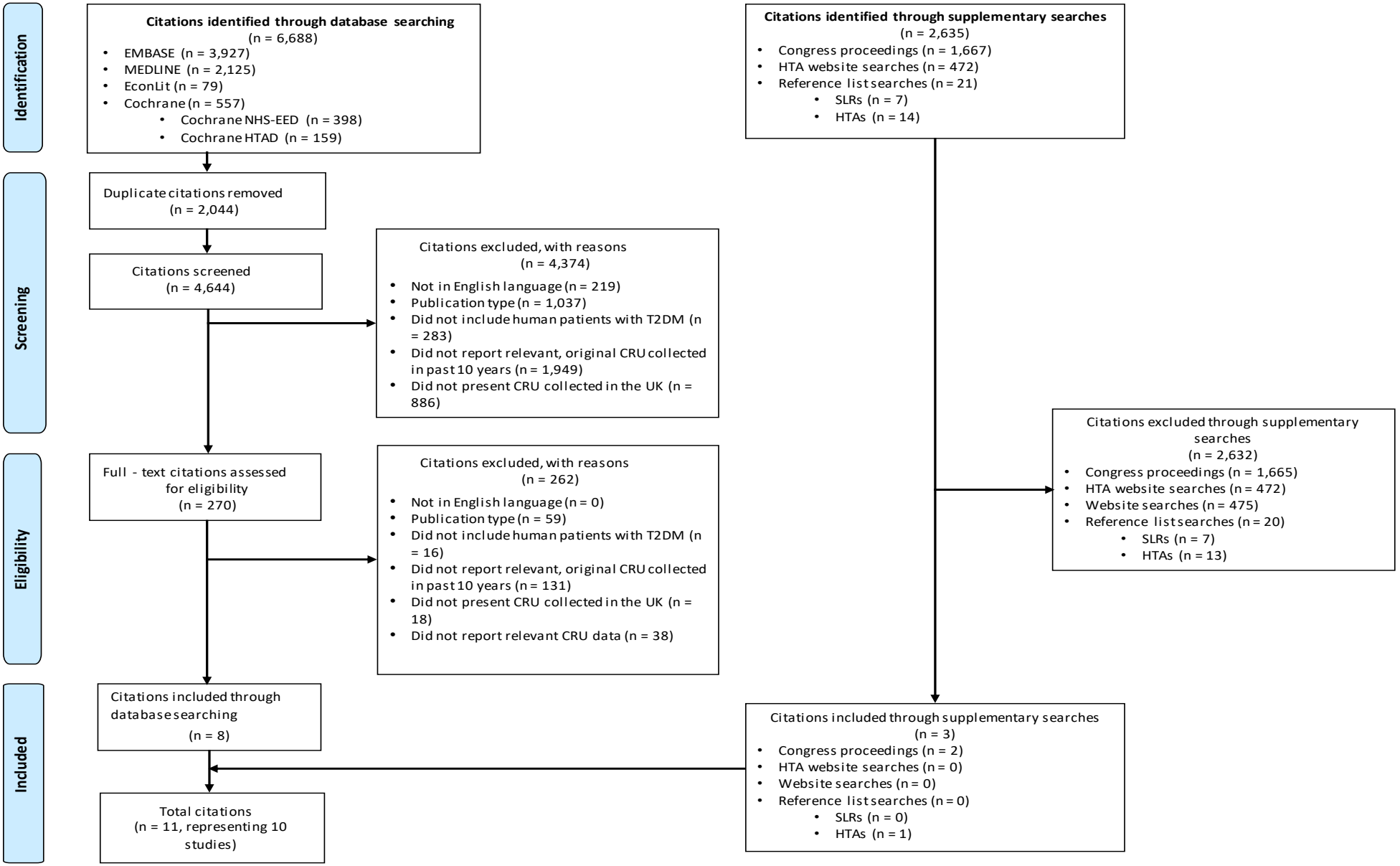
Abbreviations: HTA: health technology assessment; HTAD: Health Technology Assessment Database; NHS-EED: National Health Service Economic Evaluation Database; PRISMA: Preferred Reporting Items for Systematic Reviews; SLR: systematic literature review; T2DM: type 2 diabetes mellitus; UK: United Kingdom.

Figure G.2: PRISMA diagram of the utility studies identified for the economic systematic literature review



Abbreviations: EQ-5D: EuroQoL 5-dimensions; HTA: health technology assessment; HTAD: Health Technology Assessment Database; NHS-EED: National Health Service Economic Evaluation Database; PRISMA: Preferred Reporting Items for Systematic Reviews; SLR: systematic literature review; SMC: Scottish Medicines Consortium; T2DM: type 2 diabetes mellitus; UK: United Kingdom.

Figure G.3: PRISMA diagram of the cost and resource use studies identified for the economic systematic literature review



Articles excluded from the economic systematic literature review

Table G.9: Articles excluded from the economic evaluations stream of the economic systematic literature review at full-text stage

No.	Article excluded	Reason for exclusion
1	Afonso M, Ryan F, Pitcher A, et al. Evaluating drug cost per responder and number needed to treat associated with lixisenatide on top of glargine when compared to rapid-acting insulin intensification regimens on top of glargine, in patients with type 2 diabetes in the UK, Italy, and Spain. Journal of Medical Economics 2017:1-7.	Not an economic evaluation
2	Agarwal R, Williams K. Incretin-based therapies for inpatient management of type 2 diabetes mellitus (Structured abstract). Health Technology Assessment Database: Center for Evidence-based Practice (CEP), 2009.	Not a publication type of interest
3	Anonymous. Abstracts of 52nd EASD Annual Meeting. Diabetologia. Conference: 52nd Annual Meeting of the European Association for the Study of Diabetes, EASD 2016;59.	Not a publication type of interest
4	Aronson R, Galstyan G, Goldfracht M, et al. Health economic impact of hypoglycemia in a global population of patients with insulin-treated diabetes. Diabetes 2015;64:A69-A70.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
5	Asche CV, Bode B, Busk AK, et al. The economic and clinical benefits of adequate insulin initiation and intensification in people with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism 2012;14:47-57.	Not a publication type of interest
6	Asche CV, Hippler SE, Eurich DT. Review of models used in economic analyses of new oral treatments for type 2 diabetes mellitus. PharmacoEconomics 2014;32:15-27.	Not a publication type of interest
7	Asche CV, Shane-McWhorter L, Raparla S. Health economics and compliance of vials/syringes versus pen devices: a review of the evidence. Diabetes Technology & Therapeutics 2010;12 Suppl 1:S101-8.	Not a publication type of interest
8	Asseburg C, Willis M, Johansen P, et al. Update of the model validation of the economic and health outcomes model of type 2 diabetes mellitus (ECHO-T2DM). Value in Health 2016;19 (3):A88.	Patients had not experienced inadequate glycaemic control
9	AVE0010 (ZP10) for type 2 diabetes mellitus (Structured abstract). Health Technology Assessment Database: National Horizon Scanning Centre (NHSC), 2008.	Not a publication type of interest
10	Baptista A, Teixeira I, Romano S, et al. The place of DPP-4 inhibitors in the treatment algorithm of diabetes type 2: a systematic review of cost-effectiveness studies. European Journal of Health Economics 2016:1-29.	Not a publication type of interest
11	Black C, Cummins E, Royle P, et al. The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: A systematic review and economic evaluation. Health Technology Assessment 2007;11:iii-70.	Not a publication type of interest
12	Blenkinsopp A, Hassey A. Effectiveness and acceptability of community pharmacy-based interventions in type 2 diabetes: A critical review of intervention design, pharmacist and patient perspectives. International Journal of Pharmacy Practice 2005;13:231-240.	Not a publication type of interest

No.	Article excluded	Reason for exclusion
13	Blonde L, Juan ZTS, Bolton P. Fixed-dose combination therapy in type 2 diabetes mellitus. Endocrine Practice 2014;20:1322-1332.	Not a publication type of interest
14	Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. Advances in Therapy 2012;29:1-13.	Not a publication type of interest
15	Bottomley JM, Raymond FD. Pharmaco-economic issues for diabetes therapy. Best Practice & Research Clinical Endocrinology & Metabolism 2007;21:657-85.	Not a publication type of interest
16	Bottomley JM, Raymond FD. Pharmaco-economic issues for diabetes therapy. Insulin 2009;4:32-60.	Not a publication type of interest
17	Breitscheidel L, Stamenitis S, Dippel FW, et al. Economic impact of compliance to treatment with antidiabetes medication in type 2 diabetes mellitus: A review paper. Journal of Medical Economics 2010;13:8-15.	Not a publication type of interest
18	Brennan VK, Mauskopf J, Colosia AD, et al. Utility estimates for patients with Type 2 diabetes mellitus after experiencing a myocardial infarction or stroke: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research 2015;15:111-23.	Not a publication type of interest
19	Brown RR. Cost-effectiveness and clinical outcomes of metformin or insulin add-on therapy in adults with type 2 diabetes. American Journal of Health-System Pharmacy 1998;55:S24-7.	Non-UK perspective
20	Burnet DL, Elliott LD, Quinn MT, et al. Preventing diabetes in the clinical setting. Journal of General Internal Medicine 2006;21:84-93.	Not a publication type of interest
21	Charokopou M, Sabater FJ, Townsend R, et al. Methods applied in cost-effectiveness models for treatment strategies in type 2 diabetes mellitus and their use in Health Technology Assessments: a systematic review of the literature from 2008 to 2013. Current Medical Research & Opinion 2016;32:207-18.	Not a publication type of interest
22	Clarke P, Gray A, Adler A, et al. Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with Type II diabetes (UKPDS no. 51). Diabetologia 2001;44:298-304.	Patients had not experienced inadequate glycaemic control
23	Czoski-Murray C, Warren E, Chilcott J, et al. Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: A systematic review and economic evaluation. Health Technology Assessment 2004;8:iii-81.	Not a publication type of interest
24	Daacke I, Kandaswamy P, Tebboth A, et al. Cost-effectiveness of empagliflozin (jardiance) in the treatment of patients with type 2 diabetes mellitus (T2DM) in the UK based on EMPA-REG outcome data. Value in Health 2016;19 (7):A673.	Patients had not experienced inadequate glycaemic control
25	Davies MJ, Glah D, Chubb B, et al. Cost Effectiveness of IDegLira vs. Alternative Basal Insulin Intensification Therapies in Patients with Type 2 Diabetes Mellitus Uncontrolled on Basal Insulin in a UK Setting. PharmacoEconomics 2016;34:953-966.	Patients had not experienced inadequate glycaemic control
26	Deshpande S, Clark JD. Cost and effectiveness of exenatide combined with insulin, compared to exenatide combined with oral hypoglycaemic agents. Practical Diabetes 2011;28:390-393.	Not an economic evaluation
27	Doyle S, Lloyd A, Moore L, et al. A systematic review and critical assessment of health state utilities: Weight change and type 2 diabetes mellitus. PharmacoEconomics 2012;30:1133-1143.	Not a publication type of interest
28	Earnshaw SR, Richter A, Sorensen SW, et al. Optimal allocation of resources across four interventions for type 2 diabetes. Medical	Patients had not experienced inadequate

No.	Article excluded	Reason for exclusion
	Decision Making 2002;22:S80-91.	glycaemic control
29	Edwards KL, Irons BK, Xu T. Cost-effectiveness of intermediate or long-acting insulin versus exenatide in type 2 diabetes mellitus patients not optimally controlled on dual oral diabetes medications (Structured abstract). Pharmacy Practice. Volume 4, 2006:129-133.	Non-UK perspective
30	Exenatide once-weekly for type 2 diabetes mellitus - second or third line (Structured abstract). Health Technology Assessment Database: National Horizon Scanning Centre (NHSC), 2008.	Not a publication type of interest
31	Geng J, Yu H, Mao Y, et al. Cost Effectiveness of Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes. PharmacoEconomics 2015;33:581-597.	Not a publication type of interest
32	Gray A, Raikou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. BMJ 2000;320:1373-8.	Did not include at least 1 relevant intervention
33	Jaspers L, Colpani V, Chaker L, et al. The global impact of non-communicable diseases on households and impoverishment: a systematic review. European Journal of Epidemiology. 2014;21.	Not a publication type of interest
34	Jennison C, Jobling A, Pearson E, et al. Assessing the benefits of a stratified treatment strategy which improves average HbA1c in a proportion of patients with type 2 diabetes: A mastermind study. Diabetic Medicine 2016;33:23.	Patients had not experienced inadequate glycaemic control
35	Jones S, Castell C, Goday A, et al. Increase in direct diabetes-related costs and resource use in the 6 months following initiation of insulin in patients with type 2 diabetes in five European countries: data from the INSTIGATE study. Clinicoeconomics & Outcomes Research 2012;4:383-93.	Patients had not experienced inadequate glycaemic control
36	Kansal A, Zheng Y, Proskorovsky I, et al. Modeling cardiovascular outcomes of treatment with empagliflozin in type 2 diabetes based on hard outcomes data. Value in Health 2016;19 (3):A203.	Not an economic evaluation
37	Kansal AR, Zheng Y, Palencia R, et al. Modeling hard clinical end-point data in economic analyses. Journal of Medical Economics 2013;16:1327-1343.	Not a publication type of interest
38	Karagiannis T, Bekiari E, Tsapas A. Canagliflozin in the treatment of type 2 diabetes: An evidence-based review of its place in therapy. Core Evidence 2017;12:1-10.	Not a publication type of interest
39	Kaura S, Nanavaty M, Seetasith A, et al. Literature review of the use of ICER thresholds in healthcare decision-making. Value in Health 2015;18 (3):A90.	Not a publication type of interest
40	Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. Diabetes Care 2000;23:390-404.	Patients had not experienced inadequate glycaemic control
41	Korczak D, Dietl M, Steinhauser G. Effectiveness of programmes as part of primary prevention demonstrated on the example of cardiovascular diseases and the metabolic syndrome. GMS Health Technology Assessment 2011;7:Doc02.	Not a publication type of interest
42	Leal J, Ahrabian D, Davies MJ, et al. Cost-effectiveness of a pragmatic structured education intervention for the prevention of type 2 diabetes: economic evaluation of data from the Let's Prevent Diabetes cluster-randomised controlled trial. BMJ Open 2017;7:e013592.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately

No.	Article excluded	Reason for exclusion
43	Li R, Zhang P, Barker LE, et al. Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review. Diabetes Care 2010;33:1872-1894.	Not a publication type of interest
44	Long E, Fang Y, Hu M, et al. Pharmacoeconomic evaluation of GLP-1 receptors agonist versus DPP-4 inhibitors in patients with Type 2 Diabetes: A systematic review. Value in Health 2015;18 (3):A63.	Not a publication type of interest
45	Loveman E, Cave C, Green C, et al. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2003;7:iii, 1-190.	Not a publication type of interest
46	McEwan P, Bennett H, Fellows J, et al. Alternative approaches to modelling hba1c progression in type 2 diabetes and their impact on health economic outcomes. Value in Health 2016;19 (3):A88.	Not a publication type of interest
47	McEwan P, Bennett H, Ward T, et al. Refitting of the UKPDS 68 Risk Equations to Contemporary Routine Clinical Practice Data in the UK. PharmacoEconomics 2015;33:149-161.	Patients had not experienced inadequate glycaemic control
48	McEwan P, Foos V, Lamotte M, et al. Quantifying the health economic benefit of key therapeutic outcomes in the management of type 2 diabetes and assessing their inter-relationahip. Value in Health 2016;19 (3):A88.	Patients had not experienced inadequate glycaemic control
49	McEwan P, Gordon J, Bennett H, et al. Flexibly modelling HBA1C progression in type 2 diabetes to estimate the impact of clinical inertia on costs and quality adjusted life years. Value in Health 2016;19 (7):A675.	Patients had not experienced inadequate glycaemic control
50	McEwan P, Peters JR, Bergenheim K, et al. Evaluation of the costs and outcomes from changes in risk factors in type 2 diabetes using the Cardiff stochastic simulation cost-utility model (DiabForecaster). Current Medical Research and Opinion 2006;22:121-129.	Patients had not experienced inadequate glycaemic control
51	Muka T, Imo D, Jaspers L, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. European Journal of Epidemiology 2015;30:251-277.	Not a publication type of interest
52	Oliver A, Pritchard C. Economic evaluations relating to diabetes: a descriptive review and their compliance with guidance. Value in Health 2000;3 Suppl 1:7-14.	Not a publication type of interest
53	Owens D, Tilling C, Keech M. Insulin glargine plus oral antidiabetic agents in comparison with biphasic insulin in type 2 diabetes: A UK cost comparison. British Journal of Diabetes and Vascular Disease 2011;11:141-144.	Not an economic evaluation
54	Palmer AJ, Roze S, Valentine WJ, et al. What impact would pancreatic beta-cell preservation have on life expectancy, quality-adjusted life expectancy and costs of complications in patients with Type 2 diabetes: a projection using the CORE diabetes model (Structured abstract). Current Medical Research and Opinion. Volume 20, 2004:S59-s66.	Patients had not experienced inadequate glycaemic control
55	Palmer AJ, Valentine WJ, Ray JA. Thiazolidinediones for diabetes mellitus: Considerations for reimbursements by third-party payers. Disease Management and Health Outcomes 2004;12:363-375.	Not a publication type of interest
56	Pollock R, Muduma G, Valentine W. Evaluating the cost-effectiveness of laparoscopic adjustable gastric banding versus standard medical management in obese patients with type 2	Patients had not experienced inadequate glycaemic control

No.	Article excluded	Reason for exclusion
	diabetes in the UK (Provisional abstract). Diabetes Obesity and Metabolism. Volume 15, 2013:121-129.	
57	Ricci-Cabello I, Ruiz-Perez I, Rojas-Garcia A, et al. Characteristics and effectiveness of diabetes self-management educational programs targeted to racial/ethnic minority groups: a systematic review, meta-analysis and meta-regression. BMC Endocrine Disorders 2014;14:60.	Not a publication type of interest
58	Richter B, Bandeira-Echtler E, Bergerhoff K, et al. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007;(3) (no pagination).	Not a publication type of interest
59	Strain WD. Cost effectiveness of insulin sparing treatment regimens early in Type 2 diabetes: Real world data using a clinical practice database. Diabetic Medicine 2017;34:183.	Patients had not experienced inadequate glycaemic control
60	Strain WD. Cost effectiveness of insulin sparing treatment regimes in type 2 diabetes: Data from a real world clinical database. Diabetologia 2016;59 (1 Supplement 1):S438.	Patients had not experienced inadequate glycaemic control
61	Suraj B, Tripathi CD, Biswas K, et al. A Comparative Evaluation of Safety, Efficacy and Cost Effectiveness of Three Add on Treatment Regimens in Type 2 Diabetics; Not Controlled by Metformin Alone. Research Journal of Pharmacy and Technology 2015;8:44-50.	Not an economic evaluation
62	Tao L, Wilson EC, Wareham NJ, et al. Cost-effectiveness of intensive multifactorial treatment compared with routine care for individuals with screen-detected Type 2 diabetes: analysis of the ADDITION-UK cluster-randomized controlled trial. Diabetic Medicine 2015;32:907-19.	Patients had not experienced inadequate glycaemic control
63	Tarride JE, Hopkins R, Blackhouse G, et al. A review of methods used in long-term cost-effectiveness models of diabetes mellitus treatment. PharmacoEconomics 2010;28:255-277.	Not a publication type of interest
64	Torre C, Guerreiro J, Longo P, et al. Comparison of glucose lowering drugs usage between portugal and 6 european countries, in 2014. Pharmacoepidemiology and Drug Safety 2016;25:195-196.	Not an economic evaluation
65	Tricco AC, Antony J, Khan PA, et al. Safety and effectiveness of dipeptidyl peptidase-4 inhibitors versus intermediate-acting insulin or placebo for patients with type 2 diabetes failing two oral antihyperglycaemic agents: a systematic review and network meta-analysis. BMJ Open 2014;4:e005752.	Not a publication type of interest
66	Tucker DM, Palmer AJ. The cost-effectiveness of interventions in diabetes: a review of published economic evaluations in the UK setting, with an eye on the future. Primary care diabetes 2011;5:9-17.	Not a publication type of interest
67	Turk E, Zaletel J, Ormstad SS, et al. Is a multi-disciplinary approach in the delivery of care for patients with Diabetes mellitus Type 2 cost effective? A systematic review. HealthMED 2012;6:711-719.	Not a publication type of interest
68	Wong CK, Jiao FF, Siu SC, et al. Cost-Effectiveness of a Short Message Service Intervention to Prevent Type 2 Diabetes from Impaired Glucose Tolerance. Journal of Diabetes Research 2016;2016:1219581.	Patients had not experienced inadequate glycaemic control

Table G.10: Articles excluded from the utility studies stream of the economic systematic literature review at full-text stage

No.	Reference	Reason for exclusion
1	Al-Aboudi IS, Hassali MA, Shafie AA, et al. A cross-sectional assessment of health-related quality of life among type 2 diabetes patients in Riyadh, Saudi Arabia. SAGE Open Medicine 2015;3:2050312115610129.	Did not report relevant utility values
2	Al-Aboudi IS, Hassali MA, Shafie AA. Knowledge, attitudes, and quality of life of type 2 diabetes patients in Riyadh, Saudi Arabia. Journal of Pharmacy and Bioallied Sciences 2016;8:195-202.	Did not report relevant utility values
3	Alfonso-Rosa RM, del Pozo-Cruz J, del Pozo-Cruz B, et al. Cost-utility analysis of a 12-week whole-body vibration based treatment for people with type 2 diabetes: Reanalysis of a RCT in a primary care context. Public Health 2015;129:993-995.	Did not report utility data for the population of interest
4	Alouki K, Delisle H, Bermudez-Tamayo C, et al. Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies. Journal of Diabetes Research 2016;2016:2159890.	Did not report utility data for the population of interest
5	Anonymous. Abstracts of 52nd EASD Annual Meeting. Diabetologia. Conference: 52nd Annual Meeting of the European Association for the Study of Diabetes, EASD 2016;59.	Not a publication type of interest
6	Aral KD, Chick SE, Grabosch A. Multi-level preventive care for Type 2 diabetes. IIE Transactions on Healthcare Systems Engineering 2015;5:165-182.	Did not report utility data for the population of interest
7	Asakura R, Miyatake N, Mochimasu KD, et al. Comparison of health-related quality of life between type 2 diabetic patients with and without locomotive syndrome. Environmental Health & Preventive Medicine 2016;21:356-360.	Did not report relevant utility values
8	Ascher-Svanum H, Zagar A, Jiang D, et al. Associations Between Glycemic Control, Depressed Mood, Clinical Depression, and Diabetes Distress Before and After Insulin Initiation: An Exploratory, Post Hoc Analysis. Diabetes Therapy 2015;6:303-316.	Did not report utility data for the population of interest
9	Ashley D, Vega G, Hunt B, et al. Evaluating the Cost-Effectiveness of GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes in the UK. Value in Health 2015;18:A606.	Did not report utility data for the population of interest
10	Asseburg C, Johansen P, Nilsson A, et al. Impact of the Framingham Offspring Study (FOS) vs Kaiser Permanente NorthWest (KPNW) prediction equations for diabetes mellitus in economic modelling of type 2 diabetes mellitus. Diabetologia 2015;1):S481.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
11	Athanasakis K, Zhuo J, Chen J, et al. Cost-effectiveness of sitagliptin compared to sulphonylurea as an add-on to metformin in the treatment of type 2 diabetes in Greece. Value in Health 2015;18 (7):A608.	Did not report utility data for the population of interest
12	Aung E, Donald M, Williams GM, et al. Influence of patient-assessed quality of chronic illness care and patient activation on health-related quality of life. International Journal for Quality in Health Care 2016;28:306-10.	Did not report relevant utility values
13	Baptista A, Teixeira I, Romano S, et al. The place of DPP-4 inhibitors in the treatment algorithm of diabetes type 2: a systematic review of cost-effectiveness studies. European Journal of Health Economics 2016:1-29.	Not a publication type of interest

No.	Reference	Reason for exclusion
14	Bauer M. Burden of disease of diabetes mellitus typ-2 in Austria. Value in Health 2015;18 (7):A619.	Did not report utility data for the population of interest
15	Bell KF, Flood EM, Ginchereau-Sowell F, et al. Most influential factors determining patient preferences for type 2 diabetes treatment. Diabetes 2015;64:A54.	Did not report utility data for the population of interest
16	Black JA, Long GH, Sharp SJ, et al. Change in cardio-protective medication and health-related quality of life after diagnosis of screen-detected diabetes: Results from the ADDITION-Cambridge cohort. Diabetes Research & Clinical Practice 2015;109:170-7.	Did not report relevant utility values
17	Boulin M, Diaby V, Tannenbaum C. Preventing Unnecessary Costs of Drug-Induced Hypoglycemia in Older Adults with Type 2 Diabetes in the United States and Canada. PLoS ONE [Electronic Resource] 2016;11:e0162951.	Did not report original utility data
18	Breeze PR, Thomas C, Squires H, et al. Impact of Type 2 diabetes prevention programmes based on risk identification and lifestyle intervention intensity strategies: A cost-effectiveness analysis. Diabetic Medicine. 2015.	Did not report utility data for the population of interest
19	Breeze PR, Thomas C, Squires H, et al. The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. Diabetic Medicine 2017;34:632-640.	Did not report original utility data
20	Brennan VK, Mauskopf J, Colosia AD, et al. Utility estimates for patients with Type 2 diabetes mellitus after experiencing a myocardial infarction or stroke: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research 2015;15:111-23.	Not a publication type of interest
21	Cadth. Glucose replacement agents in frail elderly patients with type ii diabetes in long-term care: clinical and cost-effectiveness, harms, and guidelines (Structured abstract). Health Technology Assessment Database: Canadian Agency for Drugs and Technologies in Health (CADTH), 2015.	Not a publication type of interest
22	Campbell JA, Venn A, Neil A, et al. Diverse approaches to the health economic evaluation of bariatric surgery: a comprehensive systematic review. Obesity Reviews 2016;17:850-894.	Not a publication type of interest
23	Carris N, Miladinovic B, Kelly W. Updated cost-savings of metformin for diabetes prevention. Pharmacotherapy 2016;36 (12):e262.	Did not report utility data for the population of interest
24	Charokopou M, Chuang L, Verheggen B, et al. Cost-Effectiveness Analysis of Exenatide Once-Weekly Versus Dulaglutide, Liraglutide and Lixisenatide for the Treatment of Type 2 Diabetes Mellitus: An Analysis from the UK NHS Perspective. Value in Health 2015;18:A606.	Did not report utility data for the population of interest
25	Charokopou M, McEwan P, Lister S, et al. Cost-effectiveness of dapagliflozin versus DPP-4 inhibitors as an add-on to Metformin in the Treatment of Type 2 Diabetes Mellitus from a UK Healthcare System Perspective. BMC Health Services Research 2015;15:496.	Did not report utility data for the population of interest
26	Charokopou M, McEwan P, Lister S, et al. The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. Diabetic Medicine 2015;32:890-898.	Did not report original utility data
27	Charokopou M, Sabater FJ, Townsend R, et al. Methods applied	Not a publication type

No.	Reference	Reason for exclusion
	in cost-effectiveness models for treatment strategies in type 2 diabetes mellitus and their use in Health Technology Assessments: a systematic review of the literature from 2008 to 2013. Current Medical Research & Opinion 2016;32:207-18.	of interest
28	Chen T, Lang HC. Effect of a pay-for-performance program for diabetes on health status (EQ-5D) in Taiwan. Value in Health 2016;19 (7):A899-A900.	Did not report utility data for the population of interest
29	Chuang LH, Verheggen BG, Charokopou M, et al. Cost-effectiveness analysis of exenatide once-weekly versus dulaglutide, liraglutide, and lixisenatide for the treatment of type 2 diabetes mellitus: an analysis from the UK NHS perspective. Journal of Medical Economics 2016;19:1127-1134.	Did not report original utility data
30	Collins B, Capewell S, O'Flaherty M, et al. Modelling the Health Impact of an English Sugary Drinks Duty at National and Local Levels. PLoS ONE [Electronic Resource] 2015;10:e0130770.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
31	Corey KE, Klebanoff MJ, Tramontano AC, et al. Screening for Nonalcoholic Steatohepatitis in Individuals with Type 2 Diabetes: A Cost-Effectiveness Analysis. Digestive Diseases & Sciences 2016;61:2108-17.	Did not report original utility data
32	Culic M, Russel-Szymczyk M, Chubb B, et al. Cost-utility analysis of insulin degludec vs. insulin glargine u100 treatment in patients with diabetes mellitus type 1 and 2 in Serbia. Value in Health 2016;19 (7):A674.	Did not report utility data for the population of interest
33	da Mata AR, Alvares J, Diniz LM, et al. Quality of life of patients with Diabetes Mellitus Types 1 and 2 from a referal health centre in Minas Gerais, Brazil. Expert Review of Clinical Pharmacology 2016;9:739-46.	Did not report relevant utility values
34	Daacke I, Kandaswamy P, Tebboth A, et al. Cost-effectiveness of empagliflozin (jardiance) in the treatment of patients with type 2 diabetes mellitus (T2DM) in the UK based on EMPA-REG outcome data. Value in Health 2016;19 (7):A673.	Did not report utility data for the population of interest
35	Davies M, McEwan P, Glah D, et al. Cost-effectiveness analysis of insulin degludec/liraglutide (IDegLira) vs other basal insulin intensification strategies in Type 2 diabetes patients uncontrolled on basal insulin in a UK setting. Diabetic Medicine 2016;33:155.	Did not report utility data for the population of interest
36	Davies MJ, Glah D, Chubb B, et al. Cost Effectiveness of IDegLira vs. Alternative Basal Insulin Intensification Therapies in Patients with Type 2 Diabetes Mellitus Uncontrolled on Basal Insulin in a UK Setting. PharmacoEconomics 2016;34:953-966.	Did not report utility data for the population of interest
37	De Ranitz-Greven W, Beulens J, Biesma D, et al. Is higher glycemic variability in type 2 diabetes patients associated with reduced quality of life? Endocrine Reviews. Conference: 97th Annual Meeting and Expo of the Endocrine Society, ENDO 2015;36.	Did not report utility data for the population of interest
38	Dennick K, Bridle C, Sturt J. Written emotional disclosure for adults with Type 2 diabetes: a primary care feasibility study. Primary health care research & development 2015;16:179-187.	Did not report relevant utility values
39	DiBonaventura MD, Le Lay A, Fournier J, et al. The burden of obesity in Mexico: Prevalence, comorbidities, and associations with quality of life, resource utilization and productivity. Value in Health 2015;18 (7):A843.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately

No.	Reference	Reason for exclusion
40	Dilla T, Alexiou D, Chatzitheofilou I, et al. The cost-effectiveness of dulaglutide versus liraglutide for the treatment of type 2 diabetes mellitus in Spain in patients with BMI >30 kg/m². Journal of Medical Economics 2017;20:443-452.	Did not report original utility data
41	D'Souza MS, Venkatesaperumal R, Ruppert SD, et al. Health Related Quality of Life among Omani Men and Women with Type 2 Diabetes. Journal of Diabetes Research 2016;2016:8293579.	Did not report utility data for the population of interest
42	Dudzinska M, Tarach JS, Zwolak A, et al. Quality of life among patients with type 2 diabetes after insulin therapy introduction: A prospective study. Diabetologia Kliniczna 2015;4:226-231.	Did not report relevant utility values
43	Eaglehouse YL, Schafer GL, Arena VC, et al. Impact of a community-based lifestyle intervention program on health-related quality of life. Quality of Life Research 2016;25:1903-1912.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
44	Echouffo-Tcheugui JB, Simmons RK, Prevost AT, et al. Long-term effect of population screening for diabetes on cardiovascular morbidity, self-rated health, and health behavior. Annals of family medicine 2015;13:149-157.	Did not report utility data for the population of interest
45	Einarson TR, Bereza BG, Acs A, et al. Cost effectiveness of screening for type 2 diabetes mellitus and pre-diabetes: Systematic literature review. Value in Health 2016;19 (3):A302.	Not a publication type of interest
46	Einarson TR, Bereza BG, Acs A, et al. Systematic literature review of the health economic implications of early detection by screening populations at risk for type 2 diabetes. Current Medical Research & Opinion 2017;33:331-358.	Not a publication type of interest
47	Ekwunife OI, Ezenduka CC, Uzoma BE. Evaluating the sensitivity of EQ-5D in a sample of patients with type 2 diabetes mellitus in two tertiary health care facilities in Nigeria. BMC Research Notes 2016;9:24.	Did not report relevant utility values
48	Elgart JF, Gonzalez L, Prestes M, et al. Cost-effectiveness of dapagliflozin in the treatment of type 2 diabetes mellitus in Peru. Value in Health 2016;19 (3):A203.	Did not report utility data for the population of interest
49	Elgart JF, Gonzalez L, Prestes M, et al. Dapagliflozin versus sulfonylurea as an add-on therapy to metformin: A cost-effectiveness analysis in Costa Rica. Value in Health 2016;19 (3):A202.	Did not report utility data for the population of interest
50	Elgart JF, Prestes M, Gonzalez L, et al. Cost-effectiveness of type 2 diabetes (T2dm) treatment with dapa gliflozin as add-on to metformin in the dominican republic and Guatemala. Value in Health 2016;19 (7):A671-A672.	Did not report utility data for the population of interest
51	Elgart JF, Prestes M, Gonzalez L, et al. Dapagliflozin: Cost effectiveness as an add-on therapy to metformin in the treatment of type 2 diabetes in ecuador. Value in Health 2016;19 (3):A202.	Did not report utility data for the population of interest
52	Evans M, McEwan P, Foos V. Insulin degludec early clinical experience: Does the promise from the clinical trials translate into clinical practice-a case-based evaluation. Journal of Medical Economics 2015;18:96-105.	Did not report utility data for the population of interest
53	Evans M, Ridderstrale M, Jensen HH, et al. Quantifying the short-term impact of changes in HbA1c, weight and insulin regimen on health related quality-of-life. Value in Health 2015;18 (7):A616.	Utility tool other than EQ-5D used
54	Farshchi A, Aghili R, Oskuee M, et al. Biphasic insulin Aspart 30	Did not report relevant

No.	Reference	Reason for exclusion
	vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. BMC Endocrine Disorders 2016;16:35.	utility values
55	Flood EM, Bell KF, de la Cruz MC, et al. Patient preferences for diabetes treatment attributes and drug classes. Current Medical Research & Opinion 2017;33:261-268.	Did not report utility data for the population of interest
56	Flores NM, Gupta S, Goren A, et al. Recent hypoglycemia episodes are associated with poorer quality of life, healthcare resource use, and work impairment among patients with type II diabetes in Brazil. Value in Health 2015;18 (7):A865.	Utility tool other than EQ-5D used
57	Foos V, Lamotte M, McEwan P. Assessing the impact of simulated time horizon on predicted incremental quality adjusted life years in type 2 diabetes. Value in Health 2016;19 (3):A87.	Did not report utility data for the population of interest
58	Freemantle N, Lingvay I, Kongso JH, et al. Ideglira improves health utility compared with insulin glargine in patients with type 2 diabetes. Value in Health 2015;18 (7):A614.	Did not report relevant utility values
59	Freund T, Peters-Klimm F, Boyd CM, et al. Medical assistant-based care management for high-risk patients in small primary care practices: A cluster randomized clinical trial. Annals of Internal Medicine 2016;164:323-330.	Did not report utility data for the population of interest
60	Geng J, Yu H, Mao Y, et al. Cost Effectiveness of Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes. PharmacoEconomics 2015;33:581-597.	Not a publication type of interest
61	Gillett M, Brennan A, Watson P, et al. The cost-effectiveness of testing strategies for type 2 diabetes: a modelling study (Structured abstract). Health Technology Assessment Database: Health Technology Assessment, 2015.	Did not report original utility data
62	Golicki D, Dudzinska M, Zwolak A, et al. Quality of life in patients with type 2 diabetes in Poland - comparison with the general population using the EQ-5D questionnaire. Advances in Clinical & Experimental Medicine 2015;24:139-46.	Did not report relevant utility values
63	Gordon J, McEwan P, Evans M, et al. Managing glycaemia in older people with type 2 diabetes: A retrospective, primary care-based cohort study, with economic assessment of patient outcomes. Diabetes, Obesity & Metabolism 2017;19:644-653.	Did not report utility data for the population of interest
64	Gordon J, McEwan P, Hurst M, et al. The Cost-Effectiveness of Alogliptin Versus Sulfonylurea as Add-on Therapy to Metformin in Patients with Uncontrolled Type 2 Diabetes Mellitus. Diabetes Therapy 2016;7:825-845.	Did not report utility data for the population of interest
65	Gordon J, McEwan P, Sabale U, et al. The cost-effectiveness of exenatide twice daily (BID) vs insulin lispro three times daily (TID) as add-on therapy to titrated insulin glargine in patients with type 2 diabetes. Journal of Medical Economics 2016;19:1167-1174.	Did not report original utility data
66	Grandy S, Sternhufvud C, Ryden A, et al. Patient-reported outcomes among patients with type 2 diabetes mellitus treated with dapagliflozin in a triple-therapy regimen for 52 weeks. Diabetes, Obesity & Metabolism 2016;18:306-9.	Did not report relevant utility values
67	Gu S, Deng J, Shi L, et al. Cost-effectiveness of saxagliptin vs glimepiride as a second-line therapy added to metformin in Type 2 diabetes in China. Journal of Medical Economics 2015;18:808-820.	Did not report original utility data
68	Gu S, Mu Y, Zhai S, et al. Cost-Effectiveness of Dapagliflozin versus Acarbose as a Monotherapy in Type 2 Diabetes in China. PLoS ONE [Electronic Resource] 2016;11:e0165629.	Did not report original utility data

No.	Reference	Reason for exclusion
69	Gu S, Shao H, Zeng Y, et al. Cost-effectiveness of saxagliptin versus acarbose as second-line therapy in type 2 diabetes in China. Value in Health 2016;19 (7):A898.	Did not report utility data for the population of interest
70	Gu S, Wang X, Qiao Q, et al. Cost-Effectiveness of Exenatide twice daily versus Insulin Glargine as add-on Therapy to Oral Anti-diabetic Agents in Type 2 Diabetes in China. Diabetes, Obesity & Metabolism 2017;28:28.	Did not report original utility data
71	Gu S, Zeng Y, Yu D, et al. Cost-Effectiveness of Saxagliptin versus Acarbose as Second-Line Therapy in Type 2 Diabetes in China. PLoS ONE [Electronic Resource] 2016;11:e0167190.	Did not report utility data for the population of interest
72	Gupta V, Baabbad R, Hammerby E, et al. An analysis of the cost-effectiveness of switching from biphasic human insulin 30, insulin glargine, or neutral protamine Hagedorn to biphasic insulin aspart 30 in people with type 2 diabetes. Journal of Medical Economics 2015;18:263-272.	Did not report utility data for the population of interest
73	Haig J, Barbeau M, Ferreira A. Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema. Journal of Medical Economics 2016;19:663-671.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
74	Hoerger TJ, Zhuo X, Gregg EW, et al. Controlling the ABCS: The cost-effectiveness of A1C, blood pressure, and cholesterol control in type 2 diabetes. Diabetes 2015;64:A69.	Did not report utility data for the population of interest
75	Home P, Slim I, Gupta V, et al. Predictive and explanatory factors of change in health-related quality of life after starting insulin analogs. Diabetes 2015;64:A268.	Did not report utility data for the population of interest
76	Hsieh HM, Tsai SL, Shin SJ, et al. Cost-effectiveness of diabetes pay-for-performance incentive designs. Medical Care 2015;53:106-115.	Did not report utility data for the population of interest
77	Hua X, Lung TW, Palmer A, et al. How Consistent is the Relationship between Improved Glucose Control and Modelled Health Outcomes for People with Type 2 Diabetes Mellitus? a Systematic Review. Pharmacoeconomics 2017;35:319-329.	Not a publication type of interest
78	Huetson P, Palmer JL, Levorsen A, et al. Cost-effectiveness of once daily GLP-1 receptor agonist lixisenatide compared to bolus insulin both in combination with basal insulin for the treatment of patients with type 2 diabetes in Norway. Journal of Medical Economics 2015;18:573-585.	Did not report original utility data
79	Hunt B, Mocarski M, Valentine WJ, et al. Evaluation of the long-term cost-effectiveness of IDegLira versus liraglutide added to basal insulin for patients with type 2 diabetes failing to achieve glycemic control on basal insulin in the USA. Journal of Medical Economics 2017:1-8.	Did not report original utility data
80	Hunt B, Mocarski M, Valentine WJ, et al. IDegLira Versus Insulin Glargine U100: A Long-term Cost-effectiveness Analysis in the US Setting. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2017;27:27.	Did not report original utility data
81	Hunt B, Vega-Hernandez G, Valentine WJ, et al. Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. Diabetes, Obesity & Metabolism 2017;26:26.	Did not report original utility data
82	Ionova T, Nikitina T, Kurbatova K. Health Utilities Associated with Hypoglycemic Events in Type 2 Diabetes Mellitus (T2DM) Patients	Utility tool other than EQ-5D used

No.	Reference	Reason for exclusion
	Receiving Basal-Bolus Insulin Therapy. Value in Health 2015;18:A610.	
83	Ionova T, Nikitina T, Rodionova A, et al. Quality of life (QoL) and health utility (UT) in patients with type 2 diabetes mellitus (DM2) receiving different oral hypoglycemic therapy in a real-world setting. Value in Health 2016;19 (7):A678.	Utility tool other than EQ-5D used
84	Jennison C, Jobling A, Pearson E, et al. Assessing the benefits of a stratified treatment strategy which improves average HbA1c in a proportion of patients with type 2 diabetes: A mastermind study. Diabetic Medicine 2016;33:23.	Did not report utility data for the population of interest
85	Jeon A, Pandharipande PV, Kong CY, et al. Metformin chemoprevention against pancreatic adenocarcinoma in patients with type 2 diabetes mellitus: Results of a disease simulation model. Value in Health 2016;19 (3):A137.	Did not report utility data for the population of interest
86	Johansson T, Keller S, Winkler H, et al. Effectiveness of a Peer Support Programme versus Usual Care in Disease Management of Diabetes Mellitus Type 2 regarding Improvement of Metabolic Control: A Cluster-Randomised Controlled Trial. Journal of Diabetes Research 2016;2016:3248547.	Did not report relevant utility values
87	Johnson JA, Lier DA, Soprovich A, et al. Cost-Effectiveness Evaluation of Collaborative Care for Diabetes and Depression in Primary Care. American Journal of Preventive Medicine 2016;51:e13-20.	Did not report utility data for the population of interest
88	Johnson ST, Qiu W, Mundt C, et al. Sleep and health-related quality of life in adults with type 2 diabetes. Diabetologia 2015;1):S456-S457.	Did not report utility data for the population of interest
89	Johnson ST, Thiel D, Al Sayah F, et al. Objectively measured sleep and health-related quality of life in older adults with type 2 diabetes: a cross-sectional study from the Alberta's Caring for Diabetes Study. Sleep Health 2017;3:102-106.	Did not report relevant utility values
90	Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2017;21:1-218.	Did not report original utility data
91	Kabul S, Hood RC, Duan R, et al. Patient-reported outcomes in transition from high-dose U-100 insulin to human regular U-500 insulin in severely insulin-resistant patients with type 2 diabetes: analysis of a randomized clinical trial. Health & Quality of Life Outcomes 2016;14:139.	Did not report relevant utility values
92	Kansal A, Zheng Y, Proskorovsky I, et al. Modeling cardiovascular outcomes of treatment with empagliflozin in type 2 diabetes based on hard outcomes data. Value in Health 2016;19 (3):A203.	Did not report utility data for the population of interest
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95	Kasteleyn MJ, Vos RC, Rijken M, et al. Effectiveness of tailored support for people with Type 2 diabetes after a first acute coronary event: a multicentre randomized controlled trial (the Diacourse-ACE study). Diabetic Medicine 2016;33:125-33.	Did not report relevant utility values
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98	Kim D, Basu A. New metrics for economic evaluation in the presence of heterogeneity: Focusing on evaluating policy alternatives rather than treatment alternatives. Value in Health 2016;19 (3):A80.	Did not report utility data for the population of interest
99	Koekkoek PS, Biessels G, Kooistra M, et al. Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes. Diabetologia 2015;1):S414.	Did not report utility data for the population of interest
100	Koekkoek PS, Biessels GJ, Kooistra M, et al. Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes. Journal of Diabetes & its Complications 2015;29:1217-22.	Did not report relevant utility values
101	Koh D, Abdullah AM, Wang P, et al. Validation of Brunei's Malay EQ-5D Questionnaire in Patients with Type 2 Diabetes. PLoS ONE [Electronic Resource] 2016;11:e0165555.	Did not report relevant utility values
102	Konerding U, Bowen T, Elkhuizen SG, et al. The impact of travel distance, travel time and waiting time on health-related quality of life of diabetes patients: An investigation in six European countries. Diabetes Research & Clinical Practice 2017;126:16-24.	Did not report relevant utility values
103	Kragh N, Nauck MA, Mann JFE, et al. Health status assessed with EQ-5D in people with Type 2 diabetes participating in the LEADER trial. Diabetic Medicine 2017;34:80.	Did not report relevant utility values
104	Kragh N, Ye E, Hunt B, et al. Evaluating the cost-effectiveness of liraglutide 1.8mg versus lixisenatide 20mu G for patients with type 2 diabetes mellitus in the UK setting. Value in Health 2016;19 (7):A672.	Did not report utility data for the population of interest
105	Kragh N, Ye E, Hunt B, et al. Evaluating the cost-effectiveness of liraglutide 1.8mg versus lixisenatide 20mu g for the treatment of type 2 diabetes mellitus in the Spanish setting. Value in Health 2016;19 (7):A673.	Did not report utility data for the population of interest
106	Kragh N, Ye E, Valentine WJ, et al. Cost-effectiveness analysis of liraglutide 1.8mg versus lixisenatide 20mug for patients with type 2 diabetes mellitus in Italy. Value in Health 2016;19 (7):A672.	Did not report utility data for the population of interest
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108	Krysanov I, Tiapkina M. The Long-Term Cost-Effectiveness of Twice-Daily Exenatide with Insulin Glargine Versus Once-Daily Liraglutide with Insuline Detemir in Adult Patients with Type 2 Diabetes in Russia. Value in Health 2015;18:A606.	Did not report utility data for the population of interest
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110	Lamotte M, Foos V, McEwan P. Contrasting eight cardiovascular risk equations for use in type 2 diabetes cohorts using the CORE Diabetes Model. Diabetologia 2015;1):S556.	Did not report utility data for the population of interest
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No.	Reference	Reason for exclusion
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116	Lima LR, Stival MM, Funez MM, et al. Analysis of factors associated with diabetic neuropathy in a group of elderly patients with pain in primary care Health System/SUS in Brazil. European Geriatric Medicine 2016;7:S95.	Did not report utility data for the population of interest
117	Lin H, Babineaux S, Lew T, et al. The cost-effectiveness of dulaglutide versus liraglutide in patients with type 2 diabetes mellitus in Taiwan. Value in Health 2016;19 (7):A898.	Did not report utility data for the population of interest
118	Long E, Fang Y, Hu M, et al. Pharmacoeconomic evaluation of GLP-1 receptors agonist versus DPP-4 inhibitors in patients with Type 2 Diabetes: A systematic review. Value in Health 2015;18 (3):A63.	Not a publication type of interest
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120	Malhan S, Guler S, Yetkin I, et al. Dapagliflozin versus a dipeptidyl peptidase 4 inhibitor (DPP4) both added to metformin in patients with type 2 diabetes mellitus (T2DM): Impact on health, quality of life and costs in the Turkish clinical setting. Value in Health 2015;18 (7):A607.	Did not report utility data for the population of interest
121	Mann J, Nauck M, Ludemann J, et al. Health status assessed with Eq-5D in people with type 2 diabetes participating in the leader trial. Internist 2017;58:S7-S8.	Did not report relevant utility values
122	Mash R, Kroukamp R, Gaziano T, et al. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. Patient Education & Counseling 2015;98:622-6.	Did not report utility data for the population of interest
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125	Matza LS, Stewart KD, Davies EW, et al. Health State Utilities Associated With Attributes of Weekly Injection Devices for Treatment of Type 2 Diabetes. Value in Health 2015;18:A363.	Utility tool other than EQ-5D used
126	Mavrodi A, Dafoulas GE, Bargiota A, et al. Cost utility analysis of long-term telemonitoring of DMT2 patients among different eu health systems: The renewing health multicenter trial. Diabetes Technology and Therapeutics 2015;17:A118.	Utility tool other than EQ-5D used
127	McEwan P, Bennett H, Ward T, et al. Refitting of the UKPDS 68 Risk Equations to Contemporary Routine Clinical Practice Data in the UK. PharmacoEconomics 2015;33:149-161.	Did not report utility data for the population of interest
128	McEwan P, Evans M, Foos V, et al. A health economic evaluation of the edge study using the IMS core diabetes model. Value in Health 2015;18 (3):A60.	Did not report utility data for the population of interest
129	McEwan P, Evans M, Foos V, et al. Cost-effectiveness of second-line therapies in real-world setting: An economic evaluation of the EDGE study using patient level data. Diabetologia 2015;1):S482.	Did not report utility data for the population of interest
130	McEwan P, Evans M, Lamotte M, et al. Assessing the relative contribution to changes in quality-adjusted life expectancy associated with HbA1c, weight and hypoglycaemia across multiple risk equations with the Core Diabetes Model (CDM). Value in Health 2015;18 (3):A23.	Did not report utility data for the population of interest
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133	McEwan P, Gordon J, Foos V, et al. Cost effectiveness of type 2 diabetes treatments in middle eastern countries: An economic evaluation of the EDGE study using patient level data. Value in Health 2016;19 (3):A202.	Did not report utility data for the population of interest
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136	Meng F, Sun Y, Leow MK. Optimal treatment strategies in prevention of stroke and coronary heart disease among type 2 diabetes patients using Markov decision process. Value in Health 2016;19 (3):A296.	Did not report utility data for the population of interest
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139	Moller AH, Erntoft S, Vinding GR, et al. A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. Patient Related Outcome Measures 2015;6:167-77.	Not a publication type of interest
140	Morales C, de Luis D, de Arellano AR, et al. Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain. Diabetes Therapy 2015;6:593-610.	Did not report original utility data
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142	Muka T, Imo D, Jaspers L, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. European Journal of Epidemiology 2015;30:251-277.	Not a publication type of interest
143	Mukkamala L, Bhagat N, Zarbin M. Practical Lessons from Protocol T for the Management of Diabetic Macular Edema. Developments in Ophthalmology 2017;60:109-124.	Did not report utility data for the population of interest
144	Nagarajan M, Padula WV. Societal impact of one-time screening for diabetes at age 30 in the Indian population: A cost-effectiveness analysis. Value in Health 2016;19 (7):A606.	Did not report original utility data
145	Nagy B, Zsolyom A, Nagyjanosi L, et al. Cost-effectiveness of a risk-based secondary screening programme of type 2 diabetes. Diabetes/Metabolism Research and Reviews 2016;32:710-729.	Did not report original utility data
146	Najafi B, Farzadfar F, Ghaderi H, et al. Cost effectiveness of type 2 diabetes screening: A systematic review. Medical Journal of the Islamic Republic of Iran 2016;30:326.	Not a publication type of interest
147	Nazir SU, Hassali MA, Saleem F, et al. A cross-sectional assessment of health-related quality of life among type 2 diabetic patients in Pakistan. Value in Health 2015;18 (7):A616.	Did not report relevant utility values
148	Nazir SU, Hassali MA, Saleem F, et al. Does treatment adherence correlates with health-related quality of life: Findings from a cross sectional analysis of type 2 diabetes mellitus patients in Pakistan. Value in Health 2015;18 (7):A613.	Did not report relevant utility values
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150	Neidell M, Lamster IB, Shearer B. Cost-effectiveness of diabetes screening initiated through a dental visit. Community Dentistry & Oral Epidemiology 2017;01:01.	Did not report utility data for the population of interest
151	Nerat T, Locatelli I, Kos M. Type 2 diabetes: cost-effectiveness of medication adherence and lifestyle interventions. Patient preference & adherence 2016;10:2039-2049.	Did not report utility data for the population of interest
152	Neslusan C, Teschemaker A, Johansen P, et al. Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus in Mexico.	Did not report original utility data

No.	Reference	Reason for exclusion
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154	Nguyen HV, Tan GS, Tapp RJ, et al. Cost-effectiveness of a National Telemedicine Diabetic Retinopathy Screening Program in Singapore. Ophthalmology 2016;123:2571-2580.	Did not report original utility data
155	Nielsen AT, Pitcher A, Lovato E, et al. The cost-effectiveness evaluation of canagliflozin versus dapagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy in Spain. Value in Health 2015;18 (3):A61.	Did not report utility data for the population of interest
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157	Odnoletkova I, Ramaekers D, Nobels F, et al. Delivering Diabetes Education through Nurse-Led Telecoaching. Cost-Effectiveness Analysis. PLoS ONE [Electronic Resource] 2016;11:e0163997.	Did not report original utility data
158	Oksman E, Linna M, Horhammer I, et al. Cost-effectiveness analysis for a tele-based health coaching program for chronic disease in primary care. BMC Health Services Research 2017;17:138.	Did not report utility data for the population of interest
159	Pagkalos E, Thanopoulou A, Sampanis C, et al. The real-life effectiveness and care patterns of diabetes management study for Greece. "recap-dm". Value in Health 2016;19 (7):A677.	Did not report utility data for the population of interest
160	Palmer AJ, Vale MJ, Wells CL, et al. The long term cost effectiveness of the "coaching patients on achieving cardiovascular health" (coach) program in type 2 diabetes in Tasmania. Value in Health 2016;19 (7):A899.	Did not report utility data for the population of interest
161	Pan CW, Sun HP, Wang X, et al. The EQ-5D-5L index score is more discriminative than the EQ-5D-3L index score in diabetes patients. Quality of Life Research 2015;24:1767-74.	Did not report relevant utility values
162	Pan CW, Sun HP, Zhou HJ, et al. Valuing Health-Related Quality of Life in Type 2 Diabetes Patients in China. Medical Decision Making 2016;36:234-41.	Did not report relevant utility values
163	Partha G, Agrawal R, Paldanius PM, et al. Vildagliptin is cost-effective in real-world: Economic evaluation evidence from EDGE study. Diabetologia 2015;1):S481.	Did not report utility data for the population of interest
164	Pawaskar M, Iglay K, Engel SS, et al. Severity of hypoglycaemia and health related quality of life and work productivity in type 2 diabetes patients. Diabetologia 2016;59 (1 Supplement 1):S393.	Utility tool other than EQ-5D used
165	Perez A, Mezquita Raya P, Ramirez de Arellano A, et al. Cost-Effectiveness Analysis of Incretin Therapy for Type 2 Diabetes in Spain: 1.8 mg Liraglutide Versus Sitagliptin. Diabetes Therapy 2015;6:61-74.	Did not report utility data for the population of interest
166	Permsuwan U, Chaiyakunapruk N, Dilokthornsakul P, et al. Long-Term Cost-Effectiveness of Insulin Glargine Versus Neutral Protamine Hagedorn Insulin for Type 2 Diabetes in Thailand. Applied Health Economics and Health Policy 2016;14:281-292.	Did not report utility data for the population of interest
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169	Piercy J, Milligan G, Davies MJ, et al. The relationship between glucose-lowering medications, adherence, and outcomes in patients with type 2 diabetes. Value in Health 2015;18 (7):A343.	Did not report utility data for the population of interest
170	Pititto L, Neslusan C, Teschemaker AR, et al. Cost-Effectiveness of Canagliflozin (Cana) Versus Sitagliptin (Sita) As Add-On To Metformin Plus Sulfonylurea In Patients With Type 2 Diabetes Mellitus (T2dm) In Brazil. Value in Health 2015;18:A864.	Did not report utility data for the population of interest
171	Pockett RD, McEwan P, Ray J, et al. Prospective utility study of patients with multiple cardiovascular events. Value in Health 2016;19 (7):A348-A349.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
172	Pollock RF, Tikkanen CK. A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark. Journal of Medical Economics 2017;20:213-220.	Did not report original utility data
173	Prades M, Lizan L, Hunt B, et al. Long-term cost effectiveness analysis of ideglira versus GLP-1 added to basal insulin as intensification therapies in type 2 diabetes mellitus in Spain. Value in Health 2016;19 (3):A99.	Did not report utility data for the population of interest
174	Protheroe J, Rathod T, Bartlam B, et al. The Feasibility of Health Trainer Improved Patient Self-Management in Patients with Low Health Literacy and Poorly Controlled Diabetes: A Pilot Randomised Controlled Trial. Journal of Diabetes Research 2016;2016:6903245.	Did not report relevant utility values
175	Raibouaa A, Borgeke H, Alexiou D, et al. Cost-effectiveness of dulaglutide 1.5mg once weekly for the treatment of patients with type two diabetes mellitus in Sweden. Value in Health 2015;18 (7):A607.	Did not report utility data for the population of interest
176	Rajan N, Boye KS, Gibbs M, et al. Utilities for Type 2 Diabetes Treatment-Related Attributes in a South Korean and Taiwanese Population. Value in Health Regional Issues 2016;9:67-71.	Utility tool other than EQ-5D used
177	Ramirez De Arellano A, Mezquita P, Darba J. Cost-effectiveness analysis of insulin degludec compared with insulin glargine in the management of type 1 and type 2 diabetes mellitus from the Spanish national health system perspective. Value in Health 2016;19 (7):A673.	Did not report utility data for the population of interest
178	Reinders P, Zoellner YF, Wood R, et al. Quantification of quality of life differences due to common diseases in the age group 50+ in the United Kingdom. Value in Health 2016;19 (7):A483.	Did not report original utility data
179	Ridderstrale M, Evans LM, Jensen HH, et al. Estimating the impact of changes in HbA<inf>1c</inf>, body weight and insulin injection regimen on health related quality-of-life: A time trade off study. Health and Quality of Life Outcomes 2016;14 (1) (no pagination).	Utility tool other than EQ-5D used

No.	Reference	Reason for exclusion
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181	Roze S, Duteil E, Smith-Palmer J, et al. Cost-effectiveness of continuous subcutaneous insulin infusion in people with type 2 diabetes in the Netherlands. Journal of Medical Economics 2016;19:742-9.	Did not report utility data for the population of interest
182	Sabale U, Ekman M, Granstrom O, et al. Cost-effectiveness of dapagliflozin (Forxiga) added to metformin compared with sulfonylurea added to metformin in type 2 diabetes in the Nordic countries. Primary care diabetes 2015;9:39-47.	Did not report original utility data
183	Sabapathy S, Neslusan C, Yoong K, et al. Cost-effectiveness of Canagliflozin versus Sitagliptin When Added to Metformin and Sulfonylurea in Type 2 Diabetes in Canada. Journal of Population Therapeutics & Clinical Pharmacology 2016;23:e151-68.	Did not report original utility data
184	Sabapathy S, Neslusan C, Yoong K, et al. The cost-effectiveness of canagliflozin versus sitagliptin as third-line therapy in Type 2 Diabetes Mellitus (T2dm) in a Canadian setting. Value in Health 2015;18 (3):A61.	Did not report utility data for the population of interest
185	Saffari M, Karimi T, Koenig HG, et al. Psychometric evaluation of the Persian version of the Type 2 Diabetes and Health Promotion Scale (T2DHPS): a diabetes-specific measure of lifestyle. Scandinavian Journal of Caring Sciences 2015;29:603-12.	Did not report utility data for the population of interest
186	Safita N, Islam SM, Chow CK, et al. The impact of type 2 diabetes on health related quality of life in Bangladesh: results from a matched study comparing treated cases with non-diabetic controls. Health & Quality of Life Outcomes 2016;14:129.	Did not report original utility data
187	Salampessy BH, Veldwijk J, Jantine Schuit A, et al. The Predictive Value of Discrete Choice Experiments in Public Health: An Exploratory Application. The Patient: Patient-Centered Outcomes Research 2015;8:521-9.	Did not report utility data for the population of interest
188	Saleh F, Ara F, Mumu SJ, et al. Assessment of health-related quality of life of Bangladeshi patients with type 2 diabetes using the EQ-5D: a cross-sectional study. BMC Research Notes 2015;8:497.	Did not report utility data for the population of interest
189	Samah S, Neoh CF, Wong YY, et al. Linguistic and psychometric validation of the Malaysian version of Diabetes Quality of Life-Brief Clinical Inventory (DQoL-BCI). Research In Social & Administrative Pharmacy 2016;24:24.	Did not report utility data for the population of interest
190	Sanchez R, Marino E, Daniel A, et al. Cost-effectiveness of bariatric surgery for the treatment of morbid obesity patients compared with conservative management in Spain. Value in Health 2016;19 (7):A587.	Did not report utility data for the population of interest
191	Sayah FA, Qiu W, Johnson JA. Health literacy and health-related quality of life in adults with type 2 diabetes: a longitudinal study. Quality of Life Research 2016;25:1487-1494.	Did not report relevant utility values
192	Sayah FA, Qiu W, Xie F, et al. Comparative performance of the EQ-5D-5L and SF-6D index scores in adults with type 2 diabetes. Quality of Life Research 2017:1-10.	Did not report relevant utility values
193	Schroeder M, Johansen P, Willis M, et al. The cost-effectiveness of canagliflozin (CANA) versus dapagliflozin (DAPA) 10mg and empagliflozin (EMPA) 25mg in patients with type 2 diabetes	Did not report utility data for the population of interest

No.	Reference	Reason for exclusion
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194	Schroeder M, Johansen P, Willis M, et al. The cost-effectiveness of canagliflozin versus sulphonylurea in patients with Type 2 diabetes with inadequate control on metformin monotherapy in the UK. Diabetic Medicine 2015;32:205.	Did not report utility data for the population of interest
195	Schunk M, Reitmeir P, Schipf S, et al. Health-related quality of life in women and men with type 2 diabetes: a comparison across treatment groups. Journal of Diabetes & its Complications 2015;29:203-11.	Did not report utility data for the population of interest
196	Segal L, Nguyen H, Schmidt B, et al. Economic evaluation of indigenous health worker management of poorly controlled type 2 diabetes in north Queensland. Medical Journal of Australia 2016;204:196.e1-196.e9.	Utility tool other than EQ-5D used
197	Shao H, Shi L. Cost-effectiveness analysis of dapagliflozin versus glimepiride as monotherapy in patients with type 2 diabetes mellitus in China. Value in Health 2016;19 (7):A898.	Did not report utility data for the population of interest
198	Shao H, Zhai S, Zou D, et al. Cost-effectiveness analysis of dapagliflozin versus glimepiride as monotherapy in a Chinese population with type 2 diabetes mellitus. Current Medical Research & Opinion 2017;33:359-369.	Did not report original utility data
199	Shingler S, Fordham B, Evans M, et al. Utilities for treatment-related adverse events in type 2 diabetes. Journal of Medical Economics 2015;18:45-55.	Utility tool other than EQ-5D used
200	Siaw M, Tai B, Lee J. Psychometric properties of the Chinese version of problem areas in diabetes scale (SG-PAID-c) among high-risk polypharmacy patients with uncontrolled type 2 diabetes in Singapore. Value in Health 2016;19 (7):A901.	Did not report relevant utility values
201	Siaw MY, Tai BB, Lee JY. Psychometric properties of the Chinese version of the Problem Areas in Diabetes scale (SG-PAID-C) among high-risk polypharmacy patients with uncontrolled type 2 diabetes in Singapore. Journal of Diabetes Investigation 2017;8:235-242.	Did not report relevant utility values
202	Sikirica M, Mansfield C, Pugh A, et al. Patient preferences for attributes of type 2 diabetes mellitus treatments in Germany. Diabetologia 2015;1):S348.	Did not report utility data for the population of interest
203	Simmons RK, Borch-Johnsen K, Lauritzen T, et al. A randomised trial of the effect and cost-effectiveness of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with screen-detected type 2 diabetes: the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) study. Health Technology Assessment (Winchester, England) 2016;20:1-86.	Did not report relevant utility values
204	Simon D, de Pablos-Velasco P, Parhofer KG, et al. Hypoglycaemic episodes in patients with type 2 diabetes--risk factors and associations with patient-reported outcomes: The PANORAMA Study. Diabetes & Metabolism 2015;41:470-9.	Did not report utility data for the population of interest
205	Slee A, Traina S, Neslusan C. Analyzing EQ-5D in phase 3 clinical trials of type 2 diabetes mellitus (T2DM): Is mean change capturing patient impact? Value in Health 2015;18 (3):A66.	Did not report relevant utility values
206	Suraj B, Tripathi CD, Biswas K, et al. A Comparative Evaluation of Safety, Efficacy and Cost Effectiveness of Three Add on Treatment Regimens in Type 2 Diabetics; Not Controlled by	Did not report utility data for the population

No.	Reference	Reason for exclusion
	Metformin Alone. Research Journal of Pharmacy and Technology 2015;8:44-50.	of interest
207	Tang Q, Sun Z, Zhang N, et al. Cost-Effectiveness of Bariatric Surgery for Type 2 Diabetes Mellitus. Medicine (United States) 2016;95 (20) (no pagination).	Did not report utility data for the population of interest
208	Tang Q, Sun Z, Zhang N, et al. Cost-Effectiveness of Bariatric Surgery for Type 2 Diabetes Mellitus: A Randomized Controlled Trial in China. Medicine 2016;95:e3522.	Did not report utility data for the population of interest
209	Teschemaker AR, Neslusan C, Sabapathy S, et al. The cost-effectiveness of canagliflozin (CANA) versus saxagliptin (SAXA) among older Individuals living with type 2 diabetes mellitus (T2DM) in canada. Value in Health 2015;18 (3):A62-A63.	Did not report utility data for the population of interest
210	Thiel DM, Al Sayah F, Vallance J, et al. Physical Activity and Health-Related Quality of Life in Adults with Type 2 Diabetes: Results from a Prospective Cohort Study. Journal of Physical Activity & Health 2017:1-23.	Did not report relevant utility values
211	Thiel DM, Al Sayah F, Vallance JK, et al. Association between Physical Activity and Health-Related Quality of Life in Adults with Type 2 Diabetes. Canadian Journal of Diabetes 2017;41:58-63.	Did not report relevant utility values
212	Thomas RL, Winfield TG, Luzio SD, et al. Economic and patient impact of changing to biennial screening iIntervals for diabetic retinopathy. Diabetic Medicine 2017;34:172-173.	Did not report utility data for the population of interest
213	Tilden D, Makino K, Cottrell S, et al. Quantifying the cost and quality of life implications of adverse events associated with long-term oral corticosteroid use. Value in Health 2015;18 (7):A688.	Not a publication type of interest
214	Tin ST, Iro G, Gadabu E, et al. Counting the Cost of Diabetes in the Solomon Islands and Nauru. PLoS ONE [Electronic Resource] 2015;10:e0145603.	Did not report utility data for the population of interest
215	Toscano CM, Zhuo X, Imai K, et al. Cost-effectiveness of a national population-based screening program for type 2 diabetes: the Brazil experience. Diabetology & metabolic syndrome 2015;7:95.	Did not report utility data for the population of interest
216	Tsukube S, Ikeda Y, Kadowaki T, et al. Improved Treatment Satisfaction and Self-reported Health Status after Introduction of Basal-Supported Oral Therapy Using Insulin Glargine in Patients with Type 2 Diabetes: Sub-Analysis of ALOHA2 Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2015;6:153-71.	Did not report relevant utility values
217	Vaidya V, Anupindi VR, Pinto S, et al. Cost utility analysis of fixed-dose and free-dose combinations of oral medications in type 2 diabetes patients. Journal of Pharmaceutical Health Services Research 2016;7:181-187.	Utility tool other than EQ-5D used
218	Valentine WJ, Curtis BH, Pollock RF, et al. Is the current standard of care leading to cost-effective outcomes for patients with type 2 diabetes requiring insulin? A long-term health economic analysis for the UK. Diabetes Research & Clinical Practice 2015;109:95-103.	Not a publication type of interest
219	Van Brunt K, Adetunji O, Yu M, et al. Change in patient-reported outcomes (PROs) and the relationship with clinical parameters in patients with Type 2 diabetes receiving once weekly dulaglutide or insulin glargine in the Assessment of Weekly Administration of Dulaglutide in Diabetes (AWARD-2 and-4) studies. Diabetic Medicine 2015;32:76.	Did not report utility data for the population of interest

No.	Reference	Reason for exclusion
220	van Giessen A, Boonman-de Winter LJ, Rutten FH, et al. Cost-effectiveness of screening strategies to detect heart failure in patients with type 2 diabetes. Cardiovascular Diabetology 2016;15:48.	Did not report original utility data
221	Varney JE, Liew D, Weiland TJ, et al. The cost-effectiveness of hospital-based telephone coaching for people with type 2 diabetes: a 10 year modelling analysis. BMC Health Services Research 2016;16:521.	Did not report utility data for the population of interest
222	Vega-Hernandez G, Wojcik R, Schlueter M. Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2017;27:27.	Did not report original utility data
223	Venkataraman K, Wee HL, Khoo EYH, et al. Role of functional status in health related quality of life in individuals with diabetic peripheral neuropathy. Archives of Physical Medicine and Rehabilitation 2016;97 (10):e102-e103.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
224	Vohra Y, Patidar V, Alexander A, et al. Assessment of Health Related Quality of Life (Hrql) Using Eq-5d In Type 2 Diabetes Mellitus Patients In A University Teaching Hospital. Value in Health 2015;18:A616.	Utility tool other than EQ-5D used
225	Wainwright TW, Immins T, Middleton RG. An evaluation of a new education and cycling programme that aims to promote the self-management of hip osteoarthritis through education, advice and exercise. Osteoarthritis and Cartilage 2016;24:S418.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
226	Wan EY, Fung CS, Choi EP, et al. Main predictors in health-related quality of life in Chinese patients with type 2 diabetes mellitus. Quality of Life Research 2016;25:2957-2965.	Utility tool other than EQ-5D used
227	Wang H, Liu X, Wan L, et al. Cost-effectiveness of biphasic insulin aspart 50 versus biphasic human insulin 50 in people with type 2 diabetes mellitus in china. Value in Health 2016;19 (7):A897-A898.	Did not report utility data for the population of interest
228	Wang P, Luo NES, Tai ES, et al. The EQ-5D-5L is More Discriminative Than the EQ-5D-3L in Patients with Diabetes in Singapore. Value in Health Regional Issues 2016;9:57-62.	Did not report relevant utility values
229	Wang Y, Marwick T. Cost-effectiveness of myocardial imaging to identify subclinical left ventricular dysfunction in elderly patients with asymptomatic type 2 diabetes. Journal of the American College of Cardiology 2016;1):2033.	Did not report utility data for the population of interest
230	Wang Y, Tan NC, Tay EG, et al. Cross-cultural measurement equivalence of the 5-level EQ-5D (EQ-5D-5L) in patients with type 2 diabetes mellitus in Singapore. Health & Quality of Life Outcomes 2015;13:103.	Did not report relevant utility values
231	Wang Y, Yang H, Wright L, et al. Exercise intolerance in elderly asymptomatic type 2 diabetes: Left ventricular dysfunction, diabetes control, therapy or insulin resistance? European Heart Journal 2015;36:641-642.	Did not report utility data for the population of interest
232	Wang Y, Yeo QQ, Ko Y. Economic evaluations of pharmacist-managed services in people with diabetes mellitus: a systematic review. Diabetic Medicine 2016;33:421-7.	Not a publication type of interest
233	Wentworth JM, Dalziel KM, O'Brien PE, et al. Cost-effectiveness	Utility tool other than

No.	Reference	Reason for exclusion
	of gastric band surgery for overweight but not obese adults with type 2 diabetes in the U.S. Journal of Diabetes and its Complications. 2017;11.	EQ-5D used
234	Wingate LT, Oishi TS, Shubar Ali NS. A cost-effectiveness analysis of alogliptin in comparison to saxagliptin. Value in Health 2015;18 (3):A61.	Did not report utility data for the population of interest
235	Wong CK, Jiao FF, Siu SC, et al. Cost-Effectiveness of a Short Message Service Intervention to Prevent Type 2 Diabetes from Impaired Glucose Tolerance. Journal of Diabetes Research 2016;2016:1219581.	Did not report original utility data
236	Wong CK, Wong WC, Wan EY, et al. Increased number of structured diabetes education attendance was not associated with the improvement in patient-reported health-related quality of life: results from Patient Empowerment Programme (PEP). Health & Quality of Life Outcomes 2015;13:126.	Utility tool other than EQ-5D used
237	Wu B, Li J, Wu H. Strategies to Screen for Diabetic Retinopathy in Chinese Patients with Newly Diagnosed Type 2 Diabetes: A Cost-Effectiveness Analysis. Medicine 2015;94:e1989.	Did not report original utility data
238	Yang H, Negishi K, Nolan M, et al. Risk of overt heart failure in stage a and b heart failure: Association with symptoms, physiology and expected outcome. Journal of the American College of Cardiology 2015;1):A1036.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
239	Yfantopoulos I, Katopodis P, Rombopoulos G, et al. The incidence of hypoglycemia in type ii diabetes mellitus (T2DM) patients treated with insulin therapy in combination with DPP-4 in Greece. A sub-analysis of hypo 2 study. Value in Health 2016;19 (7):A679.	Did not report utility data for the population of interest
240	Yfantopoulos I, Katopodis P, Rombopoulos G, et al. The influence of glycemic control in the quality of life of type 2 diabetes mellitus patients in Greece-the hypo2 study. Value in Health 2016;19 (7):A679.	Did not report relevant utility values
241	Younossi Z, Stepanova M, Omata M, et al. The impact of all oral regimen ledipasvir/sofosbuvir (LDV/SOF) on patient-reported outcomes (PROs) of Asian patients with chronic hepatitis C (CHC). Hepatology International 2017;11 (1 Supplement 1):S106.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
242	Younossi ZM, Henry L, Stepanova M, et al. Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (DM): A costly combination. Gastroenterology 2016;1):S657.	Did not report utility data for the population of interest
243	Yu M, Van Brunt K, Milicevic Z, et al. Patient-reported outcomes with once weekly dulaglutide versus placebo, both in combination with once daily insulin glargine (+/- metformin) in type 2 diabetes (AWARD-9). Diabetologia 2016;59 (1 Supplement 1):S383-S384.	Did not report relevant utility values
244	Yu M, Van Brunt K, Varnado OJ, et al. Patient-reported outcome results in patients with type 2 diabetes treated with once-weekly dulaglutide: Data from the AWARD phase III clinical trial programme. Diabetes, Obesity and Metabolism 2016;18:419-424.	Did not report relevant utility values
245	Yue X, Guan HJ, Wu J, et al. Cost-effectiveness of insulin degludec treatment in patients with type1 and type 2 diabetes mellitus: A systematic review. Value in Health 2016;19 (7):A898.	Not a publication type of interest
246	Zhang C, Hu C, Xu L. Review of economic evaluation of saxagliptin in type2 diabetes in China. Value in Health 2016;19 (7):A898-A899.	Not a publication type of interest

No.	Reference	Reason for exclusion
247	Zhang P, Bao Y, Zhu D, et al. Improvement in quality of life after initiation of basal insulin therapy, results from the ORBIT study. Diabetologia 2016;59 (1 Supplement 1):S442.	Did not report relevant utility values
248	Zhang P, Hire D, Espeland MA, et al. Impact of intensive lifestyle intervention on preference-based quality of life in type 2 diabetes: Results from the Look AHEAD trial. Obesity 2016;24:856-864.	Utility tool other than EQ-5D used
249	Zhang X, Liu S, Li Y, et al. Long-Term Effectiveness and Cost-Effectiveness of Metformin Combined with Liraglutide or Exenatide for Type 2 Diabetes Mellitus Based on the CORE Diabetes Model Study. PLoS ONE [Electronic Resource] 2016;11:e0156393.	Did not report utility data for the population of interest
250	Zhang Y, Ning F, Sun J, et al. Impact of a diabetes screening program on a rural Chinese population: a 3-year follow-up study. BMC Public Health 2015;15:198.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
251	Zolotarev AV, Tselina ME, Iskhakova A. Clinico-economic evaluation of combined treatment of diabetic macular edema. Value in Health 2016;19 (7):A570.	Did not report utility data for the population of interest
252	Zyoud SH, Al-Jabi SW, Sweileh WM, et al. Relationship of treatment satisfaction to health-related quality of life among Palestinian patients with type 2 diabetes mellitus: Findings from a cross-sectional study. Journal of Clinical and Translational Endocrinology 2015;2:66-71.	Did not report relevant utility values

Table G.11: Articles excluded from the cost and resource use stream of the economic systematic literature review at full-text stage

No.	Reference	Reason for exclusion
1	Abdulameer SA, Syed Sulaiman SA, Hassali MAA, et al. Osteoporosis and type 2 diabetes mellitus: What do we know, and what we can do? Patient Preference and Adherence 2012;6:435-448.	Did not report relevant, original cost and resource use collected in the past 10 years
2	Adams RP, Barton G, Bhattacharya D, et al. Supervised pharmacy student-led medication review in primary care for patients with type 2 diabetes: a randomised controlled pilot study. BMJ Open 2015;5:e009246.	Did not report relevant, original cost and resource use collected in the past 10 years
3	Afonso M, Ryan F, Pitcher A, et al. Evaluating drug cost per responder and number needed to treat associated with lixisenatide on top of glargine when compared to rapid-acting insulin intensification regimens on top of glargine, in patients with type 2 diabetes in the UK, Italy, and Spain. Journal of Medical Economics 2017:1-7.	Did not report relevant cost and resource use data
4	Agarwal R, Williams K. Incretin-based therapies for inpatient management of type 2 diabetes mellitus (Structured abstract). Health Technology Assessment Database: Center for Evidence-based Practice (CEP), 2009.	Not a publication type of interest
5	Alfonso-Rosa RM, del Pozo-Cruz J, del Pozo-Cruz B, et al. Cost-utility analysis of a 12-week whole-body vibration based treatment for people with type 2 diabetes: Reanalysis of a RCT in a primary care context. Public Health 2015;129:993-995.	Did not report relevant, original cost and resource use collected in the past 10 years
6	Alouki K, Delisle H, Bermudez-Tamayo C, et al. Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies. Journal of Diabetes Research 2016;2016:2159890.	Did not report relevant, original cost and resource use collected in the past 10 years
7	Alva ML, Gray A, Mihaylova B, et al. The impact of diabetes-related complications on healthcare costs: New results from the UKPDS (UKPDS 84). Diabetic Medicine 2015;32:459-466.	Did not report relevant, original cost and resource use collected in the past 10 years
8	Andreassen LM, Kjome RLS, Solvik UO, et al. The potential for deprescribing in care home residents with Type 2 diabetes. International Journal of Clinical Pharmacy 2016;38:977-984.	Did not report relevant cost and resource use data
9	Anonymous. Abstracts of 52nd EASD Annual Meeting. Diabetologia. Conference: 52nd Annual Meeting of the European Association for the Study of Diabetes, EASD 2016;59.	Not a publication type of interest
10	Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. The Lancet Diabetes & Endocrinology 2017;5:355-366.	Did not report relevant, original cost and resource use collected in the past 10 years
11	Aronson R, Galstyan G, Goldfracht M, et al. Health economic impact of hypoglycemia in a global population of patients with insulin-treated diabetes. Diabetes 2015;64:A69-A70.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
12	Asche CV, Bode B, Busk AK, et al. The economic and clinical benefits of adequate insulin initiation and intensification in people with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism 2012;14:47-57.	Not a publication type of interest

No.	Reference	Reason for exclusion
13	Asche CV, Hippler SE, Eurich DT. Review of models used in economic analyses of new oral treatments for type 2 diabetes mellitus. PharmacoEconomics 2014;32:15-27.	Not a publication type of interest
14	Asche CV, Shane-McWhorter L, Raparla S. Health economics and compliance of vials/syringes versus pen devices: a review of the evidence. Diabetes Technology & Therapeutics 2010;12 Suppl 1:S101-8.	Not a publication type of interest
15	AVE0010 (ZP10) for type 2 diabetes mellitus (Structured abstract). Health Technology Assessment Database: National Horizon Scanning Centre (NHSC), 2008.	Not a publication type of interest
16	Baptista A, Teixeira I, Romano S, et al. The place of DPP-4 inhibitors in the treatment algorithm of diabetes type 2: a systematic review of cost-effectiveness studies. European Journal of Health Economics 2016:1-29.	Not a publication type of interest
17	Baxter M, Hex N, Samyshkin Y, et al. If we followed the National Institute of Health and Care Excellence (NICE) guidelines and treated people with diabetes earlier, patients and the National Health Service would benefit from a reduction in complications, mortality and direct healthcare costs. Diabetic Medicine 2015;32:198.	Did not report relevant, original cost and resource use collected in the past 10 years
18	Baxter M, Hudson R, Mahon J, et al. Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit. Diabetic Medicine 2016;33:1575-1581.	Did not report relevant, original cost and resource use collected in the past 10 years
19	Beaudet A, Palmer J, Timlin L, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK (Structured abstract). Journal of Medical Economics. Volume 14, 2011:357-366.	Did not report relevant, original cost and resource use collected in the past 10 years
20	Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773-9.	Not a publication type of interest
21	Bellary S, O'Hare J, Raymond N, et al. Enhanced diabetes care to patients of south Asian ethnic origin (the United Kingdom Asian Diabetes Study): a cluster randomised controlled trial. The Lancet 2008;371:1769-1776.	Did not report relevant, original cost and resource use collected in the past 10 years
22	Belsey JD, Pittard JB, Rao S, et al. Self blood glucose monitoring in type 2 diabetes. A financial impact analysis based on UK primary care. International Journal of Clinical Practice 2009;63:439-448.	Did not report relevant cost and resource use data
23	Bennett W, Wilson L, Bolen S, et al. Oral diabetes medications for adults with type 2 diabetes: an update (Structured abstract). Health Technology Assessment Database: Agency for Healthcare Research and Quality (AHRQ), 2011.	Not a publication type of interest
24	Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: An update including new drugs and 2-drug combinations. Annals of Internal Medicine 2011;154:602-618.	Not a publication type of interest
25	Bhikha Z, Sharma D, Meldon A, et al. The battle to maximise efficiency in preoperative diabetes care: Is there a role for a dedicated diabetes specialist led preoperative clinic? Diabetic Medicine 2017;34:182.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately

No.	Reference	Reason for exclusion
26	Bhopal RS, Douglas A, Wallia S, et al. Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: A family-cluster randomised controlled trial. The Lancet Diabetes and Endocrinology 2014;2:218-227.	Did not report relevant, original cost and resource use collected in the past 10 years
27	Bird A, O'Brien J, Candelier C. The 6-week postpartum oral glucose tolerance test for women with gestational diabetes: An opportune time for risk assessment and for implementing lifestyle changes. Archives of Disease in Childhood: Fetal and Neonatal Edition 2010;95:Fa42.	Did not report relevant, original cost and resource use collected in the past 10 years
28	Black C, Cummins E, Royle P, et al. The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: A systematic review and economic evaluation. Health Technology Assessment 2007;11:iii-70.	Not a publication type of interest
29	Black JA, Long GH, Sharp SJ, et al. Change in cardio-protective medication and health-related quality of life after diagnosis of screen-detected diabetes: Results from the ADDITION-Cambridge cohort. Diabetes Research & Clinical Practice 2015;109:170-7.	Did not report relevant cost and resource use data
30	Black JA, Simmons RK, Boothby CE, et al. Medication burden in the first 5 years following diagnosis of type 2 diabetes: Findings from the ADDITION-UK trial cohort. BMJ Open Diabetes Research and Care 2015;3 (1) (no pagination).	Did not report relevant cost and resource use data
31	Blak BT, Rigney U, Sternhufvud C, et al. Weight change and healthcare resource use in English patients with type 2 diabetes mellitus initiating a new diabetes medication class. International Journal of Clinical Practice 2016;70:45-55.	Did not report relevant cost and resource use data
32	Bockelbrink A, Stober Y, Roll S, et al. Evaluation of medical and health economic effectiveness of bariatric surgery (obesity surgery) versus conservative strategies in adult patients with morbid obesity. GMS Health Technology Assessment 2008;4:Doc06.	Not a publication type of interest
33	Bottomley JM, Raymond FD. Pharmaco-economic issues for diabetes therapy. Best Practice & Research Clinical Endocrinology & Metabolism 2007;21:657-85.	Not a publication type of interest
34	Bottomley JM, Raymond FD. Pharmaco-economic issues for diabetes therapy. Insulin 2009;4:32-60.	Not a publication type of interest
35	Boulanger M, Al-Shahi Salman R, Kerssens J, et al. Association between diabetes mellitus and incidence of intracerebral haemorrhage and case fatality rates: A retrospective population-based cohort study. Diabetes, Obesity & Metabolism 2017;09:09.	Did not report relevant, original cost and resource use collected in the past 10 years
36	Breeze PR, Thomas C, Squires H, et al. Impact of Type 2 diabetes prevention programmes based on risk identification and lifestyle intervention intensity strategies: A cost-effectiveness analysis. Diabetic Medicine. 2015.	Did not report relevant, original cost and resource use collected in the past 10 years
37	Breeze PR, Thomas C, Squires H, et al. The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. Diabetic Medicine 2017;34:632-640.	Did not report relevant, original cost and resource use collected in the past 10 years
38	Breitscheidel L, Stamenitis S, Dippel FW, et al. Economic impact of compliance to treatment with antidiabetes medication in type 2 diabetes mellitus: A review paper. Journal of Medical Economics 2010;13:8-15.	Not a publication type of interest
39	Brennan VK, Mauskopf J, Colosia AD, et al. Utility estimates for	Not a publication type

No.	Reference	Reason for exclusion
	patients with Type 2 diabetes mellitus after experiencing a myocardial infarction or stroke: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research 2015;15:111-23.	of interest
40	Brice R, Shelley S, Chaturvedi P, et al. Resource use and outcomes associated with initiation of injectable therapies for patients with type 2 diabetes mellitus. Drugs in Context 2015;4:212269.	Did not report relevant cost and resource use data
41	Briggs AH, Bhatt DL, Scirica BM, et al. Health-related quality-of-life (HRQoL) implications of cardiovascular and hypoglycaemic events in type 2 diabetes mellitus. Diabetologia 2015;1):S571.	Did not report relevant, original cost and resource use collected in the past 10 years
42	Brod M, Galstyan G, Unnikrishnan AG, et al. Self-Treated Hypoglycemia in Type 2 Diabetes Mellitus: Results from the Second Wave of an International Cross-Sectional Survey. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2016;7:279-93.	Did not present cost and resource use collected in the UK
43	Brod M, Nikolajsen A, Weatherall J, et al. The Economic Burden of Post-prandial Hyperglycemia (PPH) Among People with Type 1 and Type 2 Diabetes in Three Countries. Diabetes Therapy 2016;7:75-90.	Did not report relevant cost and resource use data
44	Brod M, Nikolajsen A, Weatherall J, et al. The impact of postprandial hyperglycaemic episodes (PPH) on health care resources among people with type 1 or type 2 diabetes in the U.S., UK, and Germany. Diabetes 2015;64:A357.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
45	Brod M, Rana A, Barnett AH. Impact of self-treated hypoglycaemia in type 2 diabetes: A multinational survey in patients and physicians. Current Medical Research and Opinion 2012;28:1947-1958.	Did not present cost and resource use collected in the UK
46	Brod M, Wolden M, Christensen T, et al. Understanding the economic burden of nonsevere nocturnal hypoglycemic events: impact on work productivity, disease management, and resource utilization. Value in Health 2013;16:1140-9.	Did not report relevant, original cost and resource use collected in the past 10 years
47	Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obesity Surgery 2013;23:427-436.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
48	Cadth. Glucose replacement agents in frail elderly patients with type ii diabetes in long-term care: clinical and cost-effectiveness, harms, and guidelines (Structured abstract). Health Technology Assessment Database: Canadian Agency for Drugs and Technologies in Health (CADTH), 2015.	Not a publication type of interest
49	Campbell JA, Venn A, Neil A, et al. Diverse approaches to the health economic evaluation of bariatric surgery: a comprehensive systematic review. Obesity Reviews 2016;17:850-894.	Not a publication type of interest
50	Casciano R, Malangone E, Ramachandran A, et al. A quantitative assessment of patient barriers to insulin. International Journal of Clinical Practice 2011;65:408-414.	Did not report relevant, original cost and resource use collected in the past 10 years
51	Cassimatis M, Kavanagh DJ. Effects of type 2 diabetes behavioural telehealth interventions on glycaemic control and adherence: A systematic review. Journal of Telemedicine and	Not a publication type of interest

No.	Reference	Reason for exclusion
	Telecare 2012;18:447-450.	
52	Chadban S, Howell M, Twigg S, et al. Cost-effectiveness and socioeconomic implications of prevention and management of chronic kidney disease in type 2 diabetes. Nephrology 2010;15:S195-S203.	Not a publication type of interest
53	Chalk D, Pitt M, Vaidya B, et al. Can the retinal screening interval be safely increased to 2 years for type 2 diabetic patients without retinopathy? Diabetes Care 2012;35:1663-1668.	Did not report relevant, original cost and resource use collected in the past 10 years
54	Chambers S, Manickam D, Wooldridge E, et al. Bariatric surgery in Type 2 Diabetics: The financial impact on the local health economy. Obesity Facts 2016;9:167.	Did not report relevant cost and resource use data
55	Chan JC, Ramachandran A, Mbanya JC, et al. Impact of diabetes management on diabetes control and resource consumption in type 2 diabetic patients. Value in Health 2016;19 (7):A683.	Did not present cost and resource use collected in the UK
56	Charokopou M, Chuang L, Verheggen B, et al. Cost-Effectiveness Analysis of Exenatide Once-Weekly Versus Dulaglutide, Liraglutide and Lixisenatide for the Treatment of Type 2 Diabetes Mellitus: An Analysis from the UK NHS Perspective. Value in Health 2015;18:A606.	Did not report relevant, original cost and resource use collected in the past 10 years
57	Charokopou M, McEwan P, Lister S, et al. Cost-effectiveness of dapagliflozin versus DPP-4 inhibitors as an add-on to Metformin in the Treatment of Type 2 Diabetes Mellitus from a UK Healthcare System Perspective. BMC Health Services Research 2015;15:496.	Did not report relevant, original cost and resource use collected in the past 10 years
58	Charokopou M, McEwan P, Lister S, et al. The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. Diabetic Medicine 2015;32:890-898.	Did not report relevant, original cost and resource use collected in the past 10 years
59	Charokopou M, Sabater FJ, Townsend R, et al. Methods applied in cost-effectiveness models for treatment strategies in type 2 diabetes mellitus and their use in Health Technology Assessments: a systematic review of the literature from 2008 to 2013. Current Medical Research & Opinion 2016;32:207-18.	Not a publication type of interest
60	Chirila C, Ziemiecki R, Davenport E, et al. Health-related quality of life analysis for patients with type 2 diabetes mellitus treated with empagliflozin. Value in Health 2014;17 (3):A257-A258.	Did not report relevant, original cost and resource use collected in the past 10 years
61	Chuang LH, Verheggen BG, Charokopou M, et al. Cost-effectiveness analysis of exenatide once-weekly versus dulaglutide, liraglutide, and lixisenatide for the treatment of type 2 diabetes mellitus: an analysis from the UK NHS perspective. Journal of Medical Economics 2016;19:1127-1134.	Did not report relevant, original cost and resource use collected in the past 10 years
62	Chubb B, Tikkanen C. The cost of non-severe hypoglycaemia in Europe. Value in Health 2015;18 (7):A611.	Did not report relevant, original cost and resource use collected in the past 10 years
63	Clarke PM, Glasziou P, Patel A, et al. Event rates, hospital utilization, and costs associated with major complications of diabetes: A multicountry comparative analysis. PLoS Medicine 2010;7 (2) (no pagination).	Did not present cost and resource use collected in the UK
64	Costanzo P, Cleland JG, Pellicori P, et al. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study.[Summary for patients in Ann Intern	Did not report relevant, original cost and resource use collected

No.	Reference	Reason for exclusion
	Med. 2015 May 5;162(9):I-26; PMID: 26146667]. Annals of Internal Medicine 2015;162:610-8.	in the past 10 years
65	Crawford F, McCowan C, Dimitrov BD, et al. The risk of foot ulceration in people with diabetes screened in community settings: findings from a cohort study. Qjm 2011;104:403-10.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
66	Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review. Annals of Internal Medicine 2017;166:191-200.	Not a publication type of interest
67	Currie CJ, Gale EAM, Poole CD. Estimation of primary care treatment costs and treatment efficacy for people with Type 1 and Type 2 diabetes in the United Kingdom from 1997 to 2007. Diabetic Medicine 2010;27:938-948.	Did not report relevant, original cost and resource use collected in the past 10 years
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83	Egan R, Dewi F, Johnson A, et al. The impact of laparoscopic adjustable gastric banding (LAGB) on an nhs cohort of type 2 diabetics: A prospective cohort study. Obesity Surgery 2015;1):S251-S252.	Did not report relevant, original cost and resource use collected in the past 10 years
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129	Hunt B, Vega-Hernandez G, Valentine WJ, et al. Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. Diabetes, Obesity & Metabolism 2017;26:26.	Did not report relevant, original cost and resource use collected in the past 10 years
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138	Kansal A, Zheng Y, Proskorovsky I, et al. Modeling cardiovascular outcomes of treatment with empagliflozin in type 2 diabetes based on hard outcomes data. Value in Health 2016;19 (3):A203.	Did not report relevant, original cost and resource use collected in the past 10 years
139	Kansal AR, Zheng Y, Palencia R, et al. Modeling hard clinical end-point data in economic analyses. Journal of Medical Economics 2013;16:1327-1343.	Not a publication type of interest
140	Karagiannis T, Bekiari E, Tsapas A. Canagliflozin in the treatment of type 2 diabetes: An evidence-based review of its place in therapy. Core Evidence 2017;12:1-10.	Not a publication type of interest
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143	Kennedy-Martin T, Boye KS, Peng X. A review of the cost of medication nonadherence in type 2 diabetes mellitus. Value in Health 2016;19 (7):A671.	Not a publication type of interest
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145	Korczak D, Dietl M, Steinhauser G. Effectiveness of programmes as part of primary prevention demonstrated on the example of cardiovascular diseases and the metabolic syndrome. GMS Health Technology Assessment 2011;7:Doc02.	Not a publication type of interest
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147	Lammert M, Hammer M, Frier BM. Management of severe hypoglycaemia: Cultural similarities, differences and resource consumption in three European countries. Journal of Medical Economics 2009;12:269-280.	Did not report relevant cost and resource use data
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149	Lauritzen T, Borch-Johnsen K, Sandbaek A. Is prevention of Type-2 diabetes feasible and efficient in primary care?. A systematic PubMed review. Primary Care Diabetes 2007;1:5-11.	Not a publication type of interest
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152	Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: A systematic review for the community preventive services task force. Annals of Internal Medicine 2015;163:452-460.	Not a publication type of interest
153	Li R, Zhang P, Barker LE, et al. Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review. Diabetes Care 2010;33:1872-1894.	Not a publication type of interest
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155	Liebl A, Andersen H, Svendsen AL, et al. Resource utilisation and quality of life following initiation of insulin detemir in patients with type 2 diabetes mellitus. International Journal of Clinical Practice 2013;67:740-749.	Did not present cost and resource use collected in the UK

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158	Lowey A, Moore S, Norris C, et al. The cost-effectiveness of pharmacist-led treatment of cardiac risk in patients with type 2 diabetes. Pharmacy World & Science 2007;29:541-5.	Did not report relevant, original cost and resource use collected in the past 10 years
159	Matthaei S, Reaney M, Mathieu C, et al. Patients with type 2 diabetes initiating exenatide twice daily or insulin in clinical practice: CHOICE study. Diabetes Therapy 2012;3:1-15.	Did not present cost and resource use collected in the UK
160	McDonell AL, Kiiskinen U, Zammit DC, et al. Estimating the real world daily usage and cost for exenatide twice daily and liraglutide in Germany, the Netherlands, and the UK based on volumes dispensed by pharmacies. Clinicoeconomics & Outcomes Research 2015;7:95-103.	Did not report relevant cost and resource use data
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162	McEwan P, Evans M, Bergenheim K. A population model evaluating the costs and benefits associated with different oral treatment strategies in people with type 2 diabetes. Diabetes, Obesity and Metabolism 2010;12:623-630.	Did not report relevant, original cost and resource use collected in the past 10 years
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167	McEwan P, Gordon J, Evans M, et al. Estimating Cost-Effectiveness in Type 2 Diabetes: The Impact of Treatment Guidelines and Therapy Duration. Medical Decision Making 2015;35:660-70.	Did not report relevant, original cost and resource use collected in the past 10 years
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170	Mostafa SA, Khunti K, Kilpatrick ES, et al. Diagnostic performance of using one- or two-HbA1c cut-point strategies to detect undiagnosed type 2 diabetes and impaired glucose regulation within a multi-ethnic population. Diabetes and Vascular Disease Research 2013;10:84-92.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
171	Muka T, Imo D, Jaspers L, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. European Journal of Epidemiology 2015;30:251-277.	Not a publication type of interest
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174	Musella M, Apers J, Rheinwalt K, et al. The role of mini gastric/one anastomosis gastric bypass (MGB/OAGB) and sleeve gastrectomy (SG) in providing diabetes resolution An European survey. Obesity Surgery 2015;1):S266-S267.	Did not report relevant, original cost and resource use collected in the past 10 years
175	Nagrebetsky A, Jin J, Stevens R, et al. Diagnostic accuracy of urine dipstick testing in screening for microalbuminuria in type 2 diabetes: a cohort study in primary care (Provisional abstract). Family Practice. Volume 30, 2013:142-152.	Did not report relevant, original cost and resource use collected in the past 10 years
176	Nagy B, Zsolyom A, Nagyjanosi L, et al. Cost-effectiveness of a risk-based secondary screening programme of type 2 diabetes. Diabetes/Metabolism Research and Reviews 2016;32:710-729.	Did not report relevant, original cost and resource use collected in the past 10 years
177	Najafi B, Farzadfar F, Ghaderi H, et al. Cost effectiveness of type 2 diabetes screening: A systematic review. Medical Journal of the Islamic Republic of Iran 2016;30:326.	Not a publication type of interest
178	Newman SP, Cooke D, Casbard A, et al. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technology Assessment (Winchester, England) 2009;13:iii-iv, ix-xi, 1-194.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
179	Nocca D, Guillaume F, Noel P, et al. Impact of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on HbA1c blood level and pharmacological treatment of type 2 diabetes mellitus in severe or morbidly obese patients. Results of a multicenter prospective study at 1 year. Obesity Surgery 2011;21:738-743.	Did not present cost and resource use collected in the UK
180	Nuhoho S, Vietri J, Worbes-Cerezo M. Increased cost of illness among European patients with type 2 diabetes treated with insulin. Current Medical Research & Opinion 2017;33:47-54.	Did not present cost and resource use collected in the UK
181	O'Brien ES, Annunziata K, Traina SB. Correlates of absenteeism and productivity at work among adults in the UK who are overweight/obese. Diabetologia 2016;59 (1 Supplement 1):S436-	Did not include human patients with T2DM or did not present

No.	Reference	Reason for exclusion
	S437.	outcomes for T2DM patients separately
182	Oksman E, Linna M, Horhammer I, et al. Cost-effectiveness analysis for a tele-based health coaching program for chronic disease in primary care. BMC Health Services Research 2017;17:138.	Did not report relevant, original cost and resource use collected in the past 10 years
183	Olry De Labry Lima A, Moya Garrido MN, Espin Balbino J. Systematic review of economic evaluation studies and budget impact on ambulatory monitoring of capillary glucose in type 2 diabetics. Primary Care Diabetes 2014;8:13-21.	Not a publication type of interest
184	Owens D, Tilling C, Keech M. Insulin glargine plus oral antidiabetic agents in comparison with biphasic insulin in type 2 diabetes: A UK cost comparison. British Journal of Diabetes and Vascular Disease 2011;11:141-144.	Did not report relevant, original cost and resource use collected in the past 10 years
185	Palmer A, Valentine W, Ray J. Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis (Structured abstract). International Journal of Clinical Practice. Volume 61, 2007:1626-1633.	Did not report relevant, original cost and resource use collected in the past 10 years
186	Parekh WA, Ashley D, Chubb B, et al. Approach to assessing the economic impact of insulin-related hypoglycaemia using the novel Local Impact of Hypoglycaemia Tool. Diabetic Medicine 2015;32:1156-1166.	Did not report relevant, original cost and resource use collected in the past 10 years
187	Partha G, Agrawal R, Paldanius PM, et al. Vildagliptin is cost-effective in real-world: Economic evaluation evidence from EDGE study. Diabetologia 2015;1):S481.	Did not report relevant, original cost and resource use collected in the past 10 years
188	Pearson K, Hill J, Cheung J, et al. Implementation of formulary change releases savings, where formulary change alone does not: The experience of change in blood glucose systems in Bury & Heywood, Middleton & Rochdale CCGs. Diabetic Medicine 2017;34:102.	Did not report relevant cost and resource use data
189	Pennington M, Visram S, Donaldson C, et al. Cost-effectiveness of health-related lifestyle advice delivered by peer or lay advisors: synthesis of evidence from a systematic review. Cost Effectiveness & Resource Allocation 2013;11:30.	Did not report relevant, original cost and resource use collected in the past 10 years
190	Pereira Gray DJ, Evans PH, Wright C, et al. The cost of diagnosing Type 2 diabetes mellitus by clinical opportunistic screening in general practice. Diabetic medicine : a journal of the British Diabetic Association 2012;29:863-868.	Did not report relevant, original cost and resource use collected in the past 10 years
191	Pfeiffer KM, Nikolajsen A, Weatherall J, et al. Post-prandial hyperglycaemic episodes (PPH): Impact on healthcare resource use among people with type 1 and type 2 diabetes in the US, UK and Germany. Diabetologia 2015;1):S409-S410.	Did not report relevant cost and resource use data
192	Picot J, Jones J, Colquitt J, et al. Weight loss surgery for mild to moderate obesity: a systematic review and economic evaluation (Provisional abstract). Obesity Surgery. Volume 22, 2012:1496-1506.	Did not report relevant, original cost and resource use collected in the past 10 years
193	Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: A systematic review and economic evaluation. Health Technology Assessment 2009;13:ix-214.	Did not report relevant, original cost and resource use collected in the past 10 years
194	Piercy J, Milligan G, Davies MJ, et al. The relationship between glucose-lowering medications, adherence, and outcomes in	Did not present cost and resource use

No.	Reference	Reason for exclusion
	patients with type 2 diabetes. Value in Health 2015;18 (7):A343.	collected in the UK
195	Plamper A, Van Lessen M, Kolec S, et al. Impact of mini gastric bypass on type 2 diabetes mellitus in comparison to sleeve gastrectomy-1 year results. Langenbeck's Archives of Surgery 2016;401 (1):127.	Did not report relevant, original cost and resource use collected in the past 10 years
196	Pollock R, Chilcott J, Muduma G, et al. Laparoscopic adjustable gastric banding vs standard medical management in obese patients with type 2 diabetes: a budget impact analysis in the UK (Provisional abstract). Journal of Medical Economics. Volume 16, 2013:249-259.	Did not report relevant, original cost and resource use collected in the past 10 years
197	Pollock R, Muduma G, Valentine W. Evaluating the cost-effectiveness of laparoscopic adjustable gastric banding versus standard medical management in obese patients with type 2 diabetes in the UK (Provisional abstract). Diabetes Obesity and Metabolism. Volume 15, 2013:121-129.	Did not report relevant, original cost and resource use collected in the past 10 years
198	Pollock RF, Chilcott J, Muduma G, et al. Laparoscopic adjustable gastric banding vs standard medical management in obese patients with type 2 diabetes: a budget impact analysis in the UK. Journal of medical economics 2013;16:249-259.	Did not report relevant, original cost and resource use collected in the past 10 years
199	Prescott A, Bailey JE, Kelly KJ, et al. The effectiveness and cost of single and multi-factorial cardiovascular risk factor modification to guideline targets in type 2 diabetes. Primary care diabetes 2012;6:67-73.	Did not report relevant, original cost and resource use collected in the past 10 years
200	Protheroe J, Rathod T, Bartlam B, et al. The Feasibility of Health Trainer Improved Patient Self-Management in Patients with Low Health Literacy and Poorly Controlled Diabetes: A Pilot Randomised Controlled Trial. Journal of Diabetes Research 2016;2016:6903245.	Did not report relevant cost and resource use data
201	Purayidathil FW, Gupta S, Wagner S. Comorbid depression in patients diagnosed with type 2 diabetes mellitus (T2DM): Effects on quality of life and resource use. Value in Health 2009;12 (7):A223-A224.	Did not present cost and resource use collected in the UK
202	Puttanna A, Zafar Z, Mukherjee A. An assessment of hospital admissions in patients with diabetes and dementia: The DIA-DEM project pilot study. Diabetic Medicine 2016;33:178.	Did not report relevant cost and resource use data
203	Qiao Q, Morgan CL, Jenkins-Jones S, et al. Healthcare resource utilisation associated with patients treated with either exenatide once weekly or basal insulin: A retrospective UK database analysis. Value in Health 2016;19 (7):A670-A671.	Did not report relevant cost and resource use data
204	Raikou M, McGuire A, Colhoun HM, et al. Cost-effectiveness of primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes: results from the Collaborative Atorvastatin Diabetes Study (CARDS) (Structured abstract). Diabetologia. Volume 50, 2007:733-740.	Did not report relevant, original cost and resource use collected in the past 10 years
205	Rajendran R, Scott A, Rayman G. The direct cost of intravenous insulin infusions to the NHS in England and Wales. Clinical Medicine 2015;15:330-3.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
206	Rayner HC, Hollingworth L, Higgins R, et al. Systematic kidney disease management in a population with diabetes mellitus: turning the tide of kidney failure. BMJ Quality & Safety 2011;20:903-10.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately

No.	Reference	Reason for exclusion
207	Ricci-Cabello I, Ruiz-Perez I, Rojas-Garcia A, et al. Characteristics and effectiveness of diabetes self-management educational programs targeted to racial/ethnic minority groups: a systematic review, meta-analysis and meta-regression. BMC Endocrine Disorders 2014;14:60.	Not a publication type of interest
208	Robson J, Smithers H, Chowdhury T, et al. Reduction in self-monitoring of blood glucose in type 2 diabetes: an observational controlled study in east London. British Journal of General Practice 2015;65:e256-63.	Did not report relevant cost and resource use data
209	Roze S, Duteil E, Hallas N, et al. Reduction of complications and associated costs for type 2 diabetic patients using continuous subcutaneous insulin infusion in the UK. Value in Health 2015;18 (7):A360.	Did not report relevant, original cost and resource use collected in the past 10 years
210	Schlueter M, Vega-Hernandez G, Wojcik R. Cost-effectiveness of liraglutide versus dapagliflozin for the treatment of patients with type-2 diabetes mellitus in the UK. Value in Health 2016;19 (7):A675.	Did not report relevant, original cost and resource use collected in the past 10 years
211	Schroeder M, Johansen P, Willis M, et al. The cost-effectiveness of canagliflozin (CANA) versus dapagliflozin (DAPA) 10mg and empagliflozin (EMPA) 25mg in patients with type 2 diabetes mellitus (T2DM) as monotherapy in the united kingdom. Value in Health 2015;18 (7):A607.	Did not report relevant, original cost and resource use collected in the past 10 years
212	Schroeder M, Johansen P, Willis M, et al. The cost-effectiveness of canagliflozin versus sulphonylurea in patients with Type 2 diabetes with inadequate control on metformin monotherapy in the UK. Diabetic Medicine 2015;32:205.	Did not report relevant, original cost and resource use collected in the past 10 years
213	Schroeder M, Schubert A, Chan E, et al. A UK analysis of the differential drug costs per 1% point decrease in HbA1c among antihyperglycemic agents that inhibit SGLT2. Value in Health 2016;19 (3):A201.	Did not report relevant, original cost and resource use collected in the past 10 years
214	Schwarz B, Gouveia M, Chen J, et al. Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy. Diabetes, Obesity and Metabolism, Supplement 2008;10:43-55.	Did not report relevant cost and resource use data
215	Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. The Lancet Diabetes and Endocrinology 2015;3:105-114.	Did not report relevant cost and resource use data
216	Shaya FT, Chirikov VV, Rochester C, et al. Impact of a comprehensive pharmacist medication-therapy management service. Journal of Medical Economics 2015;18:828-37.	Did not include human patients with T2DM or did not present outcomes for T2DM patients separately
217	Shepherd M, Shields BM, Knight B, et al. Use of analogue insulin in patients with Type 2 diabetes: An unnecessary expense for the NHS. Diabetic Medicine 2012;29:126.	Did not report relevant, original cost and resource use collected in the past 10 years
218	Simmons D, Wingate L, Holman D, et al. Cost analysis in rapsid: Randomised controlled trial of peer support in diabetes. Diabetes 2015;64:A80-A81.	Did not report relevant cost and resource use data
219	Simmons RK, Borch-Johnsen K, Lauritzen T, et al. A randomised trial of the effect and cost-effectiveness of early intensive multifactorial therapy on 5-year cardiovascular outcomes in	Did not report relevant, original cost and resource use collected

No.	Reference	Reason for exclusion
	individuals with screen-detected type 2 diabetes: the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) study. Health Technology Assessment (Winchester, England) 2016;20:1-86.	in the past 10 years
220	Strain WD. Cost effectiveness of insulin sparing treatment regimens early in Type 2 diabetes: Real world data using a clinical practice database. Diabetic Medicine 2017;34:183.	Did not report relevant, original cost and resource use collected in the past 10 years
221	Strain WD. Cost effectiveness of insulin sparing treatment regimes in type 2 diabetes: Data from a real world clinical database. Diabetologia 2016;59 (1 Supplement 1):S438.	Did not report relevant cost and resource use data
222	Strongman H, D'Oca K, Langerman H, et al. Comparison of diabetes-associated secondary healthcare utilization between alternative oral antihyperglycaemic dual therapy combinations with metformin in patients with type 2 diabetes: An observational cohort study. Diabetes, Obesity and Metabolism 2015;17:573-580.	Did not report relevant, original cost and resource use collected in the past 10 years
223	Suh DC, Aagren M. Cost-effectiveness of insulin detemir: a systematic review. Expert Review of Pharmacoeconomics & Outcomes Research 2011;11:641-55.	Not a publication type of interest
224	Suraj B, Tripathi CD, Biswas K, et al. A Comparative Evaluation of Safety, Efficacy and Cost Effectiveness of Three Add on Treatment Regimens in Type 2 Diabetics; Not Controlled by Metformin Alone. Research Journal of Pharmacy and Technology 2015;8:44-50.	Did not report relevant, original cost and resource use collected in the past 10 years
225	Swift J. Are finances constraining structured diabetes education for people newly diagnosed with Type 2 diabetes? Diabetic Medicine 2016;33:124.	Did not report relevant cost and resource use data
226	Tamblyn R, Girard N, Dixon WG, et al. Pharmacosurveillance without borders: electronic health records in different countries can be used to address important methodological issues in estimating the risk of adverse events. Journal of Clinical Epidemiology 2016;77:101-111.	Did not report relevant cost and resource use data
227	Tao L, Wilson ECF, Wareham NJ, et al. Cost-effectiveness of intensive multifactorial treatment compared with routine care for individuals with screendetected Type 2 diabetes: Analysis of the ADDITION-UK cluster-randomized controlled trial. Diabetic Medicine 2015;32:907-919.	Did not report relevant, original cost and resource use collected in the past 10 years
228	Tarride JE, Hopkins R, Blackhouse G, et al. A review of methods used in long-term cost-effectiveness models of diabetes mellitus treatment. PharmacoEconomics 2010;28:255-277.	Not a publication type of interest
229	Taylor-Phillips S, Mistry H, Leslie R, et al. Extending the diabetic retinopathy screening interval beyond 1 year: systematic review. British Journal of Ophthalmology 2016;100:105-14.	Not a publication type of interest
230	Thiel DM, Al Sayah F, Vallance JK, et al. Association between Physical Activity and Health-Related Quality of Life in Adults with Type 2 Diabetes. Canadian Journal of Diabetes 2017;41:58-63.	Did not report relevant, original cost and resource use collected in the past 10 years
231	Thomas RL, Winfield TG, Luzio SD, et al. Economic and patient impact of changing to biennial screening iIntervals for diabetic retinopathy. Diabetic Medicine 2017;34:172-173.	Did not report relevant, original cost and resource use collected in the past 10 years
232	Thompson G, Schroeder M, Neslusan C, et al. The cost-effectiveness of canagliflozin (CANA) versus sitagliptin (SITA) as	Did not report relevant, original cost and

No.	Reference	Reason for exclusion
	third-line therapy in the treatment of type 2 diabetes mellitus (T2DM) in the UK. Diabetologia 2014;1):S330.	resource use collected in the past 10 years
233	Tilden DP, Mariz S, O'Bryan-Tear G, et al. A lifetime modelled economic evaluation comparing pioglitazone and rosiglitazone for the treatment of type 2 diabetes mellitus in the UK. PharmacoEconomics 2007;25:39-54.	Did not report relevant, original cost and resource use collected in the past 10 years
234	Torre C, Guerreiro J, Longo P, et al. Comparison of glucose lowering drugs usage between portugal and 6 european countries, in 2014. Pharmacoepidemiology and Drug Safety 2016;25:195-196.	Did not report relevant, original cost and resource use collected in the past 10 years
235	Tricco AC, Antony J, Khan PA, et al. Safety and effectiveness of dipeptidyl peptidase-4 inhibitors versus intermediate-acting insulin or placebo for patients with type 2 diabetes failing two oral antihyperglycaemic agents: a systematic review and network meta-analysis. BMJ Open 2014;4:e005752.	Not a publication type of interest
236	Trueman P, Haynes SM, Felicity Lyons G, et al. Long-term cost-effectiveness of weight management in primary care. International Journal of Clinical Practice 2010;64:775-83.	Did not report relevant, original cost and resource use collected in the past 10 years
237	Tucker DM, Palmer AJ. The cost-effectiveness of interventions in diabetes: a review of published economic evaluations in the UK setting, with an eye on the future. Primary care diabetes 2011;5:9-17.	Not a publication type of interest
238	Turk E, Zaletel J, Ormstad SS, et al. Is a multi-disciplinary approach in the delivery of care for patients with Diabetes mellitus Type 2 cost effective? A systematic review. HealthMED 2012;6:711-719.	Not a publication type of interest
239	Valentine WJ, Bottomley JM, Palmer AJ, et al. PROactive 06: Cost-effectiveness of pioglitazone in Type 2 diabetes in the UK. Diabetic Medicine 2007;24:982-1002.	Did not report relevant, original cost and resource use collected in the past 10 years
240	Valentine WJ, Curtis BH, Pollock RF, et al. Is the current standard of care leading to cost-effective outcomes for patients with type 2 diabetes requiring insulin? A long-term health economic analysis for the UK. Diabetes Research & Clinical Practice 2015;109:95-103.	Not a publication type of interest
241	Valentine WJ, Pollock RF, Plun-Favreau J, et al. Systematic review of the cost-effectiveness of biphasic insulin aspart 30 in type 2 diabetes. Current Medical Research and Opinion 2010;26:1399-1412.	Not a publication type of interest
242	Van Brunt K, Curtis B, Brooks K, et al. Insulin use in long term care settings for patients with type 2 diabetes mellitus: A systematic review of the literature. Journal of the American Medical Directors Association 2013;14:809-816.	Not a publication type of interest
243	Vega-Hernandez G, Wojcik R, Schlueter M. Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2017;27:27.	Did not report relevant, original cost and resource use collected in the past 10 years
244	Vora J, Christensen T, Kapur R, et al. Duration and impact of hypoglycaemic events in patients with Type 2 diabetes treated with insulin degludec and insulin glargine: A meta-analysis. Diabetic Medicine 2015;32:67.	Did not present cost and resource use collected in the UK

No.	Reference	Reason for exclusion
245	Vora JP, Punekar YS, Keech ML. A cost comparison of a basal-bolus regimen (glargine and glulisine) with a premixed insulin regimen in type 2 diabetes patients: The GINGER study. British Journal of Diabetes and Vascular Disease 2011;11:314-318.	Did not report relevant, original cost and resource use collected in the past 10 years
246	Wang Y, Yang H, Wright L, et al. Exercise intolerance in elderly asymptomatic type 2 diabetes: Left ventricular dysfunction, diabetes control, therapy or insulin resistance? European Heart Journal 2015;36:641-642.	Did not report relevant, original cost and resource use collected in the past 10 years
247	Wanniarachchige D, Anthony J, Carroll M, et al. Quicker and reinforced communication results in substantial improvement in DESMOND education course attendance among patients with new and ongoing Type 2 diabetes. Diabetic Medicine 2016;33:126-127.	Did not report relevant, original cost and resource use collected in the past 10 years
248	Waugh N, Cummins E, Royle P, et al. Newer agents for blood glucose control in type 2 diabetes: Systematic review and economic evaluation. Health Technology Assessment 2010;14:3-247.	Did not report relevant, original cost and resource use collected in the past 10 years
249	Waugh N, Scotland G, McNamee P, et al. Screening for type 2 diabetes: literature review and economic modelling (Structured abstract). Health Technology Assessment Database: Health Technology Assessment, 2007:1.	Did not report relevant, original cost and resource use collected in the past 10 years
250	Webb DR, Gray LJ, Khunti K, et al. Screening for diabetes using an oral glucose tolerance test within a western multi-ethnic population identifies modifiable cardiovascular risk: the ADDITION-Leicester study. Diabetologia 2011;54:2237-46.	Did not report relevant, original cost and resource use collected in the past 10 years
251	White S, Mukhopadhyay B, Littlejohn N, et al. Audit of basal insulin prescribing in an outpatient setting. Diabetic Medicine 2013;30:83-84.	Did not report relevant cost and resource use data
252	Wild SH, Byrne CD. Type 2 diabetes is associated with increased incidence of hospital admission and mortality from liver disease in a national retrospective cohort study. Diabetes 2014;63:A405.	Did not report relevant, original cost and resource use collected in the past 10 years
253	Wild SH, Hanley J, Lewis SC, et al. Supported Telemonitoring and Glycemic Control in People with Type 2 Diabetes: The Telescot Diabetes Pragmatic Multicenter Randomized Controlled Trial. PLoS Medicine 2016;13 (7) (no pagination).	Did not report relevant cost and resource use data
254	Wild SH, Morling JR, McAllister DA, et al. Type 2 diabetes and risk of hospital admission or death for chronic liver diseases. Journal of Hepatology 2016;64:1358-1364.	Did not report relevant, original cost and resource use collected in the past 10 years
255	Wilding J, Bailey C, Rigney U, et al. Glycated Hemoglobin, Body Weight and Blood Pressure in Type 2 Diabetes Patients Initiating Dapagliflozin Treatment in Primary Care: A Retrospective Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 2016;7:695-711.	Did not report relevant cost and resource use data
256	Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial.[Summary for patients in Ann Intern Med. 2012 Mar 20;156(6):I-44; PMID: 22431686]. Annals of Internal Medicine 2012;156:405-15.	Did not present cost and resource use collected in the UK
257	Wilson A, O'Hare J, Hardy A, et al. Evaluation of the clinical and cost effectiveness of Intermediate Care Clinics for Diabetes (ICCD): a multicentre cluster randomised controlled trial (Provisional abstract). Plos One. Volume 9, 2014:e93964.	Did not report relevant cost and resource use data

No.	Reference	Reason for exclusion
258	Woehl A, Evans M, Tetlow AP, et al. Evaluation of the cost effectiveness of exenatide versus insulin glargine in patients with sub-optimally controlled type 2 diabetes in the United Kingdom. Cardiovascular Diabetology 2008;7:24.	Did not report relevant, original cost and resource use collected in the past 10 years
259	Wu H, Walker J, Damhuis RA, et al. Metformin and survival of people with type 2 diabetes and pleural mesothelioma: A population-based retrospective cohort study. Lung Cancer 2016;99:194-199.	Did not report relevant, original cost and resource use collected in the past 10 years
260	Wu JHY, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. The Lancet Diabetes and Endocrinology 2016;4:411-419.	Not a publication type of interest
261	Yi Y, Philips Z, Bergman G, et al. Economic models in type 2 diabetes. Current Medical Research & Opinion 2010;26:2105-18.	Not a publication type of interest
262	Yue X, Guan HJ, Wu J, et al. Cost-effectiveness of insulin degludec treatment in patients with type1 and type 2 diabetes mellitus: A systematic review. Value in Health 2016;19 (7):A898.	Not a publication type of interest

G.2.1 Economic evaluations identified in the review

In total, 78 records reporting on 73 published economic evaluations were identified in the SLR. These have been presented by therapy type, as detailed below.

Table G.12Table summarises the nine records reporting on nine published economic evaluations investigating monotherapy; Table G.13 summarises the 33 records reporting on 30 published economic evaluations investigating dual therapy; Table G.14 summarises the 11 records reporting on 11 published economic evaluations investigating triple therapy; Table G.15 summarises the four records reporting on three published economic evaluations investigating mono- and dual therapy; Table G.16 summarises the 20 records found reporting on 19 published economic evaluations investigating dual and triple therapy; and Table G.17 summarises the sole record found investigating mono-, dual and triple therapy.

Within these tables, the studies reported have been stratified by intervention class (dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, multiple interventions, other interventions, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and thiazolidinediones (TZDs)).

Monotherapy economic evaluations

Table G.12: Summary of published economic evaluations included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td colspan="9">Dipeptidyl peptidase-4 (DPP-4) inhibitors</td></tr>
<tr><td>AWMSG 1531 (2013)[64]</td><td>To conduct a cost-minimisation analysis of vildagliptin 50 mg twice daily vs sitagliptin 100 mg once daily as monotherapy for the treatment of T2DM.</td><td>Wales, perspective not mentioned but likely to be NHS Wales.</td><td>• Cost-minimisation of vildagliptin 50 mg was performed
• The analysis assumed no difference in medicine administration and service costs other than liver function monitoring costs for vildagliptin and renal function test costs for sitagliptin
• The costs were projected over a 5 year time</td><td>T2DM patients inadequately controlled by diet and exercise alone and for whom MET is inappropriate due to contraindications or intolerance.</td><td colspan="3"><table><tr><th>Intervention</th><th>Total cost, £</th><th>Cost difference with VDG, £</th></tr><tr><td colspan="3">First year</td></tr><tr><td>VDG 50 mg twice daily</td><td>470.51</td><td rowspan="2">21.66</td></tr><tr><td>SITA 100 mg once daily</td><td>448.85</td></tr><tr><td colspan="3">First 5 years</td></tr><tr><td>VDG 50 mg twice daily</td><td>2,171.75</td><td rowspan="2">-41.94</td></tr><tr><td>SITA 100 mg once daily</td><td>2,213.69</td></tr></table></td><td>Applicable as the study was conducted in Wales and likely from the perspective of NHS Wales (despite not being explicitly stated).</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			horizon					
SMC 607/10 (2010)[65]	To conduct cost-minimisation and cost utility analyses investigating sitagliptin and pioglitazone 30 mg for the treatment of T2DM patients inadequately controlled by diet and exercise alone and for whom MET and SU are inappropriate due to contraindications or intolerance.	Scotland, perspective not reported but likely to be NHS Scotland.	• A cost-minimisation analysis between sitagliptin and pioglitazone 30 mg was conducted • A cost-utility analysis comparing sitagliptin with pioglitazone 30 mg was also performed, using the JADE model to project costs and outcomes over a lifetime horizon	T2DM patients inadequately controlled by diet and exercise alone and for whom MET and SU are inappropriate due to contraindications or intolerance.	**Cost-minimisation analysis** • Cost difference: sitagliptin was less expensive than pioglitazone 30 mg by £34 per patient per annum **Cost utility analysis** • Incremental QALYs with sitagliptin: 0.025 • Incremental costs with sitagliptin: -£274 • ICER/QALY gained for sitagliptin vs pioglitazone 30 mg: dominates			Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).
SMC 826/12 (2012)[66]	To conduct a cost-minimisation analysis of vildagliptin vs sitagliptin for	Scotland, perspective not reported but likely to be NHS Scotland.	• Cost-minimisation of vildagliptin was	T2DM patients inadequately controlled by diet and exercise alone and for whom	<table><tr><th>Intervention</th><th>Total cost, £</th><th>Cost difference with VDG over a 5 year time horizon, £</th></tr><tr><td>VDG</td><td>2,182</td><td>-36</td></tr></table>			Applicable as the study was conducted in the UK and likely from the perspective of

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	the treatment T2DM.		performed, justified by the results of an NMA • The economic analysis compared the total costs per patient for vildagliptin vs sitagliptin • Costs included drug costs and the costs of increased liver function and renal function tests • The costs were projected over a 5 year time horizon	MET is inappropriate due to contraindications or intolerance.	SITA	2,218		NHS Scotland (despite not being explicitly stated).
Glucagon-like peptide-1 (GLP-1) agonists								
Beaudet et al.	To compare the cost-utility of exenatide	UK, from the perspective	• Cost-utility of EQW vs	Cohort of patients with T2DM, based	**Discounted QALYs:** • EQW: 8.032 (SD	**Discounted Costs:** • EQW: £21,551 (SD	**ICER:** • £10,597/QALY	Applicable as conducted from the perspective

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
2011[67]	once-weekly (EQW) and insulin glargine in patients with type 2 diabetes mellitus in the UK.	of the NHS.	insulin glargine was compared • The IMS CORE Diabetes model was used to project costs and outcomes over a time horizon of 50 years (covering the remaining lifetime of patients in the cohort) • Treatment effects were taken from the DURATION-3 trial • HRQoL data were taken from the UKPDS and other published sources • Costs for	on DURATION-3 trial subjects	0.108) • Insulin glargine: 7.849 (SD 0.112)	425) • Insulin glargine: £19,616 (SD 408)	gained	of the UK NHS.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			diabetes management and complications were included • The cost year was 2009 • Costs and benefits were discounted annually at 3.5%					
Multiple interventions								
Clarke et al. 2005[68]	To assess the cost-utility of intensive blood glucose and tight blood pressure control in newly diagnosed T2DM patients who also had hypertension and of MET therapy in T2DM patients who	UK, healthcare payer perspective.	• Cost-utility of intensive blood glucose control with insulin or SU, or in overweight patients with MET therapy was performed, using a probabilistic discrete-time illness-death	Cohort of patients with newly diagnosed T2DM who were shown to have a fasting plasma glucose level >6.0 mmol/l on two separate occasions. These patients were enrolled in the UKPDS study.	**Discounted incremental QALYs:** • Intensive blood glucose control with insulin or SU vs conventional control: 0.15 • Intensive blood glucose control with MET vs conventional control in overweight patients: 0.55	**Discounted incremental costs:** • Intensive blood glucose control with insulin or SU vs conventional control: £844 • Intensive blood glucose control with MET vs conventional control in overweight patients: £1,021	**ICERs:** • Intensive blood glucose control with insulin or SU vs conventional control: £6,028/QALY • Intensive blood glucose control with MET vs conventional control in overweight patients: Intensive	Applicable as conducted from the perspective of the UK healthcare payer.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	were overweight and enrolled in the UKPDS study. For the purposes of this review, only the outcomes of blood glucose control were relevant and so the blood pressure outcomes have not been presented here.		model • Healthcare resource use was collected directly in the UKPDS study between 1996 and 1997 • Costs were taken from published UK-specific sources • Only direct health service costs were included • The cost year was 2004 • Clinical outcomes and direct costs were projected over patients' lifetimes • Costs and				control dominant	

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			benefits were discounted annually at 3.5%					
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors								
ASAR 2746 (2015)[69]	To compare the cost-utility of empagliflozin 10 mg and 25 mg with pioglitazone 45 mg, sitagliptin 100 mg, dapagliflozin 5 mg and 10 mg, canagliflozin 100 mg and 300 mg for the treatment of T2DM.	UK, from the perspective of the NHS and social services.	• Cost-utility of empagliflozin 10 mg and 25 mg was compared to other OADs • The cost-utility analysis consisted of a two-part model; a short-term decision tree for a year followed by the projection of costs and outcomes over a horizon of 40 years using the UKPDS OM1 outcomes	T2DM patients not adequately controlled on OADs	Cost-utility analysis: • NR (data commercial in confidence) Cost-minimisation analysis: • NR	Cost for cost-utility analysis: **Base case costs using 52-week data:** • Empagliflozin 25 mg: £22,598 • Pioglitazone 45 mg: £22,343 • Empagliflozin 10 mg: £22,622 • Sitagliptin 100 mg: £22,690 • SU: £22,342 **Base case costs using 24-week data:** • Empagliflozin 25 mg: £22,591 • Canagliflozin £22,561 • Empagliflozin 10 mg: £22,610 • Canagliflozin 300 mg: £22,620 • Dapagliflozin 5 mg: £22,617	Cost-utility analysis: **ICERs using 52-week data:** • Empagliflozin 10 mg or 25 mg vs pioglitazone 45 mg or SU: Empagliflozin cost-effective* • Empagliflozin 10 mg or 25 mg vs sitagliptin 100 mg: Empagliflozin 10 mg dominates **ICERs using 24-week data:** • Empagliflozin 10 mg or 25 mg vs dapagliflozin 5 mg or 10 mg: Empagliflozin dominates • Empagliflozin	Applicable as conducted from the perspective of the UK NHS and social services.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>model
• Cost and utility data were derived from the SLR conducted in support of NICE TA336[70] as well as some additional sources
• Costs and benefits were discounted annually at 3.5%
• A cost-minimisation analysis was also conducted on the SGLT-2 inhibitors but no further details were provided</td><td></td><td></td><td>• Dapagliflozin 10 mg: £22,626

<u>Costs for cost-minimisation analysis:</u>
• NR</td><td>10 mg or 25 mg vs canagliflozin 100 mg: Canagliflozin dominates
• Empagliflozin 10 mg or 25 mg vs canagliflozin 300 mg: NR

*WTP threshold of £20,000/QALY but ICER was NR as data were commercial in confidence.

<u>Cost-minimisation analysis:</u>
• Empagliflozin 10 mg and 25 mg is as cost-effective as dapagliflozin 5 mg and 10 mg and canagliflozin 100 mg</td><td></td></tr>
<tr><td>NICE TA390 (2016)[71</td><td>Multiple technology appraisal</td><td>UK, from the perspective of the NHS</td><td>• Cost-utility analyses of canagliflozin</td><td>Adult T2DM patients inadequately</td><td colspan="3"><u>MS for canagliflozin:</u>
<table><tr><th></th><th>Incremental</th><th>Incremental</th><th>ICER, £/QALY</th></tr></table></td><td>Applicable as conducted from the perspective</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>]</td>
<td>with economic models presented by 3 different manufacturers and an Assessment Group (AG) to evaluate the cost-effectiveness of the following:
Canagliflozin
Dapagliflozin
Empagliflozin</td>
<td>and personal social services for all models.</td>
<td>, dapagliflozin and empagliflozin were performed
In the manufacturer's submission (MS) for canagliflozin, the ECHO-T2DM model was used; in the MS for dapagliflozin the Cardiff Diabetes Model was used; in the MS for empagliflozin the results of two modelling exercises were presented, one of which (Model A) was a decision tree based on</td>
<td>controlled with diet and exercise alone and unable to take MET starting monotherapy.</td>
<td colspan="3">
<table>
<tr><th></th><th>QALYs</th><th>costs, £</th><th></th></tr>
<tr><td colspan="4">vs Pioglitazone</td></tr>
<tr><td>GLICL</td><td>-0.049</td><td>2,956</td><td>Dominated*</td></tr>
<tr><td>SITA</td><td>-0.017</td><td>3,179</td><td>Dominated*</td></tr>
<tr><td>CANA 100</td><td>0.041</td><td>3,261</td><td>79,537</td></tr>
<tr><td>EMPA 25 mg</td><td>0.026</td><td>3,264</td><td>125,538</td></tr>
<tr><td>EMPA 10 mg</td><td>0.012</td><td>3,316</td><td>276,333</td></tr>
<tr><td>DAPA</td><td>0.008</td><td>3,330</td><td>416,250</td></tr>
<tr><td>CANA 100/300</td><td>0.053</td><td>3,405</td><td>64,245</td></tr>
<tr><td>CANA 300</td><td>0.085</td><td>4,038</td><td>47,456</td></tr>
</table>
*Dominated by pioglitazone
<table>
<tr><th></th><th>Incremental QALYs</th><th>Incremental costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">vs Gliclazide</td></tr>
<tr><td>SITA</td><td>0.032</td><td>223</td><td>6,969</td></tr>
<tr><td>CANA 100</td><td>0.090</td><td>305</td><td>3,377</td></tr>
<tr><td>EMPA 25 mg</td><td>0.075</td><td>308</td><td>4,107</td></tr>
<tr><td>EMPA 10 mg</td><td>0.061</td><td>360</td><td>5,902</td></tr>
<tr><td>DAPA</td><td>0.057</td><td>374</td><td>6,561</td></tr>
<tr><td>CANA 100/300</td><td>0.102</td><td>449</td><td>4,402</td></tr>
<tr><td>CANA 300</td><td>0.134</td><td>1,082</td><td>8,075</td></tr>
</table>
<table>
<tr><th></th><th>Incremental QALYs</th><th>Incremental costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">vs Sitagliptin</td></tr>
<tr><td>CANA 100</td><td>0.058</td><td>82</td><td>1,414</td></tr>
</table>
</td>
<td>of the UK NHS and personal social services.</td>
</tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			the UKPDS model, while the other (Model B) took a similar approach to that used in the Original Health Economic Model from the Guideline Development Group and NICE; in the AG group report the UKPDS outcomes model 1 was used • For all models, data on relative treatment effects were derived from the manufacturer's/AG's own NMA • For all					

EMPA 25 mg	0.043	85	1,977
EMPA 10 mg	0.029	137	4,724
DAPA	0.025	151	6,040
CANA 100/300	0.070	226	3,229
CANA 300	0.102	859	8,422

MS for dapagliflozin:

	Total QALYs	Total costs, £	ICER, £/QALY
vs flozins			
Flozins	13.206	27,979	N/A
Gliptins	13.188	27,873	5,904
PIO	13.111	26,067	20,089
SU	13.179	26,582	52,047

MS for empagliflozin:

	Incremental QALYs	Incremental costs, £	ICER, £/QALY
Model A: vs pioglitazone, 52 week analysis			
GLICL	0.008	4	500
REPAG 1 mg	0.009	30	3,333
EMPA 25 mg	0.050	283	5,634
EMPA 10 mg	0.043	304	7,070
SITA 100 mg	0.014	363	25,929

	Incremental QALYs	Incremental costs, £	ICER, £/QALY
Model A: vs canagliflozin 100 mg, 24 week analysis			
EMPA 25 mg	-0.008	26	Dominated

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			models, the time horizon was 40 years, and costs and benefits were discounted annually at 3.5%					

EMPA 10 mg	-0.015	43	Dominated
DAPA 10 mg	-0.018	44	Dominated
DAPA 5 mg	-0.020	55	Dominated
CANA 300 mg	0.021	64	3,048

	Incremental QALYs	Incremental costs, £	ICER, £/QALY
Model B: vs pioglitazone, 52 week analysis			
REPAG 1 mg	0.025	635	25,349
GLICL	0.013	1,527	122,000
SITA 100 mg	0.015	2,504	164,000
EMPA 25 mg	0.061	2,834	46,480
EMPA 10 mg	0.056	2,837	50,892

	Incremental QALYs	Incremental costs, £	ICER, £/QALY
Model B: vs dapagliflozin 10 mg, 24 week analysis			
CANA 100 mg	0.033	1	39
DAPA 5 mg	0.001	43	31,840
EMPA 25 mg	0.021	46	2,172
EMPA 10 mg	0.007	68	9,835
CANA 300 mg	0.056	970	17,363

	Incremental QALYs	Incremental costs, £	ICER, £/QALY
Model B: vs canagliflozin 100 mg, 24 week analysis			
DAPA 5 mg	-0.032	42	Dominated
EMPA 25 mg	-0.012	45	Dominated

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">
<table>
<tr><td>EMPA 10 mg</td><td>-0.026</td><td>67</td><td>Dominated</td></tr>
<tr><td>CANA 300 mg</td><td>0.023</td><td>969</td><td>42,951</td></tr>
</table>

<u>AG</u>
Note that the following ICERs are not relative to the least costly treatment, but are relative to the next least costly treatment which is not dominated.
<table>
<tr><th></th><th colspan="6">ICERs, £/QALY</th></tr>
<tr><th></th><th>No BMI</th><th>BMI 1</th><th>BMI 2</th><th>BMI 3</th><th>BMI 4</th><th>BMI 5</th></tr>
<tr><td>GLICL</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>REPAG</td><td>Dominated</td><td>3,331</td><td>3,331</td><td>3,331</td><td>Dominated</td><td>18,507</td></tr>
<tr><td>PIO</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr>
<tr><td>SITA 100 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr>
<tr><td>CANA 300 mg</td><td>Dominated</td><td>44,994</td><td>192k</td><td>119k</td><td>Dominated</td><td>235k</td></tr>
<tr><td>EMPA 25 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr>
<tr><td>DAPA 10 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr>
</table>
The base case where none of these scenarios has been modelled is indicated as ‘No BMI’.
</td><td></td></tr>
<tr><td>Johnston et al. 2017[72]</td><td>To review the cost-effectiveness of dapagliflozin, canagliflozin and empagliflozin in monotherapy</td><td>UK, from the perspective of the NHS and PSS.</td><td>• Assessment group (AG) economic modelling was undertaken using the UKPDS Outcomes</td><td>Adult patients with T2DM who cannot tolerate MET starting monotherapy.</td><td colspan="3">Five scenarios were modelled by the AG based on changes in patient weight over the course of treatment, following discussions over the duration of weight effects following treatment:
• Treatment weight changes maintained, with no rebound to natural history (BMI 1)
• Treatment weight gains maintained, weight losses rebound to natural history after 1 year (BMI 2)
• Treatment weight gains maintained, weight losses rebound to natural history at intensification (BMI 3)
• Treatment weight changes rebound to natural history after 1 year (BMI 4)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>in patients with T2DM.</td><td></td><td>Model 1 (OM1) to expand the analyses conducted by the manufacturers in support of TA390
• Patient BMI, hypoglycaemia event rates, adverse events and treatment costs were modelled over a 40 year time horizon in annual cycles
• Clinical evidence was extracted from a NMA
• Utility data were sourced from published literature</td><td></td><td colspan="3">• Treatment weight changes rebound to natural history at intensification (BMI 5).
The base case where none of these scenarios has been modelled is indicated as ‘No BMI’.

Base case lifetime total costs and QALYs
<table><tr><th rowspan="2">Treatment</th><th rowspan="2">Total costs, £</th><th colspan="6">Total QALYs</th></tr><tr><th>No BMI</th><th>BMI 1</th><th>BMI 2</th><th>BMI 3</th><th>BMI 4</th><th>BMI 5</th></tr><tr><td>GLICL</td><td>27,314</td><td>10.392</td><td>9.633</td><td>9.633</td><td>9.633</td><td>9.771</td><td>9.739</td></tr><tr><td>REPAG</td><td>27,413</td><td>10.389</td><td>9.663</td><td>9.663</td><td>9.663</td><td>9.770</td><td>9.744</td></tr><tr><td>PIO</td><td>27,543</td><td>10.384</td><td>9.612</td><td>9.612</td><td>9.612</td><td>9.762</td><td>9.728</td></tr><tr><td>SITA 100 mg</td><td>£32,358</td><td>10.355</td><td>9.657</td><td>9.655</td><td>9.655</td><td>9.739</td><td>9.719</td></tr><tr><td>CANA 300 mg</td><td>32,676</td><td>10.380</td><td>9.780</td><td>9.691</td><td>9.707</td><td>9.770</td><td>9.767</td></tr><tr><td>EMPA 25 mg</td><td>32,775</td><td>10.378</td><td>9.747</td><td>9.683</td><td>9.694</td><td>9.766</td><td>9.756</td></tr><tr><td>DAPA 10 mg</td><td>32,866</td><td>10.367</td><td>9.734</td><td>9.671</td><td>9.681</td><td>9.756</td><td>9.745</td></tr></table>
Base case cost-effectiveness estimates
<table><tr><th rowspan="2">Treatment</th><th colspan="6">ICERs, £/QALY</th></tr><tr><th>No BMI</th><th>BMI 1</th><th>BMI 2</th><th>BMI 3</th><th>BMI 4</th><th>BMI 5</th></tr><tr><td>GLICL</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>REPAG</td><td>Dominated</td><td>3,331</td><td>3,331</td><td>3,331</td><td>Dominated</td><td>18,507</td></tr><tr><td>PIO</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr><tr><td>SITA 100 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr><tr><td>CANA 300 mg</td><td>Dominated</td><td>44,994</td><td>192,000</td><td>119,000</td><td>Dominated</td><td>235,000</td></tr><tr><td>EMPA 25 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>• Direct costs only were considered including: drug costs, complication costs
• Cost year was not reported
• Costs and benefits were discounted at 3.5%</td><td></td><td colspan="3">
<table>
<tr><td>DAPA 10 mg</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td><td>Dominated</td></tr>
</table>
Comparison of flozin therapies relative to sitagliptin was also conducted:
Base case incremental costs and QALYs
<table>
<tr><th rowspan="2">Treatment</th><th rowspan="2">Net costs, £</th><th colspan="6">Net QALYs</th></tr>
<tr><th>No BMI</th><th>BMI 1</th><th>BMI 2</th><th>BMI 3</th><th>BMI 4</th><th>BMI 5</th></tr>
<tr><td>SITA100 mg</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>CANA 300 mg</td><td>318</td><td>0.025</td><td>0.123</td><td>0.036</td><td>0.052</td><td>0.031</td><td>0.048</td></tr>
<tr><td>EMPA 25 mg</td><td>416</td><td>0.023</td><td>0.089</td><td>0.028</td><td>0.038</td><td>0.026</td><td>0.037</td></tr>
<tr><td>DAPA 10 mg</td><td>508</td><td>0.013</td><td>0.077</td><td>0.017</td><td>0.026</td><td>0.017</td><td>0.026</td></tr>
</table>
Base case cost-effectiveness estimates
<table>
<tr><th rowspan="2">Treatment</th><th colspan="6">ICER, £/QALY</th></tr>
<tr><th>No BMI</th><th>BMI 1</th><th>BMI 2</th><th>BMI 3</th><th>BMI 4</th><th>BMI 5</th></tr>
<tr><td>CANA 300 mg</td><td>12,623</td><td>2590</td><td>8913</td><td>6111</td><td>10,256</td><td>6627</td></tr>
<tr><td>EMPA 25 mg</td><td>18,341</td><td>4676</td><td>14,716</td><td>10,841</td><td>15,734</td><td>11,300</td></tr>
<tr><td>DAPA 10 mg</td><td>40,383</td><td>6632</td><td>30,710</td><td>19,787</td><td>30,487</td><td>19,679</td></tr>
</table>
</td><td></td></tr>
<tr><td>Schroeder et al. 2015 [A][73]</td><td>To evaluate the cost-effectiveness of canagliflozin 100 and 300 mg vs alternative SGLT-2 inhibitors in patients inadequately</td><td>UK, from the perspective of the NHS.</td><td>• ECHO-T2DM model used to evaluate outcomes and costs associated with canagliflozin 100 mg and 300 mg vs</td><td>T2DM patients inadequately controlled on MET. 2,000 cohorts of 1,000 unique hypothetical patients were simulated over 40 years.</td><td colspan="3">
<table>
<tr><th>Comparator</th><th>Total QALYs</th><th>Total costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg vs other SGLT-2i</td></tr>
<tr><td>CANA 100 mg</td><td>10.051</td><td>23,472</td><td>N/A</td></tr>
<tr><td>DAPA 10 mg</td><td>10.014</td><td>23,527</td><td>CANA dominates</td></tr>
<tr><td>EMPA 10 mg</td><td>10.027</td><td>23,565</td><td>CANA dominates</td></tr>
<tr><td>EMPA 25 mg</td><td>10.039</td><td>23,470</td><td>208</td></tr>
<tr><td colspan="4">CANA 300 mg vs other SGLT-2i</td></tr>
<tr><td>CANA 300 mg</td><td>10.084</td><td>23,509</td><td>N/A</td></tr>
<tr><td>DAPA 10 mg</td><td>10.012</td><td>23,754</td><td>CANA dominates</td></tr>
</table>
</td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	controlled on MET.		empagliflozin 10 mg and 25 mg and dapagliflozin 10 mg in monotherapy. • Patient characteristics were drawn for each patient individually from the probability distributions observed in RCTs that investigated the efficacy and safety of canagliflozin monotherapy.[74, 75] • Key treatment effects were sourced from an update to a previous NMA and pooled clinical trial results. • Time horizon: 40 years • Cost year NR		EMPA 10 mg: 10.023 EMPA 25 mg: 10.034	23,762 23,679	CANA dominates CANA dominates	

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• Costs and QALYs discounted at 3.5%					

Abbreviations: AG: Assessment Group; AWMSG: All Wales Medicines Strategy Group; BMI: body mass index; CANA: canagliflozin; DAPA: dapagliflozin; DPP-4: dipeptidyl peptidase-4 inhibitor; EMPA: empagliflozin; EQW: exenatide once-weekly; GLICL: gliclazide; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; MET: metformin; MS: manufacturer submission; ; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; NR: not reported; OAD: oral antidiabetic drug; PIO: pioglitazone; PSS: Personal and Social Services; QALY: quality-adjusted life-year; RCT: randomised controlled trial; REPAG: repaglinide; SD: standard deviation;
SGLT-2: sodium-glucose cotransporter 2 inhibitors; SITA: sitagliptin; SLR: systematic literature review; SMC: Scottish Medicines Consortium; SU: sulfonylurea; T2DM: type 2 diabetes mellitus; UK: United Kingdom; UKPDS: UK Prospective Diabetes Study; VDG: vildagliptin.

Dual therapy economic evaluations

Table G.13: Summary of published economic evaluations included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td colspan="9">Dipeptidyl peptidase-4 (DPP-4) inhibitors</td></tr>
<tr><td>SMC 408/07 (2007)[76]</td><td>• To assess the cost-utility of sitagliptin compared to rosiglitazone or SU, where each drug is added to existing treatment with MET.</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-utility of sitagliptin as add-on therapy to MET was performed
• Patients could progress to other treatments (such as insulin) depending on their response to therapy
• Long-term outcomes were estimated using the UKPDS risk factor equations
• Costs and benefits were projected over a lifetime horizon</td><td>T2DM patients inadequately controlled with diet and exercise plus MET.</td><td colspan="3"><table><tr><th>Comparison</th><th>ICER, £/QALY for sitagliptin regimen</th></tr><tr><td>SITA + MET vs SU + MET</td><td>18,437</td></tr><tr><td>SITA + MET vs ROSI + MET</td><td>619</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>SMC 571/09 (2009)[77]</td>
<td>To conduct a cost-minimisation analysis comparing vildagliptin 50 mg once daily with sitagliptin 100 mg once daily, when both used in combination with SU in patients who are uncontrolled on SU alone for the treatment of T2DM.</td>
<td>Scotland, perspective not reported but likely to be NHS Scotland.</td>
<td>Cost-minimisation of vildagliptin was performed, justified by a simple indirect comparison of the two treatments
Only drug acquisition costs for vildagliptin and sitagliptin and the cost of LFTs for patients prescribed vildagliptin were included in the analysis
The costs of SU were not included on the implicit assumption that this cost would be the same between treatments
The costs were projected over a 1 year time</td>
<td>T2DM patients inadequately controlled on maximal tolerated dose of a SU or for whom MET is inappropriate due to contraindications or intolerance.</td>
<td colspan="3"><table>
<tr><th>Intervention</th><th>Total annual cost, £</th><th>Annual cost difference with VDG, £</th></tr>
<tr><td>VDG</td><td>287.01</td><td rowspan="2">-146.56</td></tr>
<tr><td>SITA</td><td>433.57</td></tr>
</table></td>
<td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>horizon</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td rowspan="2">SMC 603/10 (2010)[76]</td><td>To assess the cost-minimisation of saxagliptin + MET vs sitagliptin + MET.</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>One head-to-head trial demonstrated clinical equivalence
No further information on the cost-minimisation model was reported</td><td>T2DM patients not adequately controlled on MET alone and in whom the addition of SU is inappropriate.</td><td>QALYs:
N/A</td><td>Annual cost saving:
Using saxagliptin + MET vs sitagliptin + MET: £22</td><td>ICER:
N/A</td><td rowspan="2">Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
<tr><td>To assess the cost-effectiveness of saxagliptin + MET vs TZD + MET.</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>For the comparison of saxagliptin + MET with TZD + MET, the Cardiff Type 2 Diabetes model was with a 40 year time horizon</td><td>T2DM patients not adequately controlled on MET alone and in whom the addition of SU is appropriate.</td><td>Incremental QALYs:
Saxagliptin + MET vs TZD + MET: 0.11</td><td>Incremental costs:
Saxagliptin + MET vs TZD + MET: £52</td><td>ICER:
£494/QALY gained</td></tr>
<tr><td>Gordon et al. 2016[78]</td><td>To assess the cost-effectiveness of alogliptin compared with SU to treat patients</td><td>Study subjects from North and South America, Europe, Asia, South Africa, Australia and New</td><td>Cost-effectiveness analysis of the combined use of MET and alogliptin compared with MET and glipizide was</td><td>Cohort of patients with uncontrolled T2DM, based on the ENDURE trial[79]

Study treatment arms:
MET +</td><td colspan="3"><table><tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>MET + GPZ</td><td>9.720</td><td>27,835</td><td>NR</td></tr><tr><td>MET + ALO 12.5 mg</td><td>9.824</td><td>28,966</td><td>NR</td></tr><tr><td>MET + ALO 25 mg</td><td>9.861</td><td>28,847</td><td>NR</td></tr></table></td><td>Applicable as the analysis was conducted from a UK perspective using direct costs only.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	with type 2 diabetes in the UK clinical settting.	Zealand. A UK perspective was adopted for costs and cost-effectiveness settings.	performed • Changes in HbA1c, SBP, cholesterol, LDL, HDL, triglycerides and BMI taken from the ENDURE head-to-head trial of uncontrolled T2DM patients • Utility values were sourced from relevant literature of patients with T2DM • Costs were estimated from a UK perspective • The cost year was 2015 • Direct costs included the treatment and consumables (test strips, lancets and needles) required to administer and	alogliptin 12.5 mg OD • MET + alogliptin 25 mg OD • MET + glipizide 5 mg OD titrated to a maximum of 20 mg	**Incremental results, vs MET + ALO** MET + ALO 12.5 mg: 0.103 MET + ALO 25 mg: 0.14	1,131 1,012	10,959 7,217	

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			managed the treatment. • Clinical outcomes and direct costs were projected over patients' lifetimes (max. 50 years) using the IMS Health CORE Diabetes Model • Costs and benefits were discounted annually at 3.5%					
McEwan et al. 2015[80]	• Cost-utility analysis of therapy escalation thresholds of patients with T2DM in the UK clinical setting.	UK, from the perspective of the NHS.	• Cost-utility analysis of therapy escalation thresholds was performed • Changes in HbA1c, weight, cholesterol, and SBP, was taken from two trials of uncontrolled T2DM patients • Utility values were derived	Cohort of patients with inadequately controlled T2DM, based on two trials: Nauck (2011)[81] Monami (2008)[82] Study treatment arms: • MET + dapagliflozin • MET + SU	**Discounted QALYs:** NR	**Discounted costs:** NR	**ICERs:** MET + dapagliflozin vs MET + SU or MET + basal insulin Baseline HbA1c of 7.5%: • Therapy escalation threshold = 7.5%: £3,063 • Therapy escalation threshold = 8.5%: £8,649	Applicable as conducted from the perspective of the UK NHS, however costs and QALYs were not reported.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			from relevant literature of patients with T2DM • Costs estimated from relevant literature • Cost year: NR • Direct costs included therapy costs • Clinical outcomes and direct costs were projected over a 40 year time horizon using the Cardiff stochastic simulation cost-utility model (DiabForecaster) • Costs and benefits were discounted annually at 3.5%	• MET + basal insulin			• Therapy escalation threshold = 9.5%: £12,443 Baseline HbA1c of 6.5%: • Therapy escalation threshold = 7.5%: £2,679 • Therapy escalation threshold = 8.5%: • Therapy escalation threshold = 9.5%: £12,223 Fixed threshold of 7.5%: • Baseline HbA1c of 6.5%: £5,662 • Baseline HbA1c of 8.5%: £79	
McEwan et al. 2015[83]	• To perform a health	UK, perspective	• IMS CORE Diabetes Model	Patient data obtained from	**QALYs:** NR	**Costs:** • MET+SU:	**ICERs:** NR	Conducted in the UK,

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	economic evaluation based on data from the EDGE study, to evaluate the lifetime costs and outcomes of MET + vildagliptin vs MET + SU.	NR.	used • Cost year NR • UK costs and health benefits discounted at 3.5%	the EDGE study[84]		£28,512 • MET+VIL: £27,507		however the perspective was not explicitly stated and so may not align with the perspective of relevant payers and decision makers.
Partha et al. 2015[85]	• To evaluate the cost-effectiveness of MET + vildagliptin vs MET + SU in T2DM patients uncontrolled with MET.	UK, perspective not reported.	• Patient-level simulation cost effectiveness model constructed using REs from the UKPDS model[86] to predict micro/macrovascular complications in yearly cycles was used to simulate a cohort of 10,000 patients in yearly cycles over a lifetime	Simulated 10,000 patient cohort based on a previous RCT:[87] age 70 years, HbA1c 8.0%, duration of diabetes 6.30 years. All patients were uncontrolled on MET.	**Total QALYs:** • MET + vildagliptin: 5.40 • MET + SU: 5.37 **Incremental** QALYs: • MET + vildagliptin vs MET + SU: 0.03 **Total LYs:** • MET + vildagliptin: 7.42	**Total costs:** • MET + vildagliptin: £24,992 • MET + SU: £23,444 **Incremental cost:** • MET + vildagliptin vs MET + SU: £548	**ICER:** £18,801/QALY	Conducted in the UK but the perspective was not explicitly stated and so may not align with the perspective of relevant payers and decision makers.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>time horizon
• Clinical data were derived from the UKPDS and EDGE studies
• Direct costs of drugs and complications were included
• Cost year NR
• Costs and benefits discounted at 3.5%</td><td></td><td>• MET + SU: 7.43</td><td></td><td></td><td></td></tr>
<tr><td>Schwarz et al. 2008[88]</td><td>• To assess the cost-effectiveness of adding sitagliptin, compared with a SU or TZD, to MET in patients with T2DM from several countries in Europe.</td><td>Austria, Finland, Portugal, Scotland (UK), Spain, Sweden. Perspective not reported.

For the purposes of this review, only the outcomes from the UK were relevant and so</td><td>• Cost-effectiveness analysis of adding sitagliptin compared with rosiglitazone and SU to existing MET regimens was performed
• Changes in HbA1c taken from multiple trials of T2DM patients uncontrolled on</td><td>Cohort of patients with inadequately controlled T2DM on MET monotherapy.

Study treatment arms:
• Scenario 1: comparing the addition of sitagliptin vs rosiglitazo</td><td colspan="3"><table><tr><th></th><th>Discounted incremental QALYs</th><th>Discounted incremental costs, €</th><th>ICER, €/QALY</th></tr><tr><td>Scenario 1</td><td>0.016</td><td>36</td><td>2,250</td></tr><tr><td>Scenario 2</td><td>0.095</td><td>1,097</td><td>11,547</td></tr><tr><td>Scenario 3</td><td>0.103</td><td>1,109</td><td>10,767</td></tr></table></td><td>The extracted results represent part of the study that was conducted in the UK, however the perspective was not stated and so may not align with the perspective of relevant payers and</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
		outcomes from other countries have not been presented here.	MET • Utility values were taken from the UKPDS 2002.[89] • Costs were derived from UKPDS 2002[90] and converted to EUR at an exchange rate of 1 GBP = 1.43522 EUR • Cost year NR • Direct costs included medication costs, diabetes and diabetes-related complication event costs and treatment-related side effect costs • Clinical outcomes and direct costs were projected over a lifetime horizon using	ne to ongoing MET • Scenario 2: comparing the addition of sitagliptin vs SU to ongoing MET • Scenario 3: comparing the addition of sitagliptin vs SU to ongoing MET				decision makers.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>the Januvia Diabetes Economic (JADE) Model
• Costs and benefits were discounted annually according to individual country national guidelines on pharmaco-economic analyses and varied from 3%–6%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Glucagon-like peptide-1 (GLP-1) agonists</td></tr>
<tr><td>SMC 1088/15 (2015)[91]</td><td>• To assess the cost-utility of insulin degludec/ liraglutide vs basal insulin plus liraglutide for the treatment of T2DM.</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-utility of insulin degludec/ liraglutide was performed, with the published, semi-Markov CORE diabetes model used to project costs and outcomes over a lifetime (40 years) horizon</td><td>T2DM patients inadequately controlled on basal insulin analogues and for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy.</td><td colspan="3"><table><tr><th>Comparator</th><th>Incremental QALYs with insulin degludec/ LIRA</th><th>Incremental costs with insulin degludec/ LIRA, £</th><th>ICER, £/QALY gained for insulin degludec/ LIRA</th></tr><tr><td>Basal insulin + LIRA</td><td>0.113</td><td>-698</td><td>Dominant</td></tr></table></td><td></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• Relative treatment effectiveness for 1 year was derived from a pooled naïve indirect comparison, while long-term effectiveness was based on UKPDS 68 risk equations • Utilities were sourced from published studies • The analysis included medicine costs, costs of strips and lancets for self-monitoring of blood glucose levels and needle costs. Costs associated with adverse events were not included but the exclusion of these costs					

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>would not introduce any bias in the model given the evidence suggests there is likely to be little difference between the treatments. Other costs included patient management costs and post-complication management costs</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>Chuang et al. 2016[92] [Charokopou et al. 2015][93]</td><td>• To assess the cost-effectiveness of exenatide 2 mg once-weekly (EQW) compared with GLP-1 receptor agonists (dulaglutide, liraglutide and lixisenatide)</td><td>UK, from the perspective of the UK NHS.</td><td>• Cost-effectiveness of EQW was compared to dulaglutide, liraglutide and lixisenatide
• The Cardiff diabetes model was used to simulate costs and benefits over a 40 year (lifetime) time horizon with 6 month cycles in</td><td>Adult T2DM patients not adequately controlled on MET alone.</td><td colspan="3">Results reported in Chuang et al. 2016<table><tr><th>Treatment</th><th>QALYs</th><th>Cost, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>EQW</td><td>11.279</td><td>19,930</td><td>-</td></tr><tr><td>LIRA 1.8 mg</td><td>11.236</td><td>22,016</td><td>-</td></tr><tr><td>DULA</td><td>11.233</td><td>19,903</td><td>-</td></tr><tr><td>LIRA 1.2 mg</td><td>11.177</td><td>19,827</td><td>-</td></tr><tr><td>LIXI 20 µg</td><td>11.206</td><td>19,192</td><td>-</td></tr><tr><td colspan="4">Incremental results (95% CI)</td></tr><tr><td>EQW vs LIRA 1.8 mg</td><td>-2,085 (-2,143– 2,028)</td><td>0.043 (0.034– 0.053)</td><td>596</td></tr><tr><td>EQW vs</td><td>-27 (-30– -</td><td>0.046</td><td>EQW</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th colspan="3">QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>for the treatment of adults with T2DM not adequately controlled on MET alone in the UK.</td><td></td><td>1,000 cohorts of 1,000 patients
• Treatment-specific effects were derived from a NMA of 14 RCTs[94]
• Utility data were mainly sourced from the UKPDS 62 study
• Cost year was 2014
• Costs were sourced from the UKPDS 84 study and included medication and complication costs
• Costs and benefits were discounted annually at 3.5%</td><td></td><td colspan="3">DULA 85) (0.036–0.056) dominant
EQW vs LIRA 1.2 mg 103 (46–160) 0.102 (0.093–0.112) 1,002
EQW vs LIXI 738 (681–795) 0.074 (0.064–0.083) 10,002

Results reported in Charokopou et al. 2015
<table><tr><th>Treatment</th><th>QALYs</th><th>Cost, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>EQW</td><td>11.279</td><td>19,930</td><td>-</td></tr><tr><td>LIRA 1.8 mg</td><td>11.236</td><td>22,016</td><td>-</td></tr><tr><td>DULA</td><td>11.233</td><td>20,815</td><td>-</td></tr><tr><td>LIRA 1.2 mg</td><td>11.177</td><td>19,827</td><td>-</td></tr><tr><td>LIXI 20 µg</td><td>11.206</td><td>19,012</td><td>-</td></tr><tr><td colspan="4">Incremental results (95% CI)</td></tr><tr><td>EQW vs LIRA 1.8 mg</td><td>-2,085 (2,494–1,136)</td><td>0.043 (-0.080–0.117)</td><td>EQW dominant</td></tr><tr><td>EQW vs DULA</td><td>-885 (-1,277– -272)</td><td>0.046 (0.072–0.143)</td><td>EQW dominant</td></tr><tr><td>EQW vs LIRA 1.2 mg</td><td>103 (464–467)</td><td>0.102 (-0.022–0.177)</td><td>1,004</td></tr><tr><td>EQW vs LIXI</td><td>918 (466–1,256)</td><td>0.074 (-0.009–0.169)</td><td>12,440</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="3">The precise reason for the variation in results reported by the two publications was not clear however the conclusions remained unchanged.</td><td></td></tr>
<tr><td>Davies et al. 2016[95]</td><td>• To compare the cost-utility of IDegLira for the treatment of T2DM in the UK.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-utility analysis of IDegLira compared with relevant intensification therapies was performed
• Changes in HbA1c, BMI, SBP, hypoglycaemia and lipids taken from the DUAL V head-to-head trial of T2DM patients uncontrolled on basal insulin
• Utility values were taken from Beaudet et al., measured using the EQ-5D questionnaire and taken from a UK population</td><td>Cohort of patients with T2DM, based on the DUAL V head-to-head trial (adults with inadequately controlled T2DM on basal insulin).[96]

Study treatment arms:
• IDegLira
• IGlar + 3 x insulin aspart (IAsp)
• IGlar or insulin detemir [IDet]) + liraglutide 1.8 mg
• Up-titration of IGlar</td><td colspan="3"><table><tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted total costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">IDegLira vs IGlar + LIRA</td></tr><tr><td>IDegLira</td><td>7.499</td><td>54,814</td><td rowspan="2">IDegLira dominant</td></tr><tr><td>IGlar + LIRA</td><td>7.376</td><td>55,785</td></tr><tr><td colspan="4">IDegLira vs IGlar + 3 x IAsp</td></tr><tr><td>IDegLira</td><td>7.499</td><td>54,814</td><td rowspan="2">IDegLira dominant</td></tr><tr><td>IGlar + 3 x IAsp</td><td>7.086</td><td>56,512</td></tr><tr><td colspan="4">IDegLira vs IGlar + Up-titrated IGlar</td></tr><tr><td>IDegLira</td><td>7.364</td><td>49,605</td><td rowspan="2">6,090</td></tr><tr><td>IGlar + Up-titrated IGlar</td><td>7.127</td><td>48,164</td></tr></table></td><td>Applicable as conducted from the healthcare payer perspective in the UK.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			with T2DM • Costs were estimated from a UK healthcare payer perspective (NHS) • The cost year was 2015 • Direct costs included pharmacy costs, costs associated with diabetes-related complications and concomitant patient management costs. • Clinical outcomes and direct costs were projected over patients' lifetimes (40 years) using the IMS Health CORE Diabetes Model version					

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>8.5
• Costs and benefits were discounted annually at 3.5%</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>Davies et al. 2012[97]</td><td>• To investigate the cost-effectiveness of liraglutide as add-on to MET for the treatment of T2DM in the UK.</td><td>UK, from the perspective of the NHS and personal social services.</td><td>• Cost-utility analysis of liraglutide as add-on to MET compared with glimepiride (SU) and sitagliptin (DPP-4 inhibitor) was performed
• Changes in weight, cholesterol, triglycerides, SBP and HbA1c taken from the LEAD-2[98] and 1860-LIRA-DPP-4[99] studies of T2DM patients uncontrolled on MET monotherapy
• Utility values</td><td>Cohort of patients with T2DM, based on the LEAD-2[98] and 1860-LIRA-DPP-4[99] trials (adults with inadequately controlled T2DM on MET alone).</td><td colspan="3"><table><tr><th>Intervention</th><th>Discounted QALYs (SD)</th><th>Discounted costs, £ (SD)</th><th>ICERs</th></tr><tr><td colspan="4">LIRA vs GLIM</td></tr><tr><td>LIRA 1.2 mg + MET, mean</td><td>7.76 (0.11)</td><td>22,122 (502)</td><td>£9,449/QALY gained</td></tr><tr><td>LIRA 1.8 mg + MET, mean</td><td>7.73 (0.10)</td><td>23,807 (473)</td><td>£16,501/QALY gained</td></tr><tr><td>SU 4 mg + MET, mean</td><td>7.44 (0.11)</td><td>19,119 (475)</td><td>—</td></tr><tr><td colspan="4">LIRA vs SITA</td></tr><tr><td>LIRA 1.2 mg + MET, mean</td><td>7.52 (0.11)</td><td>21,793 (544)</td><td>£9,851/QALY gained</td></tr><tr><td>LIRA 1.8 mg + MET, mean</td><td>7.64 (0.11)</td><td>23,175 (510)</td><td>£10,465/QALY gained</td></tr><tr><td>SITA 100 mg + MET, mean</td><td>7.34 (0.11)</td><td>19,951 (521)</td><td>—</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS and personal social services.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			were obtained from the literature, where possible taken from populations with T2DM • Costs were accounted from a third-party payer perspective • The cost year was 2008 • Direct costs included the costs of medicine, self-monitored blood glucose testing equipment and needles • Clinical outcomes and direct costs were projected over patients' lifetimes using the IMS Health CORE Diabetes Model • Costs and					

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>benefits were discounted annually at 3.5%</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>Hunt et al. 2017[100]</td><td>• To compare the cost-effectiveness of two GLP-1 receptor agonists, liraglutide 1.8 mg and lixisenatide 20 µg, in the UK setting based on the LIRA-LIXI trial.</td><td>UK, from the NHS healthcare payer perspective.</td><td>• A cost-utility analysis of lixisenatide vs liraglutide was conducted, with the IMS CORE Diabetes Model used to project costs and benefits over a lifetime horizon
• Costs and benefits were discounted at 3.5% annually
• Annual treatment costs included: cost of GLP-1 receptor agonists, concomitant MET, needles, self-monitoring and complications.
• Costs were inflated to 2015 values using</td><td>T2DM patients enrolled in the LIRA-LIXI trial (NCT01973231) that failed to achieve glycaemic control on MET monotherapy.</td><td colspan="3"><table><tr><th>Treatment</th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/ QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>LIRA 1.8 mg</td><td>8.87</td><td>37,153</td><td>NR</td></tr><tr><td>LIXI 20 µg</td><td>8.76</td><td>36,174</td><td>NR</td></tr><tr><td colspan="4">Incremental results</td></tr><tr><td>LIRA vs LIXI</td><td>0.11</td><td>978</td><td>8,901</td></tr></table></td><td></td><td>Relevant as conducted from the perspective of the UK NHS healthcare payer.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			the Hospital and Community Health Services Index • Utility values were taken from published literature and all had been applied in previously published cost-effectiveness analyses of liraglutide					
Kragh et al. 2016[101]	• To compare the cost-effectiveness of two GLP-1RAs, liraglutide 1.8 mg and lixisenatide 20 µg, both administered once daily.	UK, perspective not reported	• Projections of costs were made over patient lifetimes using the IMS CORE Diabetes Model • Cost year: 2015 • Costs and benefits were discounted at 3.5% annually • No further details of the model were provided	Patients were adults with T2DM failing to achieve glycaemic control on MET monotherapy, enrolled in the LIRA-LIXI™ trial.[102]	**Discounted total QALYs (SD):** • Liraglutide 1.8 mg: 8.87 (0.10) • Lixisenatide 20 µg: 8.76 (0.11) **Discounted incremental QALYs (SD):** • Liraglutide 1.8 mg vs lixisenatide 20 µg: 0.11	**Discounted total costs (SD):** • Liraglutide 1.8 mg: £37,153 (£1,083) • Lixisenatide 20 µg: £36,174 (£1,136) **Discounted incremental cost (SD):** • Liraglutide 1.8 mg vs lixisenatide	**ICER:** • £8,901/QALY	Conducted in the UK, however the perspective was not explicitly stated and so may not align with the perspective of relevant payers and decision makers.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>20 µg: £978</td><td></td><td></td></tr>
<tr><td colspan="9">Multiple interventions</td></tr>
<tr><td>Gordon et al. 2017[103] [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])][104, 105]</td><td>To perform a cost-effectiveness analysis evaluating with the relative health and economic outcomes associated with escalation to second-line treatment, featuring: MET (control) and MET + SU, DPP-4i or TZD.</td><td>UK, perspective not reported.</td><td>• Cost-effectiveness of MET + second line treatment (SU, DPP-4, or TZD) was performed in comparison with MET alone (in Gordon et al. 2016) and in comparison with MET + DPP-4i (in Gordon et al. 2017)
• CORE Diabetes Model projected costs and benefits over a lifetime time horizon
• Changes in HbA1c and weight taken from patients with T2DM uncontrolled on</td><td>T2DM patients (n=6,619), approximately 72 years of age with diabetes duration 6–7 years, weight 86–90 kg and HbA1c of 8%, based on retrospective data from the UK Clinical Practice Research Datalink.

All patients were selected as they had been treated with MET monotherapy and required therapy escalation to a second line regimen between 1st January 2008 and 31st December</td><td colspan="3">Results presented in Gordon et al. 2017:
<table><tr><th>Treatment</th><th>QALYs</th><th>Costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>MET + SU</td><td>5.58</td><td>£22,960</td><td>NR</td></tr><tr><td>MET + TZD</td><td>5.55</td><td>£22,788</td><td>NR</td></tr><tr><td>MET + DPP-4i</td><td>5.64</td><td>£24,057</td><td>NR</td></tr><tr><td colspan="4">Incremental results, vs met + DPP-4i</td></tr><tr><td>MET vs MET + SU</td><td>0.06</td><td>1,097</td><td>18,680</td></tr><tr><td>MET vs MET + TZD</td><td>0.08</td><td>1,269</td><td>15,343</td></tr></table>
Results presented in Gordon et al. 2016 A and B:
<table><tr><th>Treatment</th><th>QALYs</th><th>LYs</th><th>Costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="5">Total results</td></tr><tr><td colspan="5">MET vs MET + SU</td></tr><tr><td>MET</td><td>5.34</td><td>7.98</td><td>19,228</td><td>NR</td></tr><tr><td>MET + SU</td><td>5.36</td><td>8.15</td><td>19,507</td><td>NR</td></tr><tr><td colspan="5">MET vs MET + TZD</td></tr></table></td><td>Conducted in the UK, however the perspective was not stated and so may not align with the perspective of relevant payers and decision makers.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>MET monotherapy registered on the CPRD database 2008–2014
• Cost year NR
• Costs and utilities were discounted annually at 3.5% and were sourced from published literature</td><td>2014.

Patients received the following second line regimens:
• MET + SU: n=4,451
• MET + TZD: n=705
• MET + DPP-4i: n=1,463</td><td colspan="3"><table>
<tr><td>MET</td><td>5.81</td><td>8.63</td><td>18,345</td><td>NR</td></tr>
<tr><td>MET + TZD</td><td>5.73</td><td>8.54</td><td>18,550</td><td>NR</td></tr>
<tr><td colspan="5">MET vs MET + DPP-4i</td></tr>
<tr><td>MET</td><td>5.48</td><td>8.25</td><td>18,599</td><td>NR</td></tr>
<tr><td>MET + DPP-4i</td><td>5.61</td><td>8.39</td><td>21,289</td><td>NR</td></tr>
<tr><td colspan="5">Incremental results, vs MET monotherapy</td></tr>
<tr><td>MET vs MET + SU</td><td>0.02</td><td>0.17</td><td>279</td><td>17,640</td></tr>
<tr><td>MET vs MET + TZD</td><td>0.07</td><td>0.09</td><td>-205</td><td>Dominant</td></tr>
<tr><td>MET vs MET + DPP-4i</td><td>0.13</td><td>0.15</td><td>2,690</td><td>21,318</td></tr>
</table></td><td></td></tr>
<tr><td>Marsh et al. 2016[106]</td><td>• To assess the impact of two alternative treatment regimens (OAD medication and basal insulin + OAD medication) on healthcare costs and HRQoL.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-utility analysis of OAD and OAD + basal insulin treatment regimens was performed
• Changes in HbA1c was taken from the European and LEAD-1860 trials of uncontrolled T2DM patients
• Utility values were derived</td><td>Cohort of patients with T2DM, based on a European trial (adults with inadequately controlled T2DM on OADs) and the LEAD-1860 trial (adults with inadequately controlled T2DM on MET alone).[99, 107]</td><td>Discounted total QALYs:
• Insulin + OAD: 7.20
• OAD only: 6.84

Discounted incremental QALYs:
• Insulin + OAD versus OAD only: 0.36</td><td>Discounted total costs:
• Insulin + OAD: £18,272
• OAD only: £15,604

Discounted incremental cost:
• Insulin + OAD vs OAD only: £2,668</td><td>ICERs:
£7,432/QALY</td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			from relevant literature of patients with T2DM • Costs were estimated from a UK healthcare prescription data • Cost year NR • Direct costs included pharmaceutical treatments • Clinical outcomes and direct costs were projected over a 30 year time horizon using the IMS Health CORE Diabetes Model • Costs and benefits were discounted annually at 3.5%					
McEwan et al. 2010[108]	• To compare the cost-effectivenes	UK, perspective not	• Cost-utility analysis of changes in	Cohort of patients with inadequately controlled	**Incremental QALYs:** • SU: -0.044	**Discounted costs:** • NR	**ICERs:** • NR	Conducted in the UK, however the perspective

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	s associated with changes in HbA1c, weight and hypoglycaemia and treatment with a second-line OAD added to MET for the treatment of T2DM in the UK.	reported.	HbA1c, weight and hypoglycaemia and second-line treatments with OADs was performed • Changes in HbA1c, weight, and frequency and severity of hypoglycaemic events, was taken from two trials of uncontrolled T2DM patients • Utility values were derived from relevant literature of patients with T2DM • Costs were estimated from relevant literature • Cost year: 2008 • Direct costs included those associated with macrovascular events,	T2DM, based on two trials: Nauck (2007)[109] Scott (2008)[110] Study treatment arms: • SU • TZD • DPP-4is	• TZD: -0.030 • DPP-4i: 0.215			was not stated and so may not align with the perspective of relevant payers and decision makers. Furthermore, costs and ICERs were not reported.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>amputation, healthcare maintenance, blindness, amputation, and ESRD
• Clinical outcomes and direct costs were projected over a 40 year time horizon using the Cardiff stochastic simulation cost-utility model (Diab-Forecaster)
• The discount rate for costs and benefits were NR</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Other (Nateglinide)</td></tr>
<tr><td>Ward et al. 2004[111]</td><td>• To assess the cost-effectiveness of adding nateglinide to MET for the</td><td>UK, from the perspective of the NHS.</td><td>• Cost-effectiveness analysis of adding nateglinide to existing MET therapy was</td><td>Cohort of patients with uncontrolled T2DM based on Caro 2000 and Caro 2002.[112, 113]</td><td colspan="3"><table><tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>MET</td><td>10.7</td><td>5,093</td><td>NR</td></tr><tr><td>MET + NAT</td><td>11.0</td><td>7,159</td><td>NR</td></tr></table></td><td></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	treatment of patients T2DM in the UK.		performed • Changes in HbA1c and PPG taken from Caro 2000 and Caro 2002;[112, 113] studies of patients with uncontrolled T2DM • Utility values were taken from Clarke et al. and Lawrence et al., measured using the EQ-5D questionnaire and taken from a UK population with T2DM[114] • The cost year was 1999 • Direct costs included: resource use, cost of major complications, hospital in-patient costs, non-hospital cists (GPs,		**Incremental results** MET vs MET + NAT: 0.37	2,066	5,609	

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>nurses, podiatrists, opticians, dieticians)
• Clinical outcomes and direct costs were projected over a lifetime horizon using a patient simulation model
• Costs were discounted annually at 6% and benefits were discounted at 1.5% annually</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Sodium-glucose cotransporter 2 (SGLT-2) inhibitors</td></tr>
<tr><td>NICE TA288 (2013)[115]</td><td>To assess the cost-effectiveness of:
• Dapagliflozin vs SU as an add-on to MET
• Dapagliflozin vs thiazolidine</td><td>UK, from the perspective of the NHS and personal social services.</td><td>• Cost-effectiveness of dapagliflozin was performed
• A discrete event simulation (DES) model was used to project costs</td><td>T2DM patients not adequately controlled on OADs, insulin, or a combination of both.</td><td colspan="4"><table><tr><th>Treatment</th><th>QALYs</th><th>LYG</th><th>Cost, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="5">Total</td></tr><tr><td colspan="5">Add-on to MET</td></tr><tr><td colspan="5">DAPA vs SU</td></tr><tr><td>SU</td><td>11.28</td><td>14.71</td><td>11,658</td><td>NR</td></tr><tr><td>DAPA</td><td>11.74</td><td>14.76</td><td>12,904</td><td>NR</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS and personal social services.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>dione or dipeptidyl peptidase-4 inhibitor as an add-on to MET
• Dapagliflozin vs dipeptidyl peptidase-4 inhibitor as an add-on to insulin</td><td></td><td>and outcomes over a 40 year (lifetime) time horizon with a 6 month cycle length. Following appraisal by the ERG, the CORE diabetes model was used to validate the results of the DES model
• The model used the UKPDS 68 risk equations
• Health states included T2DM with and without micro- and macrovascular diabetes-related complications
• Costs and benefits were discounted annually at 3.5%</td><td></td><td colspan="3">
<table>
<tr><td colspan="5">DAPA vs DPP-4i and TZD</td></tr>
<tr><td>DAPA</td><td>12.62</td><td>15.67</td><td>14,733</td><td>NR</td></tr>
<tr><td>TZD</td><td>12.20</td><td>15.67</td><td>14,793</td><td>NR</td></tr>
<tr><td>DPP-4i</td><td>12.60</td><td>15.64</td><td>14,882</td><td>NR</td></tr>
<tr><td colspan="5">Add-on to insulin</td></tr>
<tr><td colspan="5">DAPA vs DPP-4i</td></tr>
<tr><td>DPP-4i</td><td>12.21</td><td>15.41</td><td>17,298</td><td>NR</td></tr>
<tr><td>DAPA</td><td>12.33</td><td>15.41</td><td>17,815</td><td>NR</td></tr>
<tr><td colspan="5">Incremental</td></tr>
<tr><td colspan="5">Add-on to MET</td></tr>
<tr><td colspan="5">DAPA vs SU</td></tr>
<tr><td>DAPA vs SU</td><td>0.467</td><td>0.050</td><td>1,246</td><td>2,671</td></tr>
<tr><td colspan="5">DAPA vs DPP-4i and TZD</td></tr>
<tr><td>DAPA vs TZD</td><td>-0.42</td><td>0</td><td>60</td><td>DAPA dominates</td></tr>
<tr><td>DAPA vs DPP-4i</td><td>-0.02</td><td>-0.03</td><td>149</td><td>DAPA dominates</td></tr>
<tr><td colspan="5">Add-on to insulin</td></tr>
<tr><td colspan="5">DAPA vs DPP-4i</td></tr>
<tr><td>DAPA vs DPP-4i</td><td>0.119</td><td>0.007</td><td>517</td><td>4,358</td></tr>
</table>
</td><td></td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
SMC 799/12 (2014)b[116]	• To evaluate the cost-effectiveness of oral dapagliflozin with two GLP-1 agonists (exenatide and lixisenatide) for the management of T2DM in combination with insulin when insulin alone, with diet and exercise does not provide adequate glycaemic control.	UK, from the perspective of NHS Scotland.	• Cost-minimisation analysis of dapagliflozin was performed • Relative costs per patient for dapagliflozin vs exenatide and lixisenatide included: medicine costs, needles and nurse time • Costs were projected over a 1 year time horizon • Indirect comparisons found no significant clinical difference between dapagliflozin and either exenatide or lixisenatide • No further information on the model was	T2DM patients with inadequate glycaemic control on insulin and diet and exercise.	**QALYs:** • N/A	**First year cost savings of dapagliflozin vs:** • Exenatide: £460 • Lixisenatide: £289 **Subsequent years cost savings of dapagliflozin vs:** • Exenatide: £456 • Lixisenatide: £275	**ICER:** • N/A	Less applicable. Although the perspective of the analysis was stated, this was NHS Scotland and so this may not align precisely with the perspective of decision makers in England.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			reported					
Charokopou et al. 2015[117]	• To compare the cost-effectiveness of dapagliflozin compared to SU as an add-on to MET for the treatment of adults with type 2 diabetes in the UK.	UK, from the healthcare payer perspective.	• Cost-effectiveness of dapagliflozin was compared to SU as an add-on to MET • The Cardiff diabetes model was used to simulate costs and benefits • Costs were sourced from a UKPDS study • HRQoL data was sourced from UKPDS 62 study • The cost year was 2011 • Costs and benefits were discounted annually at 3.5%	T2DM patients included in a head-to-head phase III trial of dapagliflozin plus MET vs a SU plus MET.	**Discounted QALYs, as an add-on to MET:** • Dapagliflozin : 11.74 • SU: 11.28	**Discounted costs, as an add-on to MET:** • Dapagliflozin : £12,904 • SU: £11,658	**ICER of dapagliflozin vs SU as an add-on to MET:** • £2,671/QALY gained	Applicable as conducted from the healthcare payer perspective in the UK.
Charokopou et al. 2015[118]	• To compare the cost-effectiveness of dapagliflozi	UK, from the healthcare payer perspective	• Cost-effectiveness of dapagliflozin was compared to DPP-4	Cohort of T2DM patients, whose baseline characteristic were sourced	**Discounted QALYs, as an add-on to MET:** • Dapagliflozin	**Discounted costs, as an add-on to MET:** • Dapagliflozin	**ICER of dapagliflozin vs DPP-4i as an add-on to MET:** • £6,761/QAL	Applicable as conducted from the healthcare

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	n compared to DPP-4 inhibitors as an add-on to MET for the treatment of adults with type 2 diabetes in the UK.		inhibitors as an add-on to MET • The Cardiff diabetes model was used to simulate costs and benefits • Costs were sourced from UKPDS 65 study • HRQoL data was sourced from UKPDS 62 study • The cost year was 2011 • Costs and benefits were discounted annually at 3.5%	from SLR and class-level NMA of relevant phrase III RCTs	: 11.86 • DPP-4i: 11.83	: £13,809 • DPP-4i: £13,593	Y gained	payer perspective in the UK.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>Copley et al. 2013[119]</td>
<td>This was a report of the Evidence Review Group (ERG) analyses following NICE TA315.[120] See the entry for TA315 for the objective of the original analysis.
• The ERG undertook additional work to examine the variation in final ICER arising through re-running some of the base case analyses of dual therapy.</td>
<td>UK, from the perspective of the NHS and personal social services.</td>
<td>• See the entry for TA315 for a summary of the original model
• ERG examined variation in the original ICERs of canagliflozin 100 mg and 300 mg vs SU, dapagliflozin and dipeptidyl peptidase-4 inhibitor in 1,000 cohorts of 1,000 patients
• No further details of the analysis were provided</td>
<td>See the entry for TA315 for a summary of the patient population.</td>
<td colspan="3">
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in dual therapy</td></tr>
<tr><td>SU</td><td>0.194</td><td>303</td><td>1,566</td></tr>
<tr><td>DAPA</td><td>0.007</td><td>43</td><td>6,685</td></tr>
<tr><td>DPP-4i</td><td>0.012</td><td>45</td><td>3,926</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in dual therapy</td></tr>
<tr><td>SU</td><td>0.197</td><td>957</td><td>£4,857</td></tr>
<tr><td>DAPA</td><td>0.0250</td><td>521</td><td>£20,836</td></tr>
<tr><td>DPP-4i</td><td>0.0205</td><td>595</td><td>£28,975</td></tr>
</table>
</td>
<td>Applicable as conducted from the perspective of the UK NHS and personal social services.</td>
</tr>
<tr>
<td>Kansal et al. 2016[121]</td>
<td>• To extrapolate the outcomes of empagliflozin plus standard of care (SoC)</td>
<td>UK, perspective NR.</td>
<td>• Time dependent survival regression analysis was performed on EMPA REG Outcome</td>
<td>Patient data obtained from the EMPA REG Outcome trial, which evaluated the effect of empagliflozin in addition to SoC on CV morbidity</td>
<td colspan="3">
<table>
<tr><th></th><th>Incremental QALYs with EMPA</th><th>Incremental cost with EMPA, £</th><th>ICER, £/QALY</th></tr>
<tr><td>EMPA</td><td>0.9</td><td>3,849</td><td>4,206</td></tr>
</table>
</td>
<td>Conducted in the UK, however the perspective was not explicitly stated and so may not align with</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>compared to SoC alone over patients' remaining lifetime based on results from the EMPA REG Outcome trial.</td><td></td><td>trial[122] data for cardiovascular (CV) death, CV events including myocardial infarction and stroke, and renal outcomes to model event rates over time and the interaction between events.
• Costs and utilities were from the literature
• Future costs and QALYs were discounted annually at 3.5%</td><td>and mortality.</td><td></td><td></td><td></td><td>the perspective of relevant payers and decision makers.</td></tr>
<tr><td>Neslusan et al. 2016[123]</td><td>• To estimate the impact of SGLT-2 inhibitors delaying the progression of kidney</td><td>UK, perspective NR.</td><td>• The Economic and Health Outcomes Model for Type 2 diabetes (ECHO-T2DM) model was</td><td>T2DM patients.</td><td colspan="3"><table><tr><th>Scenario</th><th>Comparison vs SU</th><th>ICER, £/QALY</th></tr><tr><td rowspan="2">1</td><td>CANA 100 mg</td><td>15,280</td></tr><tr><td>CANA 300 mg</td><td>12,149</td></tr><tr><td>2</td><td>CANA 100 mg</td><td>11,911</td></tr></table></td><td>Conducted in the UK, however the perspective was not explicitly stated and so may not</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	disease (as measured by glomerular filtration rate [eGFR] over time) on the cost-effectiveness of canagliflozin vs SU over 30 years in dual therapy with MET.		used to inform the cost-effectiveness analysis • Four scenarios were simulated: eGFR decline according to the CDC Model of CKD for both arms (scenario 1); eGFR constant during first 4 years of canagliflozin treatment (scenario 2); eGFR constant throughout for canagliflozin only (scenario 3); and eGFR constant throughout for both canagliflozin and SU (scenario 4) • Population characteristics, treatment effects and adverse events					align with the perspective of relevant payers and decision makers.

	CANA 300 mg	9,368
3	CANA 100 mg	8,362
	CANA 300 mg	6,789
4	CANA 100 mg	"Similar to scenario 1" but NR
	CANA 300 mg	

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>were from head-to-head trials
• Costs and utilities were from the literature
• Discounting NR
• Time horizon was 30 years</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>Schroeder et al. 2015 [B][124]</td><td>• To evaluate the cost-effectiveness of canagliflozin vs SU in patients inadequately controlled on MET.</td><td>UK, from the perspective of the NHS.</td><td>• ECHO-T2DM model was used to estimate 40 year outcomes and costs associated with using canagliflozin 100 or 300 mg vs SU in dual therapy with MET
• Treatment effects were from the DIA3009 study[125]
• Utilities and costs were from the literature
• Cost year NR</td><td>T2DM patients inadequately controlled on MET alone.</td><td colspan="3"><table><tr><th>Comparator</th><th>Incremental QALYs with CANA</th><th>Incremental costs with CANA, £</th><th>ICER, £/ QALY for CANA</th></tr><tr><td colspan="4">CANA vs SU</td></tr><tr><td>CANA 100 mg</td><td>0.10</td><td>610</td><td>6,236</td></tr><tr><td>CANA 300 mg</td><td>0.11</td><td>1,203</td><td>10,857</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• Discounting NR					
Thiazolidinediones (TZDs)								
SMC 399/07 (2007)[126]	• To perform a cost-utility analysis examining combination treatment with pioglitazone and insulin compared to insulin alone.	Scotland, perspective not reported but likely to be NHS Scotland.	• A cost-utility analysis of pioglitazone was performed, using the IMS CORE Diabetes Model with costs projected over a lifetime horizon • Utility values and costs associated with diabetic complications were taken from published studies	T2DM patients with inadequate glycaemic control on insulin and for whom MET is inappropriate due to contraindications or intolerance.	**QALYs:** • NR	**Costs:** • NR	**ICER:** • Base case results of £18,740/QALY, or £17,230/QALY if the results were examined in a cohort of patients with baseline characteristics more representative of a Scottish population	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).
Beale et al. 2006[127]	• To evaluate the cost-effectiveness of rosiglitazone in combination with MET for the treatment of	UK, from the perspective of the NHS.	• Cost-effectiveness of rosiglitazone was performed • The Diabetes Decision Analysis of Cost-type 2 (DiDACT) model was	Matched age and sex cohorts of 1,000 overweight (baseline BMI 28 kg/m^2) and obese (baseline BMI 34 kg/m^2) T2DM patients failing to maintain	**Discounted QALYs per 1,000 patients:** • Overweight population: 148 • Obese population: 99	**Discounted Costs:** • Overweight population: £1.72m • Obese population: £1.65m	**ICER:** • Over-weight population £11,600/QALY gained • Obese population £16,700/QALY gained	Applicable as conducted from the perspective of the UK NHS.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	obese and overweight T2DM compared with conventional care of MET in combination with SU, in the UK.		used to project costs and outcomes over patients' lifetimes • HRQoL data was collected using the EQ-5D in the CODE-2 study • Direct costs included secondary care costs (inpatient and outpatient), primary care costs, community care costs and medication costs • The cost year was 2003 • Costs and benefits were discounted annually at 3.5%	glycaemic control on MET monotherapy.				
Tilden et al. 2007[128]	• To compare the cost-utility of pioglitazone	UK, from the perspective of the NHS.	• Cost-utility analysis of pioglitazone compared with	Cohort of patients with T2DM, based on Goldberg 2005[130]	**Discounted QALYs:** • Pioglitazone + MET:	**Discounted costs:** • Pioglitazone + MET:	**ICERs:** • Pioglitazone + MET vs rosiglitazone	Applicable as conducted from the perspective

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	for an add-on to MET for the treatment of T2DM in the UK.		rosiglitazone, both in combination with MET, was performed • Changes in HbA1c, taken from the pioglitazone vs rosiglitazone head-to-head trial of T2DM patients uncontrolled on MET monotherapy • Utility values were taken from Clarke et al., measured using the EQ-5D questionnaire and taken from a UK population with T2DM[129] • Costs were estimated from a UK healthcare payer perspective (NHS)	(adults with inadequately controlled T2DM on MET).	6.8070 • Rosiglitazone + MET: 6.7686	£9,585 • Rosiglitazone + MET: £10,299	+ MET: Pioglitazone + MET dominates (ICER NR)	of the UK NHS.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• The cost year was 2004/5 • Direct costs included the cost of medications, costs associated with diabetes-related complications and non-drug costs associated with the ongoing management of diabetes and related complications • Clinical outcomes and direct costs were projected over patients' lifetimes using a Monte Carlo simulation of a Markov process • Costs and benefits were discounted annually at 3.5%					

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
Valentine et al. 2007[131]	• To assess the cost-effectiveness of adding pioglitazone to existing treatment regimens for the treatment of patients with T2DM with a history of macrovascular disease in the UK.	UK, from the perspective of the NHS.	• Cost-effectiveness analysis of adding pioglitazone to existing treatment regimens was performed • Changes in HbA1c, cholesterol, HDL, LDL, triglycerides, SBP and BMI, taken from the pioglitazone vs PBO trial of T2DM patients uncontrolled on existing therapy • Utility values were taken from published sources. CODE-2 data were used in the base case • The cost year was 2005 • Direct costs included event costs and	Cohort of patients with T2DM and a history of macrovascular disease and at risk of further cardiovascular events, based on the PROactive study (adults with inadequately controlled T2DM on existing therapies).	**Discounted QALYs:** • Pioglitazone: 2.7441 • Placebo: 2.7251	**Discounted costs:** • Pioglitazone: £6,700 • Placebo: £6,598	**ICERs:** • Pioglitazone vs placebo: £5,396	Applicable as conducted from the perspective of the UK NHS.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			pharmacy costs • Costs and benefits were projected over a 35 year time horizon using a modified version of the CORE Diabetes Model • Costs and benefits were discounted annually at 3.5%					

Abbreviations: ALO: alogliptin; BMI: body mass index; CV: cardiovascular; DAPA: dapagliflozin; DES: discrete event simulation; DPP-4: dipeptidyl peptidase-4; DULA: dulaglutide; EQ-5D: EuroQoL-5 dimensions; EQW: exenatide once-weekly; ERG: Evidence Review Group; ESRD: end-stage renal disease; GLP-1: glucagon-like peptide 1; GP: general practitioner; GPZ: glipizide; HDL: high-density lipoprotein; HRQoL: health-related quality-of-life; IAsp: insulin aspart; ICER: incremental cost-effectiveness ratio; IDegLira: insulin degludec/liraglutide; IDet: insulin detemir; IGlar: insulin glargine; LDL: low-density lipoprotein LIRA: liraglutide; LIXI: lixisenatide; MET: metformin; NAT: nateglinide; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; NR: not reported; OAD: oral antidiabetic drug; OD: once-daily; PBO: placebo; PPG: photoplethysmogram; QALY: quality-adjusted life-year; RCT: randomised controlled trial; RE: risk equation; SBP: systolic blood pressure; SD: standard deviation; SGLT-2: sodium-glucose cotransporter 2 inhibitor; SITA: sitagliptin; SLR: systematic literature review; SMC: Scottish Medicines Consortium; SoC: standard-of-care; SU: sulfonylurea; T2DM: type 2 diabetes mellitus; TZD: thiazolidinediones; UK: United Kingdom; UKPDS: UK Prospective Diabetes Study; VDG/VIL: vildagliptin.

Triple therapy economic evaluations

Table G.14: Summary of published economic evaluations included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td colspan="9">Dipeptidyl peptidase-4 (DPP-4) inhibitors</td></tr>
<tr><td>SMC 875/13 (2013)[132]</td><td>To conduct a cost-minimisation analysis comparing vildagliptin to sitagliptin for use as triple therapy in T2DM.</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-minimisation of vildagliptin was performed, supported by the results of an NMA demonstrating comparable efficacy with sitagliptin
• The economic analysis compared the total costs per patient for vildagliptin vs sitagliptin
• Acquisition costs for both medicines were included as well as additional liver function tests (LFTs) required for patients using</td><td>T2DM patients inadequately controlled by diet and exercise plus dual therapy.</td><td colspan="3"><table><tr><th>Intervention</th><th>Total cost, £</th><th>Cost difference with VDG over a 7 year time horizon, £</th></tr><tr><td colspan="3">Scenario 1*</td></tr><tr><td>VDG</td><td>3,034.36</td><td rowspan="2">-0.63</td></tr><tr><td>SITA</td><td>3,034.99</td></tr><tr><td colspan="3">Scenario 2**</td></tr><tr><td>VDG</td><td>1,291.59</td><td rowspan="2">-9.12</td></tr><tr><td>Sitagliptin</td><td>1,300.71</td></tr></table>*Assumption that vildagliptin requires 5 additional LFTs in year 1 followed by 1 test per year for subsequent years
**Assumption that LFTs are performed annually in all patients on triple therapy, regardless of which DPP-4 is used, with vildagliptin associated with 4 additional LFTs in year 1 and none in subsequent years</td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			vildagliptin • The costs were projected over a 7 year time horizon					
SMC 918/13 (2013)[133]	To conduct a cost-minimisation analysis comparing saxagliptin with sitagliptin and linagliptin as an alternative DPP-4i as triple oral therapy, in combination with MET plus a SU.	UK, perspective not reported but likely to be NHS Scotland.	• A cost-minimisation analysis comparing saxagliptin with sitagliptin and linagliptin was performed • Data to support comparable efficacy were based on two Bucher indirect comparisons of saxagliptin with sitagliptin and linagliptin • Costs were projected over a 1 year time horizon • Only the drug acquisition costs of saxagliptin, lingaliptin and sitagliptin were included	T2DM patients not adequately controlled on diet and exercise and a combination of MET and SU.	**QALYs:** • N/A	**Cost per patient:** • Saxagliptin: £410.80 • Sitagliptin: £432.38 • Linagliptin: £432.38 (cost saving of £21.58 per patient)	**Cost saving per patient:** • Saxagliptin vs sitagliptin and linagliptin: £21.58	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• Compliance was considered to be equivalent between the therapies and other costs including monitoring were excluded on the basis that they would apply equally to both arms					
Glucagon-like peptide-1 (GLP-1) agonists								
AWMSG 863 (2013)[134]	To perform a cost-minimisation analysis of lixisenatide 10 µg and 20 µg once daily, in combination with OADs and/or basal insulin in T2DM patients in inadequate glycaemic control on diet and exercise with OADs and/or basal insulin.	UK, perspective not reported but likely to be NHS Wales.	• Cost-minimisation analysis of lixisenatide was performed • Data to support comparable efficacy were based on the GetGoal-X study for the comparison with exenatide in combination with OADs and a Bayesian mixed treatment	Adult patients with T2DM experiencing inadequate glycaemic control on OADs and/or basal insulin together with diet and exercise.	**QALYs:** • N/A	**Total annual costs**: • Lixisenatide: £739.48 • Exenatide bid: £897.71 • Liraglutide 1.2 mg: £988.57 **Total five year costs:** • Lixisenatide: £3,697 • Exenatide bid: £4,489 • Liraglutide 1.2 mg: £4,943	**Annual cost savings**: • Lixisenatide vs Exenatide bid: -£158.26 • Lixisenatide vs liraglutide 1.2 mg: -£249.09 **Five year cost savings:** • Lixisenatide vs Exenatide bid: -£791 • Lixisenatide vs liraglutide	Applicable as the study was conducted in the UK and likely from the perspective of NHS Wales (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			comparison supported equivalence vs liraglutide in combination with OADs • A Bucher indirect treatment comparison supported equivalence vs exenatide in combination with basal insulin • Costs were projected over a 1 year time horizon, but extrapolated to 5 years (the expected duration of treatment with a GLP-1 agonist) • Only the cost of medication and needles were included in the analysis vs exenatide. In the analysis				1.2 mg: -£1,246	

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>vs liraglutide, only medication costs were considered</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SMC 1024/15 (2015)[135]</td><td>To conduct a cost-minimisation analysis comparing albiglutide with exenatide extended release for glycaemic control in adult patients with type 2 diabetes.</td><td>NHS Scotland perspective.</td><td>• A cost-minimisation analysis comparing albiglutide to exenatide ER was performed
• Data to support comparable efficacy were based on a Bucher indirect comparison as no head-to-head studies were identified
• Time horizon was 1 year
• Only the drug acquisition costs per patient per year were included</td><td>T2DM patients inadequately controlled on OADs, and for whom once-weekly administration is preferable.</td><td>Incremental QALYs:
• N/A</td><td>Incremental cost:
• £31 cost saving per patient with albiglutide, assuming all patients receive the 50 mg dose</td><td>ICER:
• N/A</td><td>Applicable as conducted from the healthcare payer perspective in Scotland.</td></tr>
<tr><td>SMC 1044/15 (2015)[136]</td><td>To assess the cost-utility of liraglutide, compared to exenatide and</td><td>Scotland, perspective not reported but likely to be NHS</td><td>• Cost-utility of liraglutide was performed using the IMS</td><td>T2DM patients inadequately controlled on basal insulin together with</td><td colspan="3"><table><tr><th>Comparator</th><th>Incremental QALYs with LIRA</th><th>Incremental costs with LIRA, £</th><th>ICER, £/ QALY</th></tr><tr><td>LIXI</td><td>0.214</td><td>52</td><td>244</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	lixisenatide, as an add-on to basal insulin plus MET in the treatment of T2DM.	Scotland.	CORE Diabetes Model to project costs and benefits over a lifetime horizon • The sources for the clinical data were the LIRA-ADD2BASAL study,[137] the published literature and an indirect comparison • Utility values were sourced from literature and where possible, using EQ-5D from a UK population with T2DM • Medicine acquisition costs, costs associated with needles, test strips and lancets were included in the model.	diet and exercise.	EXE	0.100	533	5,308	perspective of NHS Scotland (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			Management costs associated with T2DM and its complications and the event costs relating to adverse events were also accounted for.					
SMC 1110/15 (2015)[138]	To conduct a cost-minimisation analysis comparing dulaglutide, as part of triple therapy, to other GLP-1 receptor agonists (liraglutide and exenatide) in T2DM inadequately controlled on two OADs.	UK, perspective not reported but likely to be NHS Scotland.	• A cost-minimisation analysis comparing dulaglutide to liraglutide (1.2 mg and 1.8 mg and at an average daily dose of 1.53 mg) and exenatide extended release was performed • Data to support comparable efficacy were based on a NMA as no head-to-head trials were available	T2DM patients inadequately controlled on 2 OADs.	**QALYs:** • N/A	**Incremental costs:** • Dulaglutide vs liraglutide 1.2 mg: -£29 • Dulaglutide vs liraglutide 1.8 mg: -£507 • Dulaglutide vs liraglutide 1.53 mg average daily dose: -£291 • Dulaglutide vs exenatide extended release: -£1	**CMA results:** • Dulaglutide vs liraglutide 1.2 mg: Dulaglutide is cost-minimising • Dulaglutide vs liraglutide 1.8 mg: Dulaglutide is cost-minimising • Dulaglutide vs liraglutide 1.53 mg average daily dose: Dulaglutide is cost-minimising • Dulaglutide vs	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>Only the costs relating to the medicines and costs of the needles were included
The time horizon was 1 year</td><td></td><td></td><td></td><td>exenatide extended release: Dulaglutide is cost-minimising</td><td></td></tr>
<tr><td>Ray et al. 2007[139]</td><td>To assess the cost-effectiveness associated with exenatide or insulin glargine as an add-on to OADs in patients with T2DM in the UK clinical setting.</td><td>UK, from the perspective of the NHS.</td><td>Cost-effectiveness analysis of exenatide or insulin glargine in addition to existing oral regimens with MET and SU was performed
Changes in HbA1c, SBP, cholesterol, LDL, HDL, triglycerides and BMI taken from Heine 2005 clinical trial of T2DM patients uncontrolled on MET and SU
Utility values were taken</td><td>Cohort of patients with T2DM, based on Heine 2005[141] (adults with inadequately controlled T2DM on MET and SU).</td><td colspan="3"><table>
<tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted direct costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">Total results</td></tr>
<tr><td>EXE, mean (SD)</td><td>7.39 (0.11)</td><td>29,401 (676)</td><td rowspan="2">N/A</td></tr>
<tr><td>Insulin glargine, mean (SD)</td><td>6.95 (0.10)</td><td>19,489 (636)</td></tr>
<tr><td colspan="4">Incremental results</td></tr>
<tr><td>EXE vs insulin glargine</td><td>N/A</td><td>N/A</td><td>22,420</td></tr>
</table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			from the UKPDS and supplemented from the 'Burden of Illness in Australia' report and Tengs et al. 2000,[140] all taken from a population with T2DM • UK-specific costs were derived from published sources. Costs for exenatide were estimated from US wholesale price and converted to GBP • The cost year was 2004 • Direct costs included pharmacy and complication costs • Clinical outcomes and direct costs					

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>were projected over a 35 year time horizon using the IMS Health CORE Diabetes Model
• Costs and benefits were discounted annually at 3.5%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Multiple interventions</td></tr>
<tr><td>Waugh et al. 2010[142]</td><td>To compare the cost-effectiveness of third line treatments for T2DM patients who have failed dual oral therapy.</td><td>UK, perspective not reported.</td><td>• Cost effectiveness of the following comparisons was performed:
• Exenatide vs glargine
• Evolution of HbA1c assumed to be slower with glargine
• Evolution of HbA1c assumed to be slower with exenatide
• Sitagliptin vs rosiglitazone</td><td>T2DM patients who have failed treatment with dual oral therapy (MET and SU). The base case patient was male with a BMI of 30 kg/m^2 and no complications.</td><td colspan="3">All results are for the base case patient (male, BMI of 30 kg/m^2, no complications).
Exenatide vs glargine:
<table>
<tr><th>Intervention</th><th>Total QALYs</th><th>Total costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">Evolution of HbA1c assumed to be slower with glargine:</td></tr>
<tr><td>EXE</td><td>8.617</td><td>19,128</td><td rowspan="2">19,854</td></tr>
<tr><td>Glargine</td><td>8.559</td><td>17,977</td></tr>
<tr><th>Intervention</th><th>Total QALYs</th><th>Total costs</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">Evolution of HbA1c assumed to be slower with exenatide:</td></tr>
<tr><td>EXE</td><td>8.567</td><td>18,953</td><td rowspan="2">6,755</td></tr>
<tr><td>Glargine</td><td>8.464</td><td>18,258</td></tr>
</table>
Sitagliptin vs rosiglitazone:</td><td>Conducted in the UK, however the perspective was not stated and so may not align with the perspective of relevant payers and decision makers.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>Vildagliptin vs pioglitazone
The UKPDS model was used to project costs and outcomes over patients' lifetimes
HRQoL and cost data associated with complications and ongoing care were estimated from the UKPDS population
Direct costs included drug costs and monitoring
The cost year was 2007, so some costs were inflated to 2007 values using the PSSRU Hospital & Community Health Services Pay and Prices</td><td></td><td colspan="3"><table>
<tr><th>Intervention</th><th>Total QALYs</th><th>Total costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td>SITA</td><td>8.479</td><td>16,083</td><td rowspan="2">Sitagliptin dominant</td></tr>
<tr><td>ROSI</td><td>8.447</td><td>16,277</td></tr>
</table>
Vildagliptin vs pioglitazone:
<table>
<tr><th>Intervention</th><th>Total QALYs</th><th>Total costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td>VDG</td><td>8.468</td><td>15,731</td><td rowspan="2">39,846</td></tr>
<tr><td>PIO</td><td>8.479</td><td>16,180</td></tr>
</table></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>Index
• Costs and benefits were discounted annually at 3.5%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Sodium-glucose cotransporter 2 (SGLT-2) inhibitors</td></tr>
<tr><td>NICE TA418 (2016)[143]</td><td>To evaluate the cost-effectiveness of dapagliflozin, compared to dipeptidyl peptidase-4 inhibitors, as an add-on combination therapy to MET and SU for the treatment of T2DM.</td><td>UK, from the perspective of the NHS and personal social services.</td><td>• Cost-utility of dapagliflozin was performed
• The Cardiff Diabetes model was used to project costs and outcomes over a lifetime horizon of 40 years using 5,000 6 month cycles
• HRQoL data and costs were obtained from published studies[129, 144-146]
• Direct costs included drug acquisition, monitoring and adverse events</td><td>T2DM patients with inadequate glycaemic control, despite treatment with MET and SU.</td><td colspan="3"><table><tr><th>Treatment</th><th>QALYs</th><th>LYG</th><th>Costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="5">Total result per patient</td></tr><tr><td>DAPA + MET + SU</td><td>9.62</td><td>11.60</td><td>20,417</td><td>N/A</td></tr><tr><td>DPP-4i + MET + SU</td><td>9.58</td><td>11.57</td><td>20,529</td><td>N/A</td></tr><tr><td>CANA 100 mg</td><td>9.62</td><td>11.61</td><td>20,351</td><td>N/A</td></tr><tr><td>CANA 300 mg</td><td>9.61</td><td>11.60</td><td>20,610</td><td>N/A</td></tr><tr><td>EMPA 10 mg</td><td>9.61</td><td>11.60</td><td>20,456</td><td>N/A</td></tr><tr><td>EMPA 25 mg</td><td>9.61</td><td>11.60</td><td>20,410</td><td>N/A</td></tr><tr><td colspan="5">Incremental result per patient, DAPA + MET + SU vs:</td></tr><tr><td>DPP-4i + MET +SU</td><td>0.032</td><td>0.026</td><td>-112</td><td>DAPA dominates</td></tr><tr><td>CANA 100 mg</td><td>-0.001</td><td>NR</td><td>66</td><td>CANA 100 mg dominated</td></tr><tr><td>CANA 300 mg</td><td>0.003</td><td>NR</td><td>-192</td><td>DAPA dominates</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS and personal social services.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>Costs and benefits were discounted annually at 3.5%</td><td></td><td colspan="3"><table>
<tr><td>EMPA 10 mg</td><td>0.005</td><td>0.000</td><td>-38</td><td>DAPA dominates</td></tr>
<tr><td>EMPA 25 mg</td><td>0.006</td><td>0.000</td><td>8</td><td>1,354</td></tr>
</table></td><td></td></tr>
<tr><td>SMC 993/14 (2014)[147]</td><td>To assess the cost-effectiveness of empagliflozin as combination for dual therapy and triple therapy in the treatment of T2DM.</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>A cost-utility analysis of empagliflozin was performed
Risk equations from the UKPDS were used as patients progressed through the model in 6 month cycles
Clinical effectiveness data were drawn from 4 NMAs
Drug acquisition costs, costs to treat complications and adverse events were included in the model
HRQoL data</td><td>T2DM patients not adequately controlled on insulin or OADs, or a combination of both.</td><td colspan="3"><table>
<tr><th>Treatment</th><th>Incremental QALYs</th><th>Incremental costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">In combination with MET + insulin</td></tr>
<tr><td>EMPA vs DAPA</td><td>NR</td><td>Cost-neutral</td><td>NR</td></tr>
<tr><td>EMPA 10 mg vs DPP-4i</td><td>0.036</td><td>29</td><td>806</td></tr>
<tr><td>EMPA 25 mg vs DPP-4i</td><td>0.018</td><td>150</td><td>8,306</td></tr>
<tr><td colspan="4">In combination with MET + TZD</td></tr>
<tr><td>EMPA 10 mg vs DPP-4i</td><td>0.04</td><td>516</td><td>12,798</td></tr>
<tr><td>EMPA 25 mg vs DPP-4i</td><td>0.031</td><td>276</td><td>8,947</td></tr>
</table></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>was sourced from published studies
• The time horizon, cost year and discounting were not reported</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>Thompson et al. 2014[148]</td><td>To evaluate the long-term cost effectiveness of using canagliflozin 300 mg vs sitagliptin 100 mg as an add-on therapy to MET and SU in patients inadequately controlled on MET + SU.</td><td>UK, from the perspective of the NHS.</td><td>• ECHO-T2DM stochastic microsimulation model was used to estimate 40 year outcomes and costs associated with canagliflozin vs sitagliptin triple therapy.
• Treatment effects, incidence of AEs and patient characteristics were derived from the DIA3015 trial[149]
• Cost year NR
• QALYs were</td><td>T2DM patients inadequately controlled on MET + SU.
1,000 simulated cohorts, each containing 2,000 hypothetical T2DM patients.

Patient characteristics sourced from the DIA3015 trial.</td><td colspan="3"><table><tr><th>Comparator</th><th>QALYs (discounted)</th><th>Total costs (discounted), £</th><th>ICER, £/ QALY for CANA</th></tr><tr><td colspan="4">CANA vs SITA</td></tr><tr><td>CANA 100 mg</td><td>9.40</td><td>28,941</td><td rowspan="2">17,813</td></tr><tr><td>SITA 100 mg</td><td>9.36</td><td>28,270</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			discounted at 3.5%					

Abbreviations: AWMSG: All Wales Medicines Strategy Group; BMI: body mass index; CANA: canagliflozin; CMA: cost-minimisation analysis; DAPA: dapagliflozin; DPP-4: dipeptidyl peptidase-4; EMPA: empagliflozin; EQ-5D: EuroQoL-5 dimensions; EXE: exenatide; GLP-1: glucagon-like peptide 1; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; LFT: liver function test; LIRA: liraglutide; LIXI: lixisenatide; MET: metformin; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; NR: not reported; OAD: oral antidiabetic drug; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life-year; ROSI: rosiglitazone; SD: standard deviation; SITA: sitagliptin; SMC: Scottish Medicines Consortium; SU: sulfonylurea; T2DM: type 2 diabetes mellitus; TZD: thiazolidinediones; UK: United Kingdom; US: United States; VDG: vildagliptin.

Mono- and dual therapy economic evaluations

Table G.15: Summary of published economic evaluations included in the economic systematic literature review

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
Dipeptidyl peptidase-4 (DPP-4) inhibitors								
SMC 746/11 (2011)[150] [SMC 850/13 (2013)][151]	To assess the cost-effectiveness of linagliptin as monotherapy and as combination therapy for the treatment of T2DM.	UK, perspective not reported but likely to be NHS Scotland.	• A cost-minimisation analysis comparing linagliptin with sitagliptin for the treatment of type 2 diabetes, both as monotherapy and in combination with MET • Costs and outcomes were projected over a one year time horizon • Only drug acquisition costs were considered as the costs of monitoring, management	Mono-therapy: T2DM patients not adequately controlled on diet and exercise and for whom MET is inappropriate. Combination therapy: T2DM patients not adequately controlled on diet and exercise plus MET. T2DM patients not adequately controlled on diet and exercise plus MET for whom the	**QALYs:** • N/A	**Cost per annum:** • Linagliptin: £434 Sitagliptin: £434	**Cost-minimisation:** • Lingaliptin was considered cost-effective in the proposed patient groups on the basis of comparable efficacy at equivalent cost to sitagliptin	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			of AEs and complications were assumed to be similar	addition of SU is inappropriate.				
SMC 772/12 (2014)[152]	To compare the cost-utility of saxagliptin with the GLP-1 receptor agonists exenatide and lixisenatide.	UK, perspective not reported but likely to be NHS Scotland.	• Cost-utility of saxagliptin was compared to exenatide and lixisenatide • A discrete event simulation model was used to project costs and outcomes over a 40 year time horizon using 6 month cycles • Risk equations from the UKPDS data were used to estimate the occurrence of complications • Clinical	T2DM patients not adequately controlled on diet and exercise and insulin, with or without MET.	**Incremental QALYs:** • Saxagliptin vs exenatide twice daily: -0.012 • Saxagliptin vs lixisenatide: 0.010	**Incremental Costs:** • Saxagliptin vs exenatide twice daily: -£1,402 • Saxagliptin vs lixisenatide: -£472	**ICER:** • Saxagliptin vs exenatide twice daily: NR • Saxagliptin vs lixisenatide: Dominant	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			effectiveness data were drawn from a NMA of 7 trials • HRQoL data was collected from published sources and had been used in previous SMC submissions • Costs of drug acquisition, adverse event, complications, hypoglycaemia, discontinuations and costs associated with weight gain were included in the model					
SMC 850/13 (2015) Resub-mission[151]	To assess the cost-effectiveness of linagliptin as monotherapy and as	UK, perspective not reported but likely to	• A cost-minimisation analysis comparing	T2DM patients with inadequate glycaemic	**QALYs:** • N/A	**Cost per annum:** • Linagliptin: £434	**Cost-minimisation:** • Lingaliptin was	Applicable as the study was conducted in

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	combination therapy for the treatment of T2DM.	be NHS Scotland.	linagliptin to the SGLT-2 inhibitors dapagliflozin, canagliflozin and empagliflozin, and to the GLP-1 agonists exenatide and lixisenatide was conducted • Costs and outcomes were projected over a one year time horizon • Drug acquisition costs only were considered as all other direct costs were assumed to be similar	control on diet and exercise plus MET with or without insulin.		**Incremental savings with linagliptin vs the SGLT-2 inhibitors and GLP-1 agonists:** • £43 to £395	considered cost-effective in the proposed patient groups on the basis of comparable efficacy at equivalent cost to SGLT-2 inhibitors and GLP-1 agonists	the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

Abbreviations: AE: adverse event; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; MET: metformin; N/A: not applicable; NHS: National Health Service; NMA: network meta-analysis; QALY: quality-adjusted life years; SGLT-2: sodium-glucose cotransporter-2; SMC: Scottish Medicines Consortium; T2DM: type 2 diabetes mellitus; UK: United Kingdom; UKPDS: UK Prospective Diabetes Study.

Dual and triple therapy economic evaluations

Table G.16: Summary of published economic evaluations included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td colspan="9">Dipeptidyl peptidase-4 (DPP-4) inhibitors</td></tr>
<tr><td>SMC 1083/15 (2015)[153]</td><td>To conduct a cost-minimisation analysis comparing sitagliptin to dapagliflozin and empagliflozin, and also to exenatide and lixisenatide.</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• A cost-minimisation was performed comparing sitagliptin to dapagliflozin and empagliflozin, and also to exenatide and lixisenatide
• Clinical data used to support the cost-minimisation approach were taken from an NMA
• The analysis only included drug costs.</td><td>T2DM patients inadequately controlled on diet and exercise, plus a stable dose of insulin, with or without MET.</td><td colspan="3"><table><tr><th>Comparison</th><th>Annual cost difference with sitagliptin regimen, £</th></tr><tr><td>SITA vs DAPA + EMPA</td><td>-43</td></tr><tr><td>SITA vs EXE</td><td>-397</td></tr><tr><td>SITA vs LIXI</td><td>-272</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>Administration or monitoring costs were not included, as these were assumed to be part of routine clinical management and therefore apply to all treatments
• The time horizon used was a year</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SMC 505/08 (2008)[154]</td><td>To assess the cost-utility of sitagliptin for the treatment of patients with inadequate glycaemic control in the following 2 scenarios:
• Added to a SU vs a TZD added</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• A cost-utility analysis of sitagliptin was performed
• A patient simulation model was used to project costs and outcomes over a</td><td>Patients whose T2DM was inadequately controlled with diet and exercise and oral OADs.</td><td colspan="3"><table><tr><th>Comparison</th><th>ICER, £/QALY for sitagliptin regimen</th></tr><tr><td>SITA + SU vs TZD + SU</td><td>5,007</td></tr><tr><td>SITA + MET vs TZD + MET + SU</td><td>1,902</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>to a SU
• Added to MET plus a SU vs a TZD added to MET plus a SU</td><td></td><td>lifetime horizon
• Patients could progress to other treatments dependent on their treatment response
• Long-term outcomes were estimated using the UKPDS risk factor equations
• Most inputs were set equal for the sitagliptin and TZD regimens</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SMC 937/14 (2014)[155]</td><td>To perform a cost-minimisation analysis of alogliptin in the following settings:</td><td>Scotland, NHS perspective.</td><td>• Cost-minimisation analysis of alogliptin was performed</td><td>Adult patients with T2DM, where MET or SU alone, together with diet and exercise, do not provide adequate glycaemic control.</td><td colspan="3"><table><tr><th>Intervention</th><th>Total annual cost, £</th><th>Annual cost difference per patient with ALO, £</th></tr><tr><td>ALO</td><td>346.75</td><td>N/A</td></tr><tr><td>SITA</td><td>433.57</td><td>-86.82</td></tr></table></td><td></td><td>Relevant as conducted within the UK (Scotland) and NHS perspective</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	• In combination with MET (dual therapy) vs sitagliptin, saxagliptin and linagliptin in combination with MET • In combination with SU (dual therapy) vs sitagliptin in combination with SU • In combination with MET and SU (triple therapy) vs sitagliptin and linagliptin in combination with MET and SU		• Data to support comparable efficacy were based on indirect comparisons between alogliptin and each of the other dipeptidyl peptidase-4 inhibitor inhibitors in combination with MET, SU or MET plus SU • Only the drug costs of alogliptin, sitagliptin, saxagliptin and linagliptin were included; the costs of MET and SU were assumed to be the same		LINA 433.57 -86.82 SAXA 411.93 -65.18		clearly stated.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			for each dipeptidyl peptidase-4 inhibitor and therefore not included • Costs were projected over a 1 year time horizon					
Glucagon-like peptide-1 (GLP-1) agonists								
SMC 376/07 (2007)[156]	To assess the cost-utility of exenatide 10 µg twice daily (BID) with biphasic insulin aspart for T2DM patients who had failed to achieve adequate glycaemic control on maximally tolerated doses of MET and/or SU.	UK, perspective not reported but likely to be NHS Scotland.	• Cost-utility of exenatide was performed • A Markov model, based on the IMS CORE Diabetes Model was used to project costs and outcomes over a 10 year time horizon • Utility	T2DM patients inadequately controlled on maximally tolerated doses of MET and/or SU	**QALYs:** • N/R	**Incremental cost:** • N/R	**ICER:** • £6,790/QALY	Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>values used in the model were taken from the CODE-2 study
• No further details of the model were reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SMC 585/09 (2009)[157]</td><td>To assess the cost-effectiveness of liraglutide at various places in the T2DM treatment pathway:
• As add-on therapy to a SU vs a thiazolidinedione
• As add-on therapy to MET vs a SU
• As add-on therapy to MET and/or a SU vs</td><td>Scotland, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-effectiveness of liraglutide was performed with the CORE diabetes model used to project costs and benefits over a lifetime horizon
• Clinical data were taken from clinical efficacy studies
• HRQoL and</td><td>T2DM patients inadequately controlled on OADs.</td><td colspan="3">For 1.2 mg liraglutide:
<table><tr><th>Comparator</th><th>Incremental QALYs with LIRA</th><th>Incremental costs with LIRA, £</th><th>ICER, £/QALY gained for LIRA</th></tr><tr><td>TZD (in addition to SU)</td><td>0.204</td><td>2,188</td><td>10,751</td></tr><tr><td>SU (in addition to MET)</td><td>0.154</td><td>3,639</td><td>23,598</td></tr><tr><td>EXE (in addition to MET and/or a SU)</td><td>0.071</td><td>80</td><td>Dominant</td></tr><tr><td>Insulin glargine (in addition to MET and a TZD)</td><td>0.248</td><td>1,933</td><td>7,801</td></tr><tr><td>Insulin glargine (in</td><td>0.187</td><td>1,652</td><td>8,847</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>exenatide
• As add-on therapy to MET and a thiazolidinedione vs insulin glargine
• As add-on therapy to MET and a SU vs insulin glargine</td><td></td><td>cost data were sourced from published sources, mainly in the UK setting</td><td></td><td colspan="3"><table><tr><td>addition to MET and a SU)</td><td></td><td></td><td></td></tr></table>
For 1.8 mg liraglutide:<table><tr><th>Comparator</th><th>ICER, £/QALY gained for LIRA</th></tr><tr><td>TZD (in addition to SU)</td><td>17,394</td></tr><tr><td>SU (in addition to MET)</td><td>43,369</td></tr><tr><td>EXE (in addition to MET and/or a SU)</td><td>15,581</td></tr><tr><td>Insulin glargine (in addition to MET and a TZD)</td><td>14,923</td></tr><tr><td>Insulin glargine (in addition to MET and a SU)</td><td>17,777</td></tr></table></td><td></td></tr>
<tr><td>SMC 684/11 (2011)[158]</td><td>To conduct a cost-minimisation analysis comparing exenatide 10 µg bid to liraglutide 1.2 mg QD for the treatment of T2DM patients with inadequate glycaemic control on MET + thiazolidinedione.</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>• A cost-minimisation analysis comparing exenatide and liraglutide was performed
• Data to support comparable efficacy were based on a naïve indirect</td><td>T2DM patients inadequately controlled on MET + TZD and for whom the treatment of choice is a GLP-1 receptor agonist.</td><td>Incremental QALYs:
• N/A</td><td>Annual treatment cost per patient:
• Exenatide bid: £925
• Liraglutide 1.2 mg: £1,002</td><td>Cost saving per patient:
• Exenatide bid vs liraglutide 1.2 mg: £77</td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS Scotland (despite not being explicitly stated).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>comparison of 2 RCTs
• Only the drug acquisition costs and costs of needles for exenatide and liraglutide were included. The cost of background therapy and other consumables were assumed to be identical and so were not included
• Duration of treatment was 1 year</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SMC 748/11 (2011)[159]</td><td>• To compare the cost-utility of EQW as dual therapy in combination</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-utility of exenatide was performed
• The CORE Diabetes Model was</td><td>T2DM patients not adequately controlled on OADs.</td><td colspan="3"><table><tr><th>Treatment</th><th>Incremental QALYs</th><th>Incremental costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Dual therapy, EQW vs:</td></tr><tr><td>SITA</td><td>0.151</td><td>644</td><td>4,262</td></tr></table></td><td>Applicable as the study was conducted in the UK and likely from the perspective</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>with MET or pioglitazone as an alternative to sitagliptin and pioglitazone
• To compare the cost-utility of EQW as triple therapy in combination with MET plus SU or MET and pioglitazone, as an alternative to exenatide bid, liraglutide and insulin</td><td></td><td>used to project costs and outcomes over a 20 year time horizon
• Resource use estimates and utility values used in the model to account for diabetes-related complications were taken from UKPDS and supplemented with data from the literature</td><td></td><td colspan="3"><table><tr><td>PIO</td><td>0.140</td><td>894</td><td>6,400</td></tr><tr><td colspan="4">Triple therapy, EQW vs:</td></tr><tr><td>Exenatide bid</td><td>0.092</td><td>-452</td><td>Dominant</td></tr><tr><td>LIRA 1.8 mg</td><td>-0.062</td><td>-1,198</td><td>19,239*</td></tr><tr><td>LIRA 1.2 mg</td><td>0.015</td><td>-172</td><td>Dominant</td></tr><tr><td>Insulin glargine</td><td>0.101</td><td>1,039</td><td>10,246</td></tr></table>*Exenatide is less costly and less effective. Indicates liraglutide 1.8 mg would be considered cost-effective vs exenatide once weekly.</td><td>of NHS Scotland (despite not being explicitly stated).</td></tr>
<tr><td>SMC 785/12 (2012)[160]</td><td>To compare cost-utility of exenatide as add-on therapy to titrated insulin glargine to insulin glargine alone in T2DM patients who had not achieved</td><td>UK, perspective not reported but likely to be NHS Scotland.</td><td>• Cost-utility of exenatide twice daily was performed
• The CORE Diabetes Model was</td><td>T2DM patients not adequately controlled on basal insulin with or without MET and/or pioglitazone.</td><td>Incremental QALYs:
• Exenatide + glargine vs glargine alone: 0.183</td><td>Incremental cost:
• Exenatide + glargine vs glargine alone: £1,721</td><td>ICER:
• Exenatide + glargine vs glargine alone: £9,411/ QALY gained</td><td>Applicable as the study was conducted in the UK and likely from the perspective of NHS</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	adequate glycaemic control with basal insulin, with or without MET and/or pioglitazone.		used to project costs and outcomes over a 20 year time horizon • HRQoL data were collected from published sources • Costs associated with treating the longer terms consequences of diabetes were taken from published studies based on UKPDS					Scotland (despite not being explicitly stated).
SMC 903/13 (2013)[161]	To perform cost-minimisation analyses comparing lixisenatide to other GLP-1	UK, perspective not reported but likely to be NHS Scotland.	• Cost-minimisation analyses of lixisenatide vs	T2DM patients uncontrolled on two OADs and/or basal insulin, when the use of a GLP-1 agonist was considered	**QALYs:** • N/A	**Total cost annual cost per patient:** Lixisenatide vs exenatide bid: • Lixisenatide	**Total cost saving per patient per year:** • Lixisenatide vs exenatide bid: £159	Applicable as the study was conducted in the UK and likely from the

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	agonists, either in combination with OADs or in combination with basal insulin. In combination with OADs, lixisenatide was compared to exenatide twice daily and liraglutide 1.2 mg. In combination with basal insulin, lixisenatide was compared to exenatide twice daily.		exenatide bid or liraglutide 1.2 mg in combination with OADs, and lixisenatide vs exenatide bid in combination with basal insulin in were performed • Data to support comparable efficacy were based a single RCT for exenatide and a mixed treatment comparison for liraglutide 1.2 mg. A Bucher pair-wise indirect comparison for the	appropriate.		: £739 • Exenatide bid: £898 Lixisenatide vs liraglutide 1.2 mg: • Lixisenatide: £705 • Liraglutide 1.2 mg: £955	(21.4% cost saving) • Lixisenatide vs liraglutide 1.2 mg: £250 (35.3% cost saving)	perspective of NHS Scotland (despite not being explicitly stated).

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			combination with basal insulin was presented • The time horizon was 1 year • Only the cost of medication and needles were included					
Ashley et al. 2015[162]	To compare the cost-effectiveness of GLP-1 receptor agonists for the treatment of diabetes in the UK.	UK, perspective not reported.	• Cost-effectiveness analysis of GLP-1 receptor agonists was performed • Changes in HbA1c, BP and BMI taken from NMA of 13 RCTs of T2DM patients uncontrolled on OADs • Costs were	Cohort of patients with T2DM, based the LEAD-6 trial (adults with inadequately controlled T2DM on maximally tolerated doses of MET, SU, or both).[163]	**Discounted QALYs:** • Liraglutide: 9.17 • Exenatide: 9.16 • Lixisenatide : 9.12	**Discounted Costs:** • Liraglutide: £37,520 • Exenatide: £37,607 • Lixisenatide : £37,126	**ICERs:** • Liraglutide vs exenatide: Dominant • Liraglutide vs lixisenatide £7,367/QALY gained	Conducted in the UK, however the perspective was not stated and so may not align with the perspective of relevant payers and decision makers.

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>taken from published UK-specific sources
• The cost year was 2013
• Clinical outcomes and direct costs were projected over patients' lifetimes
• Costs and benefits were discounted annually at 3.5%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hunt et al. 2017[164]</td><td>To compare the long-term cost-effectiveness of currently available GLP-1 RAs used for the treatment of T2DM in the UK.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-effectiveness analysis of liraglutide 1.2 mg, exenatide 10 µg BID and lixisenatide 20 µg was performed</td><td>Cohort of patients with T2DM, based the LEAD-6 trial (adults with inadequately controlled T2DM on maximally tolerated doses of MET, SU, or both).[163]</td><td colspan="3"><table><tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">Total results</td></tr><tr><td>LIRA 1.2 mg, mean (SD)</td><td>9.19 (0.11)</td><td>36,394 (1,074)</td><td>NR</td></tr><tr><td>EXE 10 µg BID, mean (SD)</td><td>9.17 (0.11)</td><td>36,547 (1,112)</td><td>NR</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			• Changes in HbA1c, SBP, and BMI taken from the LEAD-6 head-to-head trial of uncontrolled T2DM patients • Utility values were derived from relevant literature of patients with T2DM • Costs were estimated from a UK healthcare payer perspective (NHS) • The cost year was 2015 • Direct costs included medication (GLP-1RAs		LIXI 20 µg, mean (SD) | 9.12 (0.12) | 36,496 (1,144) | NR **Incremental results** LIRA 1.2 mg vs EXE 10 µg bid | 0.02 | -153 | Liraglutide dominant LIRA 1.2 mg vs LIXI 20 µg bid | 0.07 | -103 | Liraglutide dominant			

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>and concomitant MET), needles and self-monitoring of blood glucose testing
• Clinical outcomes and direct costs were projected over patients' lifetimes (max. 50 years) using the IMS Health CORE Diabetes Model
• Costs and benefits were discounted annually at 3.5%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Schlueter et al. 2016[165]</td><td>To assess the cost-effectiveness of liraglutide 1.2</td><td>UK, from the perspective</td><td>• Costs and outcomes estimated</td><td>T2DM patients with inadequate glycaemic control on MET.</td><td colspan="4">Dual therapy<table><tr><th>Comparator</th><th>Total QALYs</th><th>Total costs</th><th>ICER</th></tr></table></td><td>Applicable as conducted</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td>and 1.8 mg once daily vs dapagliflozin 10 mg once daily, for the treatment of T2DM in patients on dual and triple anti-diabetic therapy.</td><td>of the NHS.</td><td>over a lifetime horizon using the IMS CORE Diabetes Model.
• Cost year: 2016
• Future costs and outcomes discounted at 3.5%
• Comparative efficacy data were derived from an NMA
• Utilities were from the literature</td><td></td><td colspan="3">LIRA 1.2 mg vs DAPA 10 mg
LIRA 1.2 mg | 10.22 | £64,553 | Dominant
DAPA 10 mg | 10.19 | £64,710
LIRA 1.8 mg vs DAPA 10 mg
LIRA 1.8 mg | 10.26 | £65,594 | £14,768
DAPA 10 mg | 10.19 | £64,710

Triple therapy
Comparator | Total QALYs | Total costs | ICER
LIRA 1.2 mg vs DAPA 10 mg
LIRA 1.2 mg | 10.084 | £62,408 | Dominant
DAPA 10 mg | 10.039 | £62,571
LIRA 1.8 mg vs DAPA 10 mg
LIRA 1.8 mg | 10.102 | £63,416 | £15,960
DAPA 10 mg | 10.039 | £62,571</td><td>from the perspective of the UK NHS.</td></tr>
<tr><td>Vega-Hernandez et al. 2017[166]</td><td>To assess the cost-effectiveness of liraglutide compared with dapagliflozin for the treatment of patients with T2DM in the UK.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-effectiveness analysis of liraglutide vs dapagliflozin performed
• Changes in</td><td>Cohort of T2DM patients inadequately controlled on OADs.</td><td colspan="3">Intervention | Discounted QALYs | Discounted costs | ICER, £/QALY
Total results
Dual therapy
LIRA 1.2 mg | 10.169 | £64,239 | NR
DAPA 10 mg | 10.131 | £64,250 | NR</td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>HbA1c, SBP and BMI, weight, and hypoglycaemic events taken from the NMA of 17 RCTs of patients with uncontrolled T2DM
• Utility values were taken from Beaudet et al., measured using the EQ-5D questionnaire and taken from a UK population with T2DM
• The cost year was 2016
• Direct costs included the treatment and</td><td></td><td>
<table>
<tr><td>LIRA 1.8 mg</td><td>10.198</td><td>£65,137</td><td>NR</td></tr>
<tr><td colspan="4">Triple therapy</td></tr>
<tr><td>LIRA 1.2 mg</td><td>10.184</td><td>£63,158</td><td>NR</td></tr>
<tr><td>DAPA 10 mg</td><td>10.12</td><td>£63,229</td><td>NR</td></tr>
<tr><td>LIRA 1.8 mg</td><td>10.187</td><td>£64,020</td><td>NR</td></tr>
<tr><td colspan="4">Incremental results</td></tr>
<tr><td colspan="4">Dual therapy</td></tr>
<tr><td>LIRA 1.2 mg vs DAPA 10 mg</td><td>0.039</td><td>-11</td><td>Dominant</td></tr>
<tr><td>LIRA 1.8 mg vs DAPA 10 mg</td><td>0.067</td><td>888</td><td>£14,432.00</td></tr>
<tr><td colspan="4">Triple therapy</td></tr>
<tr><td>LIRA 1.2 mg vs DAPA 10 mg</td><td>0.064</td><td>-71</td><td>Dominant</td></tr>
<tr><td>LIRA 1.8 mg vs dapagliflozin 10 mg</td><td>0.067</td><td>791</td><td>£14,250.00</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			consumables (test strips, lancets and needles) required to administer and managed the treatment, costs associated with screening programs (for eye disease, proteinuria, depression and foot) and the cost of diabetes-related complications • Clinical outcomes and direct costs were projected over a lifetime horizon					

<table>
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<tr><td></td><td></td><td></td><td>using the QuintilesIMS CORE Diabetes Model
• Costs and benefits were discounted annually at 3.5%</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Woehl et al. 2008[167]</td><td>To compare the cost-utility of exenatide vs insulin glargine for the treatment of patients with T2DM in the UK.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-utility analysis of exenatide vs insulin glargine was performed
• Changes in HbA1c, PPG, weight and the rate of hypoglycaemic events was taken from Heine 2005 of patients with uncontrolled T2DM
• Utility</td><td>Cohort of patients with uncontrolled T2DM based on Heine 2005,[141] UKPDS baseline cohort and Leese 2003.[170]

Three discontinuation scenarios were modelled:
• No exenatide discontinuation
• Exenatide failures excluded
• Exenatide failures switched to insulin glargine</td><td colspan="3"><table>
<tr><th>Intervention</th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">No EXE discontinuation</td></tr>
<tr><td>EXE</td><td>7.683</td><td>14,567,526</td><td rowspan="2">EXE dominant (-29,149)</td></tr>
<tr><td>Insulin glargine</td><td>7.864</td><td>9,280,312</td></tr>
<tr><td colspan="4">EXE failures excluded</td></tr>
<tr><td>EXE</td><td>7.000</td><td>13,255,912</td><td rowspan="2">EXE dominant (-4,579)</td></tr>
<tr><td>Insulin glargine</td><td>7.865</td><td>9,296,371</td></tr>
<tr><td colspan="4">EXE failures switched to insulin glargine</td></tr>
<tr><td>EXE</td><td>7.703</td><td>14,092,624</td><td rowspan="2">EXE dominant (-29,657)</td></tr>
<tr><td>Insulin glargine</td><td>7.865</td><td>9,296,371</td></tr>
</table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			values were taken from either the UKPDS study[86] or generated via the Health Outcomes Data Repository database[168, 169] • The cost year was 2007 • Direct costs included: drug treatment costs, reagent test strips and lancets; macrovascular event costs; blindness; dialysis; amputation and costs associated with severe					

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			hypoglycaemia • Clinical outcomes and direct costs were projected over a 40 year horizon using a discrete event simulation (DES) model • Costs and benefits were discounted annually at 3.5%					
Multiple interventions								
Evans et al. 2013[171]	To compare the cost-effectiveness of GLP-1RAs with DPP-4is for the treatment of T2DM in the UK.	UK, from the perspective of the NHS.	• Cost-effectiveness analysis of GLP-1RAs compared with DPP-4is was performed • Changes in	Cohort of adult patients with T2DM commencing treatment with a DPP-4i or GLP-1RA in accordance with current NICE recommendations.[173, 174]	**Incremental LYs gained vs study baseline:** • Liraglutide: 0.12 • Exenatide: 0.08 • DPP-4i: 0.07	**Costs:** • NR	**ICERs:** • Liraglutide: £16,505/QALY gained • Exenatide: £16,648/QALY gained • DPP-4i: £20,661/QAL	Applicable as conducted from the perspective of the UK NHS.

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			HbA1c, body weight, SBP, cholesterol and plasma triglycerides were taken from patients with T2DM commencing treatment with a DPP-4i or GLP-1RA • Costs were taken from published UK-specific sources[172] • Cost year NR • Clinical outcomes and direct costs were projected over a 20 year time horizon using the				Y gained •	

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>IMS Health CORE diabetes model
• Costs and benefits discount rate NR</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Sodium-glucose cotransporter 2 (SGLT-2) inhibitors</td></tr>
<tr><td>NICE TA315 (2014)[120]</td><td>To assess the cost-effectiveness of canagliflozin for dual therapy (in combination with MET), for triple therapy (in combination with MET and SU or MET and TZD) and for add-on to insulin therapy for the treatment of T2DM in patients for whom glucose-lowering medicinal products, together with diet and exercise, do not provide adequate glycaemic control.</td><td>UK, from the perspective of the NHS and personal social services.</td><td>• Cost-effectiveness of canagliflozin was performed with the ECHO-T2DM stochastic micro-simulation model used to project costs and outcomes over a 40 year time horizon
• Health states included:</td><td>T2DM patients suitable for therapy with canagliflozin in dual therapy (in combination with MET), in triple therapy (in combination with MET + SU and in combination with MET + thiazolidinedione) and as an add-on to insulin in patients for whom glucose-lowering medicinal products, together with diet and exercise, do not provide adequate glycaemic control.</td><td colspan="3"><u>Dual therapy</u>
<table><tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">CANA 100 mg in dual therapy</td></tr><tr><td>TZD</td><td>-0.159</td><td>2,833</td><td>Dominated</td></tr><tr><td>SU</td><td>0.188</td><td>288</td><td>1,537</td></tr><tr><td>DAPA</td><td>0.007</td><td>63</td><td>8,674</td></tr><tr><td>DPP-4i</td><td>0.013</td><td>1</td><td>97</td></tr><tr><td>GLP-1 RA</td><td>-0.048</td><td>-2,424</td><td>50,005</td></tr><tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr><tr><td colspan="4">CANA 300 mg in dual therapy</td></tr><tr><td>TZD</td><td>-0.141</td><td>3,353</td><td>Dominated</td></tr><tr><td>SU</td><td>0.199</td><td>976</td><td>4,899</td></tr><tr><td>DPP-4i</td><td>0.031</td><td>576</td><td>18,349</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS and personal social services.</td></tr>
</table>

<table>
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<tr><td></td><td></td><td></td><td>complication-free, chronic kidney disease, neuropathy, retinopathy and a variety of macro-vascular events
• Data on relative treatment effects were derived from a series of NMAs conducted by the manufacturer
• HRQoL data were sourced from the published CODE-2 study[175]
• Costs and benefits</td><td></td><td colspan="3">
<table>
<tr><td>DAPA</td><td>0.023</td><td>625</td><td>27,419</td></tr>
<tr><td>GLP-1 RA</td><td>-0.025</td><td>-1,892</td><td>76,214</td></tr>
</table>
<u>Triple therapy</u>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in triple therapy (MET + SU)</td></tr>
<tr><td>DPP-4i</td><td>0.016</td><td>-42</td><td>Dominates</td></tr>
<tr><td>Insulin LA</td><td>0.514</td><td>135</td><td>263</td></tr>
<tr><td>GLP-1 RA</td><td>0.001</td><td>-1,297</td><td>Dominates</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in triple therapy (MET + SU)</td></tr>
<tr><td>DPP-4i</td><td>0.035</td><td>461</td><td>13,287</td></tr>
<tr><td>Insulin LA</td><td>0.624</td><td>379</td><td>607</td></tr>
<tr><td>GLP-1 RA</td><td>0.004</td><td>-685</td><td>Dominates</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in triple therapy (MET + TZD)</td></tr>
<tr><td>DPP-4i</td><td>0.007</td><td>7</td><td>1,095</td></tr>
</table>
</td><td></td></tr>
</table>

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<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>were discounted annually at 3.5%</td><td></td><td colspan="3">
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in triple therapy (MET + TZD)</td></tr>
<tr><td>DPP-4i</td><td>0.032</td><td>691</td><td>21,430</td></tr>
</table>
<u>Add-on therapy to insulin</u>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in add-on to insulin therapy</td></tr>
<tr><td>DPP-4i</td><td>-0.010</td><td>-13</td><td>1,340</td></tr>
<tr><td>DAPA</td><td>0.003</td><td>-72</td><td>Dominates</td></tr>
<tr><td>GLP-1 RA</td><td>-0.065</td><td>-836</td><td>12,915</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in add-on to insulin therapy</td></tr>
<tr><td>DPP-4i</td><td>0.040</td><td>322</td><td>7,975</td></tr>
<tr><td>DAPA</td><td>0.055</td><td>327</td><td>5,992</td></tr>
<tr><td>GLP-1 RA</td><td>-0.015</td><td>-526</td><td>35,575</td></tr>
</table>
</td><td></td></tr>
<tr><td>NICE TA336 (2015)[70]</td><td>To assess the cost-effectiveness of empagliflozin</td><td>UK, from the perspective</td><td>• Cost-effectiveness of</td><td>T2DM patients with inadequate glycaemic control, despite</td><td colspan="3">
<table>
<tr><th></th><th>Discounted QALYs*</th><th>Discounted costs, £*</th><th>ICER, £/QALY*</th></tr>
</table>
</td><td>Applicable as conducted</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
	as a combination therapy in the treatment of T2DM.	of the NHS and PSS.	empagliflozin in combination therapy was performed • Initially, a patient-level state transition model was developed however following appraisal by the ERG, the IMS CORE model was chosen to project costs and outcomes over a lifetime horizon using a fixed cycle length of 1 year • Clinical effectiveness data were drawn from	treatment with OADs or a combination of insulin and OADs.	**Dual therapy with MET**			from the perspective of the UK NHS and PSS.
					EMPA 25 mg	7.995	61,535	NR
					DAPA 10 mg	7.964	61,609	Dominated
					CANA 100 mg	7.955	61,719	Dominated
					EMPA 10 mg	7.963	61,761	Dominated
					SITA 100 mg	7.899	61,778	Dominated
					CANA 100 mg	7.990	61,912	Dominated
					Triple therapy with MET + SU			
					EMPA 25 mg	7.564	58,711	NR
					EMPA 10 mg	7.571	58,778	9,571
					CANA 100 mg	7.569	58,794	Dominated
					CANA 300 mg	7.616	59,000	4,933
					SITA 100 mg	7.466	59,390	Dominated
					Triple therapy with MET + TZD			
					SITA 100 mg	7.553	58,644	NR
					CANA 100 mg	7.579	58,751	4,115
					EMPA 25	7.561	58,854	Dominated

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>an NMA
• HRQoL data were sourced from UKPDS 62 and Sullivan 2011[176]
• Only direct costs were included in the model and these were sourced from published studies including
• The cost year was 2012
• Costs and benefits were discounted annually at 3.5%</td><td></td><td colspan="3"><table>
<tr><td>mg</td><td></td><td></td><td></td></tr>
<tr><td>CANA 300 mg</td><td>7.614</td><td>59,106</td><td>10,143</td></tr>
<tr><td>EMPA 10 mg</td><td>7.542</td><td>59,166</td><td>Dominated</td></tr>
<tr><td colspan="4">Add-on to insulin</td></tr>
<tr><td>CANA 100 mg</td><td>7.545</td><td>60,235</td><td>NR</td></tr>
<tr><td>DAPA 10 mg</td><td>7.545</td><td>60,360</td><td>Dominated</td></tr>
<tr><td>EMPA 25 mg</td><td>7.534</td><td>60,428</td><td>Dominated</td></tr>
<tr><td>EMPA 10 mg</td><td>7.523</td><td>60,539</td><td>Dominated</td></tr>
<tr><td>SITA 100 mg</td><td>7.511</td><td>60,564</td><td>Dominated</td></tr>
<tr><td>CANA 100 mg</td><td>7.583</td><td>60,599</td><td>9,579</td></tr>
</table>
*The results presented here are those of the updated base case, conducted by the manufacturer after the ERG identified errors in the original model which invalidated the original base case results.</td><td></td></tr>
<tr><td>SMC 799/12 (2012)[177] [SMC 799/12</td><td>To evaluate the cost-effectiveness of dapagliflozin as an add-on combination</td><td>UK, perspective not reported but likely to be NHS</td><td>• Cost-utility analysis of dapagliflozin was</td><td>Adult T2DM patients with inadequate glycaemic control, despite management of diet and exercise as</td><td colspan="3"><table>
<tr><th>Intervention</th><th>Incremental QALYs</th><th>Incremental costs, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">As add-on to MET, DAPA vs:[a]</td></tr>
</table></td><td>Applicable as the study was conducted in the UK and</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>(2014)a][65]</td>
<td>therapy with other glucose-lowering agents, including MET, SU or insulin for the treatment of T2DM.</td>
<td>Scotland.</td>
<td>performed
• Changes in HbA1c, BP, weight and hypoglycaemia were taken from an NMA conducted in support of the comparative clinical efficacy of dapagliflozin
• A discrete event simulation model was used to project costs and outcomes over a 40 year time horizon
• Direct costs included drug acquisition, adverse events and</td>
<td>well as treatment with glucose-lowering agents, including MET, SU or insulin.</td>
<td colspan="3">
<table>
<tr><td>SU</td><td>0.50</td><td>1,335</td><td>2,689</td></tr>
<tr><td>DPP-4i</td><td>0.02</td><td>-143</td><td>DAPA dominant</td></tr>
<tr><td>Pioglitazone</td><td>0.4</td><td>-80</td><td>DAPA dominant</td></tr>
<tr><td colspan="4">As add-on to MET + SU, DAPA vs:[b]</td></tr>
<tr><td>DPP-4i</td><td>0.023</td><td>253</td><td>10,995</td></tr>
<tr><td colspan="4">As add-on to insulin, DAPA vs:[a]</td></tr>
<tr><td>DPP-4i</td><td>0.126</td><td>538</td><td>4,268</td></tr>
</table>
[a]Data taken from original 2012 submission SMC summary
[b]Data taken from 2014 resubmission SMC summary
</td>
<td>likely from the perspective of NHS Scotland (despite not being explicitly stated).</td>
</tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			monitoring • Utility values were taken from published sources, except the impact of weight changes which were elicited from a bespoke study to identify utility gain or decrement per unit change in BMI • Resource use was taken from a published UKPDS study • Discounting was not reported					

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>SMC 963/14 (2014)[178]</td>
<td>To assess the cost-utility of canagliflozin for dual therapy (in combination with MET), for triple therapy (in combination with MET and SU or MET and thiazolidinedione), and for add-on to insulin therapy for the treatment of T2DM in patients for whom glucose-lowering medicinal products, together with diet and exercise, do not provide adequate glycaemic control.</td>
<td>NHS Scotland perspective.</td>
<td>• Cost-effectiveness of canagliflozin was performed
• A micro-simulation model was used to project costs and outcomes over a 40 year time horizon
• Health states included: complication-free, chronic kidney disease, neuropathy, retinopathy and a variety of macro-vascular events
• Data on relative</td>
<td>T2DM patients suitable for therapy with canagliflozin in dual therapy (in combination with MET), in triple therapy (in combination with MET + SU or in combination with MET + thiazolidinedione) and as an add-on to insulin in patients for whom glucose-lowering medicinal products, together with diet and exercise, do not provide adequate glycaemic control.</td>
<td colspan="3">
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in dual therapy</td></tr>
<tr><td>TZD</td><td>-0.142</td><td>£1,334</td><td>Dominated</td></tr>
<tr><td>SU</td><td>0.136</td><td>£319</td><td>£2,353</td></tr>
<tr><td>DPP-4i</td><td>0.007</td><td>£72</td><td>£9,676</td></tr>
<tr><td>DAPA</td><td>0.017</td><td>£138</td><td>£8,220</td></tr>
<tr><td>GLP-1 RA</td><td>-0.008</td><td>-£628</td><td>£77,706</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in dual therapy</td></tr>
</table>
</td>
<td>Applicable as conducted from the perspective of NHS Scotland.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>treatment effects were derived from a series of NMAs conducted by the manufacturer
• HRQoL data were sourced from published studies
• All relevant medicine costs were included in each analysis (except the cost of MET, as this was assumed to be equal across treatment arms). No administration costs or</td><td></td><td colspan="3">
<table>
<tr><td>TZD</td><td>-0.129</td><td>1,687</td><td>Dominated</td></tr>
<tr><td>SU</td><td>0.137</td><td>769</td><td>5,600</td></tr>
<tr><td>DPP-4i</td><td>0.016</td><td>423</td><td>26,875</td></tr>
<tr><td>DAPA</td><td>0.022</td><td>434</td><td>19,624</td></tr>
<tr><td>GLP-1 RA</td><td>-0.001</td><td>-246</td><td>229,381</td></tr>
</table>
<u>Triple therapy</u>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in triple therapy (MET + SU)</td></tr>
<tr><td>DPP-4i</td><td>0.021</td><td>45</td><td>2,158</td></tr>
<tr><td>GLP-1 RA</td><td>0.002</td><td>-721</td><td>Dominant</td></tr>
<tr><td>Insulin</td><td>0.195</td><td>380</td><td>1,951</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in triple therapy (MET +SU)</td></tr>
<tr><td>DPP-4i</td><td>0.019</td><td>426</td><td>22,187</td></tr>
<tr><td>GLP-1 RA</td><td>0.004</td><td>-256</td><td>Dominant</td></tr>
<tr><td>Insulin</td><td>0.276</td><td>704</td><td>2,555</td></tr>
</table>
<u>Add-on therapy to insulin</u>
</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td></td><td>monitoring test costs were included. Adverse event costs were included</td><td></td><td colspan="3">
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 100 mg</th><th>Incremental costs with CANA 100 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 100 mg in add-on to insulin therapy</td></tr>
<tr><td>DPP-4i</td><td>-0.003</td><td>69</td><td>Dominated</td></tr>
<tr><td>GLP-1 RA</td><td>-0.044</td><td>-391</td><td>8,879</td></tr>
</table>
<table>
<tr><th>Comparator</th><th>Incremental QALYs with CANA 300 mg</th><th>Incremental costs with CANA 300 mg, £</th><th>ICER, £/QALY</th></tr>
<tr><td colspan="4">CANA 300 mg in add-on to insulin therapy</td></tr>
<tr><td>DPP-4i</td><td>0.032</td><td>200</td><td>6,250</td></tr>
<tr><td>GLP-1 RA</td><td>-0.001</td><td>-194</td><td>132,540</td></tr>
</table>
</td><td></td></tr>
</table>

Abbreviations: ALO: alogliptin; BID: twice daily; BMI: body mass index; BP: blood pressure; CANA: canagliflozin; DAPA: dapagliflozin; DPP-4: dipeptidyl peptidase-4 inhibitor; EMPA: empagliflozin; EQ-5D: EuroQoL-5 dimensions; EQW: exenatide once-weekly; ERG: Evidence Review Group; EXE: exenatide; GLP-1: glucagon-like peptide 1; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; LINA: linagliptin; LIRA: liraglutide; LIXI: lixisenatide; LY: life-years; MET: metformin; N/A: not applicable; NHS: National Health Service; NMA: network meta-analysis; NR: not reported; OAD: oral antidiabetic drug; PIO: pioglitazone; PPG: photoplethysmogram; QALY: quality-adjusted life year; QD: once daily; RCT: randomised controlled trial; SAXA: saxagliptin; SBP: systolic blood pressure; SD: standard deviation; SGLT-2: sodium-glucose cotransporter 2 inhibitor; SITA: sitagliptin; SMC: Scottish Medicines Consortium; SU: sulfonylurea; T2DM: type 2 diabetes mellitus; TZD: thiazolidinediones; UK: United Kingdom.

Mono, dual and triple therapy economic evaluations

Table G.17: Summary of published economic evaluations included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs (intervention, comparator)</th><th>Costs (intervention, comparator)</th><th>ICER (per QALY gained)</th><th>Applicability to decision making in England</th></tr>
<tr><td colspan="9">Multiple interventions</td></tr>
<tr><td>McEwan et al. 2010[179]</td><td>To quantify the overall costs and QALYs associated with therapy escalation with OADs used to treat patients with T2DM in the UK clinical setting.</td><td>UK, from the perspective of the NHS.</td><td>• Cost-utility analysis of treatment strategies with four different combinations of OADs was performed
• Changes in HbA1c, weight, total cholesterol and HDL cholesterol, was taken from five trials of uncontrolled T2DM patients
• Utility values were derived from relevant literature of patients with T2DM
• Costs were estimated from relevant literature
• Cost year: 2008
• Direct costs</td><td>Cohort of patients with inadequately controlled T2DM, based on multiple trials:
• Nauck (2007),[109]
• Scott (2008),[110]
• Rosenstock (2006),[180]
• Hermansen (2007)[181]
• Cochrane Review (2005)[182]

Treatment strategies:

Strategy 1:
1st line – MET
2nd line – MET + SU
3rd line – MET + SU + TZD
Strategy 2:
1st line – MET</td><td colspan="3"><table><tr><th></th><th>Discounted QALYs</th><th>Discounted costs, £</th><th>ICER, £/QALY</th></tr><tr><td>Strategy 1</td><td>61,002</td><td>37,150,726</td><td>609/QALY</td></tr><tr><td>Strategy 2</td><td>61,121</td><td>48,459,147</td><td>793/QALY</td></tr><tr><td>Strategy 3</td><td>61,978</td><td>46,829,109</td><td>756/QALY</td></tr><tr><td>Strategy 4</td><td>61,254</td><td>37,404,676</td><td>611/QALY</td></tr></table></td><td>Applicable as conducted from the perspective of the UK NHS.</td></tr>
</table>

Study	Objective	Country and perspective	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Applicability to decision making in England
			included those associated with macrovascular events, ESRD, blindness and amputation and diabetes-specific therapy • Clinical outcomes and direct costs were projected over a 10 year time horizon using the Cardiff stochastic simulation cost-utility model (DiabForecaster) • The % discount for costs and benefits were NR	2nd line – MET + TZD 3rd line – MET + TZD + SU **Strategy 3:** 1st line – MET 2nd line – MET + DPP-4i 3rd line – MET + DPP-4i + SU **Strategy 4:** 1st line – MET 2nd line – MET + SU 3rd line – MET + SU + DPP-4i				

Abbreviations: DPP-4i: dipeptidyl peptidase-4 inhibitor; HDL: high density lipoprotein; ICER: incremental cost-effectiveness ratio; MET: metformin; NHS: National Health Service; NR: not reported; OAD: oral antidiabetic drug; QALY: quality-adjusted life-year; SU: sulfonylurea; TZD: thiazolidinedione; UK: United Kingdom.

G.2.2 Quality assessment of the identified studies

Critical appraisals of each published economic evaluation included in the SLR were conducted using the checklist adapted from Drummond *et al.* (1996), as recommended by NICE. The results of these critical appraisals are presented below and have been presented by therapy type, as in section 0.

Monotherapy economic evaluations

Table G.18: Quality assessments of economic evaluations included in the economic systematic literature review

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
Study design									
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N	Y	Y	N	Y	Y	Y
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	N	N	Y – UK NHS perspective	Y	Y – UK NHS and social services perspective	Y – UK NHS and PSS perspective	Y	Y – UK NHS
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the form of economic	Y – cost-	Y – cost-minimisation	Y – cost-	Y – cost-	Y – cost-	Y – cost-utility and	Y – cost-utility	Y – cost-	Y – cost-

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
evaluation stated?	minimisation	and cost-utility	minimisation	utility	effectiveness	cost-minimisation		effectiveness	effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	Y – with regard to cost-minimisation, N with regard to cost-utility	N	N	Y	N	N	N	N
Data collection									
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	N/A	N/A	Y – DURATION-3 trial	Y	N/A	N/A	N/A	N/A
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Y – NMA	Y	Y – NMA	N/A	N/A	Y – NMA of 3 studies	Y	Y	Y
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – incremental cost	Y – cost saving per patient, ICER	Y – incremental cost	Y – total costs, QALYs, ICER	Y – incremental costs, QALYs, ICER	Y – total costs, QALYs, ICER	Y– total costs, total QALYs, ICER	Y – total costs, QALYs, ICERs	Y – costs, QALYs, ICERs
Were the methods used to value health states and other benefits stated?	N/A	N/A for cost-minimisation, N for cost-utility	N/A	Y – HRQoL data was obtained from published	Y	Y – HRQoL data were taken from an existing SLR	Y	Y	Y – literature data

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
				sources					
Were the details of the subjects from whom valuations were obtained given?	Y	Y	Y	Y – DURATION-3 trial subjects	Y – patients in the UKPDS study in 1997	N	Y	Y	Y
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	Y	N	Y	N	N
Were the methods for the estimation of quantities and unit costs described?	N	N	N	N	Y	N	Y	Y	N
Were currency and price data recorded?	N	N	N	Y – GBP 2009	Y – GBP 2004	N	Y	Y – GBP 2014	Y – GBP, cost year NR
Were details of price adjustments for inflation or currency conversion given?	N	N	N	Y – Cost data were inflated to 2009 values where necessary	Y	N	Y	Y	N
Were details of any model used given?	N	Y – JADE model	N	Y – IMS CORE Diabetes model is a markov-	Y – probabilistic discrete-time illness-death model	Y – UKPDS OM1 model	Y	Y – UKPDS Outcomes Model 1	Y – ECHO-T2DM

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
				based model					
Was there a justification for the choice of model used and the key parameters on which it was based?	N	N	N	Y	Y	N	Y	Y	Y
Analysis and interpretation of results									
Was the time horizon of cost and benefits stated?	Y – 5 years	Y – lifetime	Y – 5 years	Y – 50 years (lifetime)	Y – lifetime	Y – 1 year decision tree, followed by 40 years	Y – 40 years	Y – 40 years	Y – 40 years
Was the discount rate stated?	N	N	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5%
Was the choice of rate justified?	N/A	N/A	N/A	N	Y – recommended by UK treasury	N	Y – in line with NICE guidance	N	N
Was an explanation given if cost or benefits were not discounted?	N	N	N	N/A	N/A	N/A	N/A	N/A	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N	N	Y	N
Was the approach to sensitivity analysis described?	Y	N	Y	Y	Y	Y	Y	Y	Y
Was the choice of variables for sensitivity analysis justified?	N	N	N	N	Y	N	N	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
Were the ranges over which the parameters were varied stated?	Y	N	Y	Y	Y	N	Y	Y	Y
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	N – only costs were reported, ICERs and QALYs were commercial in confidence	Y	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated form?	Y – total costs and incremental costs were reported	N – only incremental costs and QALYs reported	Y – total costs and incremental costs were reported	Y – total costs and total QALYs were reported	Y – total costs and QALYs were reported	N – only costs were reported, ICERs and QALYs were commercial in confidence	Y – total costs, QALYs and incremental costs and QALYs reported	Y	Y
Was the answer to the study question given?	Y – incremental cost per year	Y – in the form of cost-saving per patient for cost-minimisation and in the form of an ICER for	Y – incremental cost	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER and cost-minimisation result	Y – in the form of an ICER	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists	Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	AWMSG 1531 (2013)	SMC 607/10 (2010)	SMC 826/12 (2012)	Beaudet et al. 2011	Clarke et al. 2005	ASAR 2746 (2015)	NICE TA390 (2016)	Johnston et al. 2017	Schroeder et al. 2015 [A]
		cost-utility							
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – discussion of limitations provided	N – no discussion of limitations	Y – discussion of limitations provided	Y – discussion of limitations	Y – discussion of limitations	Y – discussion of limitations	Y	Y – limitations were discussed	N – no discussion of limitations

Abbreviations: HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; N: no; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PSS: personal and social services; QALY: quality-adjusted life-year; UK: United Kingdom; Y: yes.

Dual therapy economic evaluations

Table G.19: Quality assessments of economic evaluations included in the economic systematic literature review

	Dipeptidyl peptidase-4 (DPP-4) inhibitors							
	SMC 408/07 (2007)	SMC 571/09 (2009)	SMC 603/10 (2010)	Gordon et al. 2016	McEwan et al. 2015	McEwan et al. 2015	Partha et al. 2015	Schwarz et al. 2008
Study design								
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N	Y	Y	N	N	Y
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	N	N	Y – but viewpoint not justified	Y – UK payer perspective, but viewpoint not justified	N	N	N
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	N	Y	Y	Y
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	Y
Was the form of economic evaluation stated?	Y – cost-utility	Y – cost-minimisation	Y – cost-minimisation and cost-utility	Y – cost-effectiveness	Y – cost-utility analysis	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N	Y	N	N	N	N	N	N
Data collection								
Was/were the source(s) of effectiveness estimates	Y	Y	Y	Y	Y	Y – published	Y – EDGE and UKPDS	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors							
	SMC 408/07 (2007)	SMC 571/09 (2009)	SMC 603/10 (2010)	Gordon et al. 2016	McEwan et al. 2015	McEwan et al. 2015	Partha et al. 2015	Schwarz et al. 2008
used stated?						NMA	studies	
Were details of the design and results of the effectiveness study given (if based on a single study)?	Y	N	Y	Y – ENDURE trial	Y – Nauck (2011) and Monami (2008)	N	N	Y – The Scottish Health Survey: 2003
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Y – simple indirect comparison of the two treatments from a trial for vildagliptin and published study for sitagliptin	N/A	N/A	N/A	N/A	N	N/A
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – ICER	Y – incremental cost	Y – cost savings for the CMA and incremental costs, QALYs, ICER for the CUA	Y – total costs, QALYs, ICER	Y – ICER	Y – total costs	Y – costs, QALYs, ICER	Y – QALYs, costs and ICERs
Were the methods used to value health states and other benefits stated?	N	N	N	Y	Y	N	N	Y
Were the details of the subjects from whom valuations were obtained given?	Y	Y	N	Y – patients with uncontrolled T2DM	Y – patients with uncontrolled T2DM	N	Y	Y – patients with uncontrolled T2DM on MET monotherapy
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N

	Dipeptidyl peptidase-4 (DPP-4) inhibitors							
	SMC 408/07 (2007)	SMC 571/09 (2009)	SMC 603/10 (2010)	Gordon et al. 2016	McEwan et al. 2015	McEwan et al. 2015	Partha et al. 2015	Schwarz et al. 2008
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	N	N	N
Were the methods for the estimation of quantities and unit costs described?	N	N	N	Y	N	N	Y – sourced from literature	N
Were currency and price data recorded?	N	N	N	Y – GBP 2015	Y – GBP, cost year NR	Y – GBP, cost year NR	Y – GBP, cost year NR	Y – EUR
Were details of price adjustments for inflation or currency conversion given?	N	N	N	Y	N	N	N	Y
Were details of any model used given?	N	N	Y – Cardiff diabetes model for the CUA	Y – IMS Health CORE Diabetes Model	Y – Cardiff stochastic simulation cost-utility model (DiabForecaster).	Y – IMS CORE diabetes model	Y – UKPDS outcomes model	Y – JADE Model
Was there a justification for the choice of model used and the key parameters on which it was based?	N	N	N	Y	N	N	N	Y
Analysis and interpretation of results								
Was the time horizon of cost and benefits stated?	Y – lifetime	Y – 1 year	Y – 40 years for the CUA	Y – lifetime (max. 50 years)	Y – 40 years	N	Y – lifetime	N
Was the discount rate stated?	N	N	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3–6% annually
Was the choice of rate justified?	N/A	N/A	N	N	N	N	N	N
Was an explanation given if cost or benefits were not	N	N/A	N	N	N/A	N/A	N	N

	Dipeptidyl peptidase-4 (DPP-4) inhibitors							
	SMC 408/07 (2007)	SMC 571/09 (2009)	SMC 603/10 (2010)	Gordon et al. 2016	McEwan et al. 2015	McEwan et al. 2015	Partha et al. 2015	Schwarz et al. 2008
discounted?								
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N	N	N
Was the approach to sensitivity analysis described?	N	N	N	Y	N	N	N	Y
Was the choice of variables for sensitivity analysis justified?	N	N	N	N	N	N	N	Y
Were the ranges over which the parameters were varied stated?	Y	N/A	N	Y	Y	N	N	Y
Were relevant alternatives compared in the incremental analysis?	Y	Y – although TZD should also have been a comparator	Y	Y	Y	N	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	N	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated form?	N – only ICER is reported	N – only total annual cost reported, incremental cost was not reported (though was calculable)	N	N	N	N	Y	Y
Was the answer to the study question given?	Y – in the form of an ICER	Y – in the form of a conclusion	Y – in the form of a discussion of the ICER for the CUA and cost savings for the CMA	Y – in the form of an ICER	Y – in the form of an ICER	Y	Y	Y – in the form of an ICER
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors							
	SMC 408/07 (2007)	SMC 571/09 (2009)	SMC 603/10 (2010)	Gordon et al. 2016	McEwan et al. 2015	McEwan et al. 2015	Partha et al. 2015	Schwarz et al. 2008
Were conclusions accompanied by the appropriate caveats?	Y – discussion of limitations provided	Y – discussion of limitations provided	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
Study design								
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	Y	N	Y	Y	Y	N	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	Y – UK healthcare payer perspective	Y, but viewpoint not justified	Y, but viewpoint not justified	Y, but viewpoint not justified	N	Y – UK payer perspective	Y, but viewpoint not justified
Was a rationale reported for the choice of the	N	Y	Y	Y	Y	Y	Y	Y

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
alternative programs or interventions compared?								
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	Y
Was the form of economic evaluation stated?	Y – cost-utility	Y – cost-effectiveness	Y – cost-utility	Y – cost-utility	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost effectiveness	Y – cost-utility
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N	Y	N	N	N	N	N	N
Data collection								
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were details of the design and results of the	N/A	N/A	Y – DUAL V head-to-head	N/A	Y – LEAD-6 trial	Y – LIRA-LIXI trial™	Y – ENDURE trial	Y – European and LEAD-1860 trials

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
effectiveness study given (if based on a single study)?								
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Y – NMA was conducted, but the results were considered unreliable for use in the model. A pooled naïve indirect comparison approach was undertaken instead	Y – NMA of 14 studies	N/A	Y – LEAD-2 and 1860-LIRA-DPP-4	N/A	N/A	N/A	N/A
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – ICER	Y – total and incremental costs, QALYs, ICER	Y – total costs, QALYs, ICER	Y – total costs, QALYs, ICER	Y – total costs, QALYs, ICER	Y – QALYs, costs and ICER	Y – total costs, QALYs, ICER	Y – total costs and QALYs
Were the methods used to value health states and other benefits stated?	N	Y – HRQoL data were collected using EQ-5D in the UKPDS 62 study	Y – identified from a SLR	N	Y	N	Y	Y
Were the details of the subjects from whom valuations were	Y	Y	Y – T2DM cohort uncontrolled on basal insulin	Y – T2DM patients uncontrolled on MET	Y – T2DM cohort uncontrolled on OADs	N	Y – patients with uncontrolled T2DM	Y – T2DM cohort uncontrolled on OADs and MET

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
obtained given?								
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	Y	N	N	N	N	N	N
Were the methods for the estimation of quantities and unit costs described?	N	Y	Y	N	N	N	Y	N
Were currency and price data recorded?	N	Y – GBP 2011	Y – GBP 2015	Y – GBP 2008	Y – GBP 2015	Y – GBP, cost year 2015	Y – GBP 2015	Y – GBP (year NR)
Were details of price adjustments for	N	Y – Hospital and Community Health Services	Y	Y	Y	N	Y	N

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
inflation or currency conversion given?		Pay and Price Index						
Were details of any model used given?	Y – IMS CORE Diabetes Model	Y – Cardiff diabetes model	Y – IMS Health CORE Diabetes Model v8.5	Y – IMS Health CORE Diabetes Model	Y – IMS Health CORE Diabetes Model	Y – IMS CORE Diabetes Model	Y – IMS Health CORE Diabetes Model	Y – IMS Health CORE Diabetes Model
Was there a justification for the choice of model used and the key parameters on which it was based?	N	Y – previously published and validated	Y	Y	Y	N	Y	N
Analysis and interpretation of results								
Was the time horizon of cost and benefits stated?	Y – lifetime (40 years)	Y – lifetime (40 years)	Y – lifetime (40 years)	Y – lifetime	Y – lifetime (50 years)	N	Y – lifetime (max. 50 years)	Y – 30 years
Was the discount rate stated?	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually
Was the choice of rate justified?	N/A	Y – in line with NICE guidance	N	N	Y	N	N	N
Was an explanation given if cost or benefits were	N/A	N/A	N/A	N/A	N	N/A	N	N

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
not discounted?								
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N	N	N
Was the approach to sensitivity analysis described?	Y	Y	Y	Y	Y	N	Y	N
Was the choice of variables for sensitivity analysis justified?	N	Y	N	Y	Y	N	N	Y
Were the ranges over which the parameters were varied stated?	N	Y	Y	Y	Y	N	Y	N
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y	Y	Y
Was an incremental	Y	Y	Y	Y	Y	Y	Y	N

	Glucagon-like peptide-1 (GLP-1) agonists						Multiple interventions	
	SMC 1088/15 (2015)	Chuang et al. 2016 [Charokopou et al. 2015]	Davies et al. 2016	Davies et al. 2012	Hunt et al. 2017	Kragh et al. 2016	Gordon et al. 2017 [Gordon et al. 2016 [A] (Gordon et al. 2016 [B])]	Marsh et al. 2016
analysis reported?								
Were major outcomes presented in a disaggregated as well as aggregated form?	N – only incremental costs and incremental QALYs were reported	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	N	Y	N	N
Was the answer to the study question given?	Y – in the form of an ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y	Y	Y	Y
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y – in the form of an ICER	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – summary of limitations provided	Y – discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations

	Multiple interventions	Other (Nateglinide)	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors					
	McEwan et al. 2010	Ward et al. 2004	NICE TA288 (2013)	SMC 799/12 (2014)	Charokopou et al. 2015	Charokopou et al. 2015	Copley et al. 2013	Kansal et al. 2016
Study design								

	Multiple interventions	Other (Nateglinide)	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors					
	McEwan et al. 2010	Ward et al. 2004	NICE TA288 (2013)	SMC 799/12 (2014)	Charokopou et al. 2015	Charokopou et al. 2015	Copley et al. 2013	Kansal et al. 2016
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	N	Y	N	Y	Y	Y	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	Y – UK payer perspective	Y – UK NHS and personal and social services perspective	N	Y – UK healthcare payer perspective	Y – UK healthcare payer perspective	Y – UK NHS and PSS perspective	N
Was a rationale reported for the choice of the alternative programs or interventions compared?	N	Y	Y	N	Y	Y	Y	N
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	N
Was the form of economic evaluation stated?	Y – cost-utility	Y – cost-effectiveness	Y – cost-utility	Y – cost-utility	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N	N	N	N	N	Y	N	N
Data collection								
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	Y – Nauck (2007) and Scott (2008)	Y – Caro 2000 and Caro 2002	N/A	N	Y	N/A	N/A	N
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	N/A	Y – NMA	Y – NMA	N/A	Y	Y – NMA	N/A

	Multiple interventions	Other (Nateglinide)	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors					
	McEwan et al. 2010	Ward et al. 2004	NICE TA288 (2013)	SMC 799/12 (2014)	Charokopou et al. 2015	Charokopou et al. 2015	Copley et al. 2013	Kansal et al. 2016
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – QALYs	Y – QALYs, costs and ICERs	Y – total and incremental costs, life years, QALYs, ICER	Y – total costs, QALYs, ICER	Y – total costs, life years, QALYs, ICER	Y – total costs, life years, QALYs, ICER	Y – incremental costs, incremental QALYs, ICER	Y – QALYs, ICER
Were the methods used to value health states and other benefits stated?	Y	Y	Y – HRQoL data was collected from published studies	Y – HRQoL data was obtained from published sources	Y – HRQoL data was collected using EQ-5D in the UKPDS 62	Y – HRQoL data was collected using EQ-5D in the UKPDS 62	Y – HRQoL data were sourced from CODE-2 study	N
Were the details of the subjects from whom valuations were obtained given?	Y – patients with uncontrolled T2DM	N	Y	Y – T2DM cohort uncontrolled on OADs	Y	Y	Y	N
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	N	Y	N
Were the methods for the estimation of quantities and unit costs described?	N	N	Y	N	Y – acquisition costs sourced from England and Wales Drug Tariff costs	Y – acquisition costs sourced from NHS Drug Tariff	Y	N
Were currency and price data recorded?	Y– GBP 2008	Y – GBP 1999	N	N	Y – GBP 2011	Y – GBP 2011	Y	Y – GBP, cost year NR
Were details of price adjustments	Y	Y	Y – Hospital	N	Y – Hospital and	Y – Hospital and	Y	N

	Multiple interventions	Other (Nateglinide)	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors					
	McEwan et al. 2010	Ward et al. 2004	NICE TA288 (2013)	SMC 799/12 (2014)	Charokopou et al. 2015	Charokopou et al. 2015	Copley et al. 2013	Kansal et al. 2016
for inflation or currency conversion given?			and Community Health Services Pay and Price Index		Community Health Services Pay and Price Index	Community Health Services Pay and Price Index		
Were details of any model used given?	Y – Cardiff stochastic simulation cost-utility model (DiabForecaster)	N	Y – discrete event simulation model	Y – discrete event simulation model	Y – Cardiff diabetes model	Y – Cardiff diabetes model	Y – ECHO-T2DM model	N
Was there a justification for the choice of model used and the key parameters on which it was based?	Y	N	Y	N	Y – previously published and validated	Y – previously validated	N	N
Analysis and interpretation of results								
Was the time horizon of cost and benefits stated?	Y – 40 years	Y – lifetime horizon	Y – 40 years	Y – 40 years	Y - lifetime	Y - lifetime	Y – 40 years	Y – remaining lifetime
Was the discount rate stated?	N	Y – 6% (costs) and 1.5% (benefits)	Y – 3.5% annually	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually
Was the choice of rate justified?	N	Y	Y – in line with NICE guidance	N	Y – in line with NICE guidance	Y – in line with NICE guidance	Y – HRQoL data were sourced from CODE-2 study	N
Was an explanation given if cost or benefits were not discounted?	N	N/A	N/A	N	N/A	N/A	N/A	N/A
Were the details of statistical test(s) and confidence intervals	N	N	N	N	N	N	N	N

	Multiple interventions	Other (Nateglinide)	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors					
	McEwan et al. 2010	Ward et al. 2004	NICE TA288 (2013)	SMC 799/12 (2014)	Charokopou et al. 2015	Charokopou et al. 2015	Copley et al. 2013	Kansal et al. 2016
given for stochastic data?								
Was the approach to sensitivity analysis described?	Y	Y	Y	N	Y	Y	Y	N
Was the choice of variables for sensitivity analysis justified?	Y	N	Y	N	N	Y	N	N
Were the ranges over which the parameters were varied stated?	Y	Y	Y	N	Y	Y	Y	N
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	Y	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated form?	N	Y	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	Y	N
Was the answer to the study question given?	Y	Y	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of an ICER	Y
Did conclusions follow from the data reported?	N	Y	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	N – no discussion of limitations	Y	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations	Y – limitations discussed	N – no discussion of limitations

	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		Thiazolidinediones (TZDs)			
	Neslusan et al. 2016	Schroeder et al. 2015 [B]	SMC 399/07 (2007)	Beale et al. 2006	Tilden et al. 2007	Valentine et al. 2007
Was the research question stated?	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N	Y	N	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	Y – UK NHS	N	Y – UK NHS perspective	Y – UK payer perspective, but viewpoint not justified	Y – UK payer perspective, but viewpoint not justified
Was a rationale reported for the choice of the alternative programs or interventions compared?	N	Y	Y	Y	Y	N
Were the alternatives being compared clearly described?	N	Y	Y	Y	Y	N
Was the form of economic evaluation stated?	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-utility	Y – cost-effectiveness	Y – cost-utility analysis	Y – cost-effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N	N	N	N	N	N
Data collection						
Was/were the source(s) of effectiveness estimates used stated?	Y – head-to-head data	Y – DIA3009 trial	N	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N	N	N	N/A	Y – Goldberg 2005	Y – PROactive study
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	N/A	N/A	Y – SLR and model validated by ScHARR	N/A	N/A

	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		Thiazolidinediones (TZDs)			
	Neslusan et al. 2016	Schroeder et al. 2015 [B]	SMC 399/07 (2007)	Beale et al. 2006	Tilden et al. 2007	Valentine et al. 2007
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – ICERs	Y – ICERs	Y – ICERs	Y – total costs, life-years, QALYs, ICER	Y – QALYs and costs	Y – QALYs, costs and ICERs
Were the methods used to value health states and other benefits stated?	N	Y – literature data	N	Y – HRQoL data was collected using EQ-5D in the CODE-2 study	Y	Y
Were the details of the subjects from whom valuations were obtained given?	N	Y	Y	Y – 1,000 T2DM patients uncontrolled on metformin monotherapy	Y – patients with uncontrolled T2DM on MET monotherapy	Y – patients with uncontrolled T2DM
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	N
Were the methods for the estimation of quantities and unit costs described?	Y – sourced from literature	N	N	N	N	N
Were currency and price data recorded?	Y – GBP, cost year NR	Y – GBP, cost year NR	N	Y – GBP 2003	Y – GBP 2004/5	GBP – 2005
Were details of price adjustments for inflation or currency conversion given?	N	N	N	Y – Cost data from previous years were inflated using UK retail price index	N	N
Were details of any model used given?	Y – ECHO-T2DM	Y – ECHO-T2DM	Y – IMS CORE Diabetes Model	Y – The DiDACT model was used to project costs and outcomes and its	Y – Monte Carlo simulation of a Markov process	Y – CORE Diabetes Model

	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		Thiazolidinediones (TZDs)			
	Neslusan et al. 2016	Schroeder et al. 2015 [B]	SMC 399/07 (2007)	Beale et al. 2006	Tilden et al. 2007	Valentine et al. 2007
				features were described		
Was there a justification for the choice of model used and the key parameters on which it was based?	Y	N	Y – model described as 'previously validated'	N	Y	Y
Analysis and interpretation or results						
Was the time horizon of cost and benefits stated?	Y – 30 years	N	Y – lifetime	Y – lifetime	Y – lifetime	Y – 35 years
Was the discount rate stated?	N	N	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually
Was the choice of rate justified?	N	N	N/A	Y – in line with recent NICE guidance	Y	Y
Was an explanation given if cost or benefits were not discounted?	N	N	N	N/A	N	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N
Was the approach to sensitivity analysis described?	N	N	N	Y	Y	Y
Was the choice of variables for sensitivity analysis justified?	N	N	N	Y	Y	Y
Were the ranges over which the parameters were varied stated?	N	N	N	Y	Y	Y
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated	N	N	N – only ICERs presented	Y – total costs and total QALYs were	Y	Y

	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		Thiazolidinediones (TZDs)			
	Neslusan et al. 2016	Schroeder et al. 2015 [B]	SMC 399/07 (2007)	Beale et al. 2006	Tilden et al. 2007	Valentine et al. 2007
form?				reported		
Was the answer to the study question given?	Y	Y	Y – in the form of ICERs	Y – in the form of a discussion of the ICER	Y – in the form of QALYs and costs	Y – in the form of an ICER
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	N – no discussion of limitations	N – no discussion of limitations	Y – limitations discussed	N – no discussion of limitations	N – no discussion of limitations	N – no discussion of limitations

Abbreviations: CUA: cost-utility analysis; EQ-5D: EuroQoL 5-dimensions; GBP: British pound; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; MET: metformin; N: no; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OAD: oral antidiabetic drug; PSS: Personal Social Services; QALY: quality-adjusted life-year; SLR: systematic literature review; T2DM: type 2 diabetes mellitus; UK: United Kingdom; UKPDS: UK Prospective Diabetes Study; Y: yes.

Triple therapy economic evaluations

Table G.20: Quality assessments of economic evaluations included in the economic systematic literature review

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
Study design											
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N	N	N	N	N	Y	Y	N	Y
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	N	N	Y – Scotland NHS perspective	N	N	Y – UK payer perspective, but viewpoint not justified	N	Y – UK NHS and personal social services perspective	N	Y – UK NHS
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the form of economic evaluation stated?	Y – cost-minimisation	Y – cost-minimisation	Y – cost-minimisation	Y – cost-minimisation	Y – cost-utility	Y – cost-minimisation and cost-utility	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-utility	Y – cost-utility	Y – cost-effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	Y	Y	Y	N	Y – for the cost-minimisation analysis, clinical equivalence had been demonstrated	N	N	N	N	Y
Data collection											
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y – DIA3015 trial
Were details of the design and results of the effectiveness	N/A	N/A	Y – for the comparison with exenatide in	Y	Y – details of the LIRA-ADD2BASAL study were	Y – for comparison vs exenatide in the CUA	Y – Heine 2005	Y	N	N/A	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
study given (if based on a single study)?			combination with OADs		provided						
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Y – NMA of 2 double-blind RCTs	Y – 2 adjusted indirect treatment comparisons	Y – for the comparison with exenatide in combination with basal insulin and for the comparison with liraglutide 1.2 mg in combination with OADs	N/A	Y – NMA	Y – NMA for comparison vs lixisenatide in both analyses	N/A	N/A	Y – NMA	Y – 4 NMAs	N/A
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – incremental cost	Y – cost saving per patient	Y – incremental cost	Y – cost saving per patient	Y – ICER	Y – incremental cost for CMA and ICER for CUA	Y – QALYs, costs, ICER	Y – total costs, QALYs, ICER	Y – total costs, QALYs, ICER	Y – incremental costs, QALYs, ICER	Y – costs, QALYs, ICER
Were the methods used to value health states and	N/A	N/A	N/A	N/A	N	Y – HRQoL data was collected from published	Y	N – HRQoL impact of complications was taken from the	Y – HRQoL data was obtained from	Y – HRQoL data was sourced from	N

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
other benefits stated?						sources		UKPDS model	published sources	UKPDS	
Were the details of the subjects from whom valuations were obtained given?	Y	N	N	Y	Y	N	Y – patients with uncontrolled T2DM	Y – male T2DM patients with BMI of 30 kg/m^2 who had failed dual oral therapy	Y – T2DM cohort uncontrolled on OADs	N	N
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	N	N	N	N	N	N
Were the methods for the	N	N	N	N	N	N	N	N	N	N	Y – sourced from literature

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
estimation of quantities and unit costs described?											
Were currency and price data recorded?	N	N	N	N	N	N	GBP – 2004	Y – GBP 2007	N	N	Y – GBP, cost year NR
Were details of price adjustments for inflation or currency conversion given?	N	N	N	N	N	N	N	Y	N	N	N
Were details of any model used given?	N	N	N	N	Y – IMS CORE Diabetes Model	Y – CORE Diabetes Model was used for the CUA	Y – CORE Diabetes Model	Y – a full description of the UKPDS model was provided	Y – Cardiff Diabetes model is a patient-level Monte Carlo micro-simulation model	N	Y – ECHO-T2DM
Was there a justification for the choice of model used and the key parameters on which it	N	N	Y	Y	N	N	Y	Y	Y	N	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
was based?											
Analysis and interpretation of results											
Was the time horizon of cost and benefits stated?	Y – 7 years	Y – 1 year	Y – 1 year	Y – 1 year	Y – lifetime	Y – 40 years in the CUA and 1 year in the CMA	Y – 35 years	N	Y – 40 years	Y - lifetime	Y – 40 years
Was the discount rate stated?	N	N	N	N/A	N	N	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	N	Y – 3.5%
Was the choice of rate justified?	N/A	N/A	N/A	N/A	N/A	N/A	Y	Y – in line with NICE guidance	Y – in line with NICE guidance	N/A	N
Was an explanation given if cost or benefits were not discounted?	N	N/A	N/A	N	N/A	N/A	N	N/A	N/A	N/A	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N	N	N	N	N	N
Was the approach to sensitivity	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
analysis described?											
Was the choice of variables for sensitivity analysis justified?	N	N	N	N	N	N	Y	Y	N	N	N
Were the ranges over which the parameters were varied stated?	N	Y	N	Y	Y	N	Y	Y	Y	N	N
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated form?	N – total costs and incremental costs were reported	Y – total cost per patient per year reported	Y – total and incremental costs were reported	N – only overall cost saving per patient reported	N – only incremental costs and incremental QALYs were reported	N – only incremental costs and QALYs reported	Y	Y – total costs and total QALYs were reported	Y – total costs and total QALYs were reported	Y – incremental costs and incremental QALYs were reported	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		Glucagon-like peptide-1 (GLP-1) agonists					Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
	SMC 875/13 (2013)	SMC 918/13 (2013)	AWMSG 863 (2013)	SMC 1024/15 (2015)	SMC 1044/15 (2015)	SMC 1110/15 (2015)	Ray et al. 2007	Waugh et al. 2010	NICE TA418 (2016)	SMC 993/14 (2014)	Thompson et al. 2014
Was the answer to the study question given?	Y – in the form of a conclusion	Y – in the form of cost saving per patient	Y – in the form of cost savings	Y – in the form of cost saving per patient	Y – in the form of an ICER	Y – in the form of an ICER for CUA and cost-minimisation for the CMA	Y – in the form of an ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – summary of limitations provided	Y	Y – discussion of limitations	N – no discussion of limitations	Y – summary of limitations provided	Y – discussion of limitations	N – no discussion of limitations	Y – discussion of limitations	N – no discussion of limitations	Y – discussion of limitations	Y – limitations discussed

Abbreviations: CUA: cost-utility analysis; GBP: British pound; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; N: no; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OAD: oral antidiabetic drug; QALY: quality-adjusted life-year; RCT: randomised control trial; T2DM: type 2 diabetes mellitus; UK: United Kingdom; UKPDS: UK Prospective Diabetes Study; Y: yes.

Mono and dual therapy economic evaluations

Table G.21: Quality assessments of economic evaluations included in the economic systematic literature review

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		
	SMC 746/11 (2011) [SMC 850/13 (2013)]	SMC 772/12 (2014)	SMC 850/13 (2015)
Study design			
Was the research question stated?	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	N	N
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y
Were the alternatives being compared clearly described?	Y	Y	Y
Was the form of economic evaluation stated?	Y – cost-minimisation	Y – cost-utility	Y – cost-minimisation
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N	N	N
Data collection			
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	N/A	N/A
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N	Y – NMA of 7 trials	N
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – annual treatment cost	Y – cost savings and QALYs	Y – annual treatment cost
Were the methods used to value health states and other benefits stated?	N/A	Y – HRQoL data was collected from published studies	N/A

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		
	SMC 746/11 (2011) [SMC 850/13 (2013)]	**SMC 772/12 (2014)**	**SMC 850/13 (2015)**
Were the details of the subjects from whom valuations were obtained given?	Y	N	Y
Were productivity changes (if included) reported separately?	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N
Were the methods for the estimation of quantities and unit costs described?	N	N	N
Were currency and price data recorded?	N	N	N
Were details of price adjustments for inflation or currency conversion given?	N	N	N
Were details of any model used given?	N	Y – Discrete event simulation model	N
Was there a justification for the choice of model used and the key parameters on which it was based?	N	N	N
Analysis and interpretation of results			
Was the time horizon of cost and benefits stated?	Y – 1 year	Y – 40 years	Y – 1 year
Was the discount rate stated?	N	N	N
Was the choice of rate justified?	N/A	N/A	N/A
Was an explanation given if cost or benefits were not discounted?	N/A	N/A	N/A
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N
Was the approach to sensitivity analysis described?	N/A – no sensitivity analyses were conducted	N	N/A – no sensitivity analyses were conducted

	Dipeptidyl peptidase-4 (DPP-4) inhibitors		
	SMC 746/11 (2011) [SMC 850/13 (2013)]	**SMC 772/12 (2014)**	**SMC 850/13 (2015)**
Was the choice of variables for sensitivity analysis justified?	N/A	N	N/A
Were the ranges over which the parameters were varied stated?	N/A	N	N/A
Were relevant alternatives compared in the incremental analysis?	N	Y	N
Was an incremental analysis reported?	N	Y	N
Were major outcomes presented in a disaggregated as well as aggregated form?	N	N – only incremental cost savings and QALYs reported	N
Was the answer to the study question given?	Y – in the form of annual treatment cost	Y	Y – in the form of annual treatment cost
Did conclusions follow from the data reported?	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – discussion of limitations	Y	Y – discussion of limitations

Abbreviations: HRQoL: health-related quality-of-life; N: no; N/A: not applicable; NMA: network meta-analysis; QALY: quality-adjusted life-year; Y: yes.

Dual and triple therapy economic evaluations

Table G.22: Quality assessments of economic evaluations included in the economic systematic literature review

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	SMC 505/08 (2008)	SMC 937/14 (2014)	SMC 376/07 (2007)	SMC 585/09 (2009)	SMC 684/11 (2011)	SMC 748/11 (2011)	SMC 785/12 (2012)	SMC 903/13 (2013)	Ashley at al. 2015
Study design										
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	N	N	N	N	N	N	N	N	N	Y
Was/were the viewpoint(s) of the analysis clearly stated and justified?	N	N	Y	N	N	N	N	N	N	N
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Were the alternatives being compared	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	**SMC 505/08 (2008)**	**SMC 937/14 (2014)**	**SMC 376/07 (2007)**	**SMC 585/09 (2009)**	**SMC 684/11 (2011)**	**SMC 748/11 (2011)**	**SMC 785/12 (2012)**	**SMC 903/13 (2013)**	**Ashley at al. 2015**
clearly described?										
Was the form of economic evaluation stated?	Y – cost-minimisation	Y – cost-utility	Y – cost-minimisation	Y – cost-utility	Y – cost-effectiveness	Y – cost-minimisation	Y – cost-utility	Y – cost-utility	Y – cost-minimisation	Y – cost-effectiveness
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	N	Y	N	N	Y – clinical equivalence had been demonstrated by indirect comparison	N	N	Y – clinical equivalence was demonstrated	N
Data collection										
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Y	N/A	N	Y	N/A	Y – for exenatide vs sitagliptin, pioglitazone, liraglutide 1.8 mg and insulin	Y	Y – for the comparison with exenatide bid in combination with OADs	N/A
Were details of the methods of synthesis or meta-analysis	Y – NMA of 8 studies	N/A	Y	N	N/A	Y	Y – NMA of 19 studies for exenatide vs liraglutide	N/A	Y – for the comparison with liraglutide in combination	Y – NMA of 13 RCTs

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	SMC 505/08 (2008)	SMC 937/14 (2014)	SMC 376/07 (2007)	SMC 585/09 (2009)	SMC 684/11 (2011)	SMC 748/11 (2011)	SMC 785/12 (2012)	SMC 903/13 (2013)	Ashley at al. 2015
of estimates given (if based on an overview of a number of effectiveness studies)?							1.2 mg		with OADs and for the comparison with exenatide in combination with basal insulin	
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – annual cost saving	Y – incremental costs, QALYs and ICER	Y – total annual cost	Y – ICER	Y – ICER	Y – cost saving per patient	N – only incremental costs and incremental QALYs	Y – incremental costs, QALYs, ICER	Y – annual costs and cost savings per patient	Y – total costs, QALYs, ICER
Were the methods used to value health states and other benefits stated?	N	N	N	Y – HRQoL data were collected from the CODE-2 study	N	N/A	Y – HRQoL data were collected from published studies	Y – HRQoL data were collected from published studies	N/A	N
Were the details of the subjects from whom valuations were obtained given?	Y	Y	Y	N	Y	N	N	N	N/A	Y – T2DM cohort uncontrolled on OADs
Were productivity changes (if	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	SMC 505/08 (2008)	SMC 937/14 (2014)	SMC 376/07 (2007)	SMC 585/09 (2009)	SMC 684/11 (2011)	SMC 748/11 (2011)	SMC 785/12 (2012)	SMC 903/13 (2013)	Ashley at al. 2015
included) reported separately?										
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	N	N	N	N	N
Were the methods for the estimation of quantities and unit costs described?	N	N	N	N	N	N	N	N	N	N
Were currency and price data recorded?	N	N	N	N	N	N	N	N	N	Y – GBP 2013
Were details of price adjustments for inflation or currency conversion given?	N	N	N	N	N	N	N	N	N	N

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	**SMC 505/08 (2008)**	**SMC 937/14 (2014)**	**SMC 376/07 (2007)**	**SMC 585/09 (2009)**	**SMC 684/11 (2011)**	**SMC 748/11 (2011)**	**SMC 785/12 (2012)**	**SMC 903/13 (2013)**	**Ashley at al. 2015**
Were details of any model used given?	N/A	Y – patient simulation model	N	Y – Markov model based on CORE Diabetes Model	Y – IMS CORE Diabetes Model	N	Y – CORE Diabetes Model	Y – CORE Diabetes Model	N	N
Was there a justification for the choice of model used and the key parameters on which it was based?	N	N	N	N	N	N	Y – used in previous SMC submissions	N	Y	N
Analysis and interpretation of results										
Was the time horizon of cost and benefits stated?	Y – one year	Y – lifetime	Y – 1 year	Y – 10 years	Y – lifetime	Y – 1 year	Y – 20 years	Y – 20 years	Y – 1 year	Y – lifetime
Was the discount rate stated?	N	N	N	N	N	N	N	N	N/A	Y – 3.5% annually
Was the choice of rate justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N
Was an explanation given if cost or benefits were not discounted?	N	N	N	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were the details of	N	N	N	N	N	N	N	N	N	N

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	SMC 505/08 (2008)	SMC 937/14 (2014)	SMC 376/07 (2007)	SMC 585/09 (2009)	SMC 684/11 (2011)	SMC 748/11 (2011)	SMC 785/12 (2012)	SMC 903/13 (2013)	Ashley at al. 2015
statistical test(s) and confidence intervals given for stochastic data?										
Was the approach to sensitivity analysis described?	N	N	N	N	N	N	N	Y	Y	N
Was the choice of variables for sensitivity analysis justified?	N	N	N	N	N	N	N	N	N	N
Were the ranges over which the parameters were varied stated?	N	N	N	N	N	N	N	N	Y	N
Were relevant alternatives compared in the incremental analysis?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	N	Y	N	Y	Y	Y	Y

	Dipeptidyl peptidase-4 (DPP-4) inhibitors			Glucagon-like peptide-1 (GLP-1) agonists						
	SMC 1083/15 (2015)	SMC 505/08 (2008)	SMC 937/14 (2014)	SMC 376/07 (2007)	SMC 585/09 (2009)	SMC 684/11 (2011)	SMC 748/11 (2011)	SMC 785/12 (2012)	SMC 903/13 (2013)	Ashley at al. 2015
Were major outcomes presented in a disaggregated as well as aggregated form?	N – only incremental costs reported	N – only incremental costs and QALYs reported	N – only total costs were reported	N – only ICER reported	N – only incremental costs and incremental QALYs were reported	Y – annual treatment costs per patient reported	N – only incremental QALYs and costs were reported	N – only incremental QALYs and costs were reported	Y – both total and incremental annual costs reported	Y – total costs and total QALYs were reported
Was the answer to the study question given?	Y – in the form of annual saving	Y – in the form of an ICER	Y – in the form of a conclusion	Y – in the form of an ICER	Y – in the form of an ICER	Y – in the form of cost saving per patient	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of cost savings	Y – in the form of a discussion of the ICER
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – summary of limitations provided	Y – discussion of limitations provided	Y – some discussion of limitations provided	Y – discussion of limitations	N – no discussion of limitations	Y – discussion of limitations	Y – discussion of limitations	N – no discussion of limitations	Y – discussion of limitations	N – no discussion of limitations

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
Study design									
Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	Y	Y	Y	Y	N	Y	Y	N	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y	Y – UK NHS	Y – UK payer perspective	Y – UK payer perspective	Y, but viewpoint not justified	Y – UK NHS and PSS perspective	Y – UK NHS and PSS perspective	N	Y – NHS Scotland
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the form of economic evaluation stated?	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-utility	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-effectiveness	Y – cost-utility	Y – cost-utility
Was the choice of form of economic evaluation justified in relation	N	N	N	Y	N	N	N	N	N

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
to the questions addressed?									
Data collection									
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	N/A	Y	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	Y	N/A	N	Y – Heine 2005, UKPDS and Leese 2003	Y	N/A	N/A	N/A	N/A
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	N	Y – NMA of 17 RCTs	N/A	N/A	Y – NMA	Y – NMA	Y – NMA	Y – NMA
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – total and incremental costs, QALYs, ICER	Y – QALYs, costs, ICER	Y – QALYs, costs, ICER	Y – QALYs, costs, ICER	Y – total costs, QALYs	Y – total costs, total QALYs, ICER	Y – total costs, QALYs, ICER	Y – incremental costs, QALYs, ICER	Y – total costs, total QALYs, ICER
Were the methods	Y	Y – published	Y	Y	N	Y – HRQoL	Y – HRQoL data	Y – HRQoL	Y – HRQoL

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
used to value health states and other benefits stated?		SLR				data were sourced from CODE-2 study	was sourced from published studies, which used EQ-5D	data was sourced from published studies	data were sourced from published sources
Were the details of the subjects from whom valuations were obtained given?	N	N	N	N	Y – patients with uncontrolled T2DM	Y	Y	N	Y
Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the relevance of productivity changes to the study question discussed?	N	N	N	N	N	N	N	N	N
Were quantities of resources reported separately from their unit cost?	N	N	N	N	N	Y	N	N	N
Were the methods for the estimation of quantities and unit costs described?	N	Y – sourced from literature	N	N	N	Y	N	N	N
Were currency and price data recorded?	Y	Y – GBP 2016	GBP – 2016	GBP – 2007	GBP – year NR	Y	N	N	N

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
Were details of price adjustments for inflation or currency conversion given?	Y – values inflated to 2015 using the Hospital and Community Health Services price index	N	N	N	N	Y	Y	N	N
Were details of any model used given?	Y – IMS CORE Diabetes Model	Y – IMS CORE Diabetes Model	Y – CORE Diabetes Model	Y – DES model	Y – IMS Health CORE Diabetes Model	Y – ECHO-T2DM	Y – patient level microsimulation model using IMS CORE	Y – discrete events simulation model	Y – micro-simulation model
Was there a justification for the choice of model used and the key parameters on which it was based?	Y	N	Y	Y	Y	N	N	N	N
Analysis and interpretation of results									
Was the time horizon of cost and benefits stated?	Y	Y – lifetime	Y – lifetime	Y – 40 years	Y – 20 years	Y – 40 years	Y – lifetime	Y – 40 years	Y – 40 years
Was the discount rate stated?	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	Y – 3.5% annually	N	Y – 3.5% annually	Y – 3.5% annually	N	N
Was the choice of rate justified?	Y – based on health economic guidance for the UK setting	N	Y	Y	N/A	Y – in line with recent NICE guidance	Y – in line with NICE guidance	N	N/A

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
Was an explanation given if cost or benefits were not discounted?	N/A	N	N/A	N/A	N	N/A	N/A	N/A	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N	N	N	N	N	N	N	N
Was the approach to sensitivity analysis described?	Y	Y	Y	N	N	Y	Y	Y	N
Was the choice of variables for sensitivity analysis justified?	Y	N	N	Y	N	N	N	N	N
Were the ranges over which the parameters were varied stated?	Y	Y	Y	Y	Y	Y	N	N	N
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	N	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	N	Y	Y	Y	Y

	Glucagon-like peptide-1 (GLP-1) agonists				Multiple interventions	Sodium-glucose cotransporter 2 (SGLT-2) inhibitors			
	Hunt et al. 2017	Schlueter et al. 2016	Vega-Hernandez et al. 2017	Woehl et al. 2008	Evans et al. 2013	NICE TA315 (2014)	NICE TA336 (2015)	SMC 799/12 (2012) [SMC 799/12 (2014)]	SMC 963/14 (2014)
Were major outcomes presented in a disaggregated as well as aggregated form?	Y – total and incremental costs and QALYs were reported	Y	Y	N	Y – total costs and QALYs were reported	Y – total costs and QALYs as well as incremental costs and QALYs were reported	Y – total costs and total QALYs were reported	Y – incremental costs and incremental QALYs were reported	N – only incremental costs and QALYs reported
Was the answer to the study question given?	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y	N	Y – in the form of an ICER	Y – in the form of a discussion of the ICER	Y – in the form of a discussion of the ICER	Y – in the form of an ICER
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y – limitations were discussed	Y – limitations were discussed	Y – limitations were discussed	Y	N – no discussion of limitations	N – no discussion of limitations	Y – discussion of limitations	Y – discussion of limitations	Y – discussion of limitations and uncertainties provided

Abbreviations: EQ-5D: EuroQoL 5-dimensions; GBP: British pound; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; N: no; N/A: not applicable; NHS: National Health Service; NMA: network meta-analysis; OAD: oral antidiabetic drug; PSS: Personal Social Services; QALY: quality-adjusted life-year; RCT: randomised controlled trial; SMC: Scottish Medicines Consortium; T2DM: type 2 diabetes mellitus; UK: United Kingdom; Y: yes.

Mono, dual and triple therapy economic evaluations

Table G.23: Quality assessments of economic evaluations included in the economic systematic literature review

	Multiple interventions
	McEwan et al. 2010
Study design	
Was the research question stated?	Y
Was the economic importance of the research question stated?	N
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y, but viewpoint not justified
Was a rationale reported for the choice of the alternative programs or interventions compared?	N
Were the alternatives being compared clearly described?	Y
Was the form of economic evaluation stated?	Y – cost-utility
Was the choice of form of economic evaluation justified in relation to the questions addressed?	N
Data collection	
Was/were the source(s) of effectiveness estimates used stated?	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NMA – of 4 RCTs and 1 review
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – total costs, QALYs, ICER
Were the methods used to value health states and other benefits stated?	Y
Were the details of the subjects from whom valuations were obtained given?	Y – patients with uncontrolled T2DM
Were productivity changes (if included) reported separately?	N/A
Was the relevance of productivity changes to the study question discussed?	N

	Multiple interventions
	McEwan et al. 2010
Were quantities of resources reported separately from their unit cost?	N
Were the methods for the estimation of quantities and unit costs described?	N
Were currency and price data recorded?	Y – GBP 2008
Were details of price adjustments for inflation or currency conversion given?	N
Were details of any model used given?	Y – Cardiff stochastic simulation cost-utility model (DiabForecaster)
Was there a justification for the choice of model used and the key parameters on which it was based?	Y
Analysis and interpretation of results	
Was the time horizon of cost and benefits stated?	Y – 10 years
Was the discount rate stated?	N
Was the choice of rate justified?	N/A
Was an explanation given if cost or benefits were not discounted?	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N
Was the approach to sensitivity analysis described?	N
Was the choice of variables for sensitivity analysis justified?	N/A
Were the ranges over which the parameters were varied stated?	N/A
Were relevant alternatives compared in the incremental analysis?	N/A
Was an incremental analysis reported?	N
Were major outcomes presented in a disaggregated as well as aggregated form?	N
Was the answer to the study question given?	Y
Did conclusions follow from the data reported?	Y

	Multiple interventions
	McEwan et al. 2010
Were conclusions accompanied by the appropriate caveats?	N – no discussion of limitations

Abbreviations: ICER: incremental cost-effectiveness ratio; N: no; N/A: not applicable; NMA: network meta-analysis; QALY: quality-adjusted life-year; RCT: randomised controlled trial; T2DM: type 2 diabetes mellitus; Y: yes.

Appendix H: Health-related quality-of-life studies

A single review was performed to identify relevant studies in type 2 diabetes that included published economic evaluations, studies reporting utility values studies, and reporting cost and resource use data. Details of the search strategy and results of the economic SLR can be found in Appendix G. A summary of the included utilities studies is provided in Table G.24 below.

Table G.24: Summary of utilities studies included in the economic systematic literature review

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
Al Sayah et al. 2015[183]	Patients were part of a controlled trial of a collaborative primary care team model vs usual care for patients with T2DM and positive depressive symptoms (TeamCare-PCN).[184] Participants from this study were recruited from four primary care networks in rural Alberta. The average age of patients was 58.1 (SD 9.4) years. 86 (55.8%) were female. The mean number of diabetes complications was 2.4 (SD 1.9). The mean number of comorbidities	Canada	• Initial sample size: 157 patients. • Total participants: 154 patients. Note that these patients were pooled across both arms of the TeamCare-PCN trial.	Baseline utility value estimates for T2DM patients with positive depressive symptoms.	• NR	• EQ-5D utility value for T2DM with positive depressive symptoms: 0.70 (SD 0.16)	**Consistency with NICE reference case:** EQ-5D health state index values were estimated, however the value set used was not reported and so may not align with the preferences of the UK general public. **Relevance to the decision problem:** Overall utility value estimates are provided for patients with T2DM with positive depressive symptoms; a relevant health state for the current cost-effectiveness

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
	was 2.9 (SD 1.5).						evaluation.
Briggs et al. 2016[185] [Briggs et al. 2015a, Briggs et al. 2015b][186, 187]	Patients were part of a phase IV trial (SAVOR-TIMI 53) of saxagliptin vs PBO for the treatment of patients with T2DM with a history of, or at risk for, cardiovascular events. 66.9% of the total patients were male.	International multicentre trial across 26 countries.	16,492 patients randomised, 16,488 patients included in trial analysis. 2,568 patients experienced serious cardiovascular event; 1,437 provided subsequent EQ-5D measurement. 96 patients were hospital-ised following a hypoglycaemic event; 79 provided subsequent EQ-5D measurement. 373 patients were hospitalised for heart failure and	Utility estimates at baseline and up to 12 months for T2DM patients with a history or at risk of cardiovascular events. Baseline utility value estimates for T2DM patients who experienced a major cardiovascular event during the trial and for those who did not. Utility value estimates of T2DM patients within 3 months, 3–6 months and 6–12 months of a cardiovascular event. Utility decrements associated with a first cardiovascular event, hospitalisat	Patients completed the EQ-5D assessment at baseline, 12 months, 24 months and study completion. Patients who had experienced non-fatal myocardial infarction or ischaemic stroke since their previous visit additionally completed the EQ-5D as semi-annual visits. There could have been up to 6 months' delay between the occurrence of an event and	• **Mean EQ-5D index score of overall sample at baseline, 3, 6 and 12 months:** 0.776 (all confidence intervals were within ± 0.01)[c] • **Mean baseline EQ-5D index score of patients who did not experience a major cardiovascular event during the trial:** 0.778 (95% CI: 0.775–0.783)[c] • **Mean baseline EQ-5D index score of patients who experienced a major cardiovascular event during the trial:** 0.751 (95% CI: 0.739–0.763)[c] • **Mean EQ-5D index**	**Consistency with NICE reference case:** EQ-5D health state descriptions were elicited directly from patients and were valued using the UK value set, reflecting the preferences of the UK general population. **Relevance to the decision problem:** Utility value estimates are provided for patients with T2DM with a history of and experiencing cardiovascular events as well as hospitalised hypoglycaemic events; these are relevant health states for the current cost-effectiveness

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
			provided subsequent EQ-5D measurement. 415 patients were hospitalised for myocardial infarction and provided subsequent EQ-5D measurement. 208 patients were hospitalised for stroke and provided subsequent EQ-5D measurement.	ion for heart failure hospitalisation for myocardial infarction, hospitalisation for stroke and for a hypoglycaemic event whilst hospitalised adjusted for age, sex, treatment arm and baseline HRQoL.	administration of the questionnaire. The UK-specific value set was used to convert the EQ-5D health state descriptions to the EQ-5D index score (range from 0 to 1).	**score after a cardiovascular event:**[c] • 3 months = 0.691 • 3–6 months = 0.691 • 6–12 months = 0.714 • **Utility decrements after a cardiovascular event:**[a,b] • 3 months = -0.059 • 3–6 months = -0.045 • 6–12 months = -0.037 These decrements were statistically significant. • EQ-5D utility for T2DM patients with a prior cardiovascular event at the end of the study: 0.71 (SENR)[a,b] • **Utility decrement observed after a first major**	s evaluation.

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
						cardiovascular event: -0.050 (SE 0.007)[c] • **Utility decrement observed after hospitalisation for heart failure:** -0.065 (SE 0.014)[c] • **Utility decrement observed after hospitalisation for myocardial infarction:** -0.051 (SE 0.012)[c] • **Utility decrement observed after hospitalisation for stroke:** -0.111 (SE 0.022)[c] • **Utility decrement following a hypoglycaemic event whilst hospitalised:** -0.019 (SE 0.024)[c] -0.026 (SE NR)[b] This decrement was not statistically significant. [a]Briggs et al.	

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
						2015a [b]Briggs et al. 2015b [c]Briggs et al. 2016	
Hayes et al. 2016[188]	Patients were part of a trial investigating the potential benefits to T2DM patients of blood pressure lowering agents (perindopril and indapamide combination vs PBO) and of tighter glucose control (intensive gliclazide-MR-based glucose control regime vs a standard guidelines-based regimen), separately and together (ADVANCE).[189] The mean age at baseline was 65.8 (SD 6.4). 6,401 (57%) of patients were male. 4,349 (39%) of patients had a history of micro- or macrovascular disease at baseline. The mean	International multicentre trial across 20 countries in Australasia, Asia, Europe and North America.	Total: 11,140 patients. 11,130 patients with ≥1 complete EQ-5D questionnaire (99.9%). 8,723 patients with 4 complete EQ-5D questionnaires (78%).	T2DM patients with at least one risk factor for or a history of microvascular disease at randomisation, 2 and 4 years post-randomisation and at the end of the trial. Utility decrements associated with any one of and specifically for each of the following 7 complications: acute myocardial infarction, stroke, ischaemic heart disease (including angina and coronary athero-sclerosis), heart failure, blindness, amputation and renal failure.	Patients completed the EQ-5D-3L assessment at randomisation, at 2 and 4 years post-randomisation and at the end of the trial, representing 5 years of follow-up. The UK-specific value set was used to convert the EQ-5D-3L health state descriptions to the EQ-5D-3L index score.	• **Mean EQ-5D utility of patients with micro- or macrovascular disease at baseline:** • Baseline: 0.80 (SD 0.21) • 2 years: 0.79 (SD 0.23) • 4 years: 0.78 (SD 0.24) • 5 years: 0.78 (SD 0.23) • **Mean EQ-5D utility of patients without micro- or macrovascular disease at baseline:** • Baseline: 0.83 (SD 0.18) • 2 years: 0.82 (SD 0.20) • 4 years: 0.81 (SD 0.21) • 5 years: 0.81 (SD 0.22) • **Permanent**	**Consistency with NICE reference case:** EQ-5D health state descriptions were elicited directly from patients and were valued using the UK value set, reflecting the preferences of the UK general population. **Relevance to the decision problem:** Utility value estimates are provided for patients with T2DM and at least one risk factor for or a history of microvascular disease, as well as decrements for 7 complications, each being relevant for the current cost-effectiveness evaluation.

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
	number of incident non-fatal events: • Any non-fatal event: 1,366 (SD 12.0) • Myocardial infarction: 247 (SD 2.2) • Stroke: 335 (SD 3.0) • Heart failure: 270 (SD 2.4) • Ischemic heart disease: 483 (SD 4.4) • Blindness: 44 (SD 0.4) • Amputation: 39 (SD 0.3) • Renal failure: 89 (SD 0.8)					**utility decrement associated with any one of the seven complications:** -0.054 (95% CI: 0.044–0.064) • **Utility decrements associated with:** • Amputation: -0.122 • Stroke: -0.099 • Blindness: -0.083 • Renal failure: -0.049 • Heart failure: -0.045 • Myocardial infarction: -0.026 • Ischemic heart disease: -0.010	
Kamradt et al. 2017[190]	T2DM patients enrolled in a structured disease management program in 2013 were selected at random from 21 PCPs, which formed part of the GEDIMplus trial.[191]	Germany	495 patients eligible, 404 patients with complete data included in the analysis.	Utility value estimates of patients with T2DM and at least two additional chronic conditions. Utility value estimates with and without the	Patients completed the EQ-5D assessment by self-report. The European-specific value set was used to convert	• **Mean EQ-5D utility of overall sample:** 0.69 (SD 0.23) • **Mean EQ-5D utilities of T2DM patients with and without specific**	**Consistency with NICE reference case:** EQ-5D health state index values were used, however the European value set used was used, which includes five

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation

	Each patient had at least 2 chronic conditions in addition to T2DM. The number of patients with each condition:
	• CHD: 145
	• CHF: 58
	• COPD: 53
	• Asthma: 27
	• Depression: 65
	• Parkinson's disease: 2
	• Cerebrovascular diseases: 32
	• Chronic pain: 100
	• Atherosclerosis: 49
	• CHF, depression and chronic pain: 2
	• Depression and chronic pain: 17
	• CHF and chronic pain: 15
	• CHF and depression: 9
	
	The following complications were not relevant to this review and so utility data for these conditions has not been presented
				following complications:
				CHD
				Cerebro-vascular diseases
				CHF
				Depression
				Athero-scelrosis
				CHF and depression.
					the EQ-5D health state descriptions to the EQ-5D index score (range from 0 to 1). This value set was constructed using data from six European countries (Finland, Germany, The Netherlands, Spain, Sweden and UK).	**comorbidities, mean (SD):**
						• CHD
						  • With: 0.71 (0.21)
						  • Without: 0.67 (0.24)
						• Cerebrovascular diseases
						  • With: 0.68 (0.19)
						  • Without: 0.69 (0.24)
						The differences for these comorbidities were not statistically significant.
						• CHF
						  • With: 0.62 (0.25)
						  • Without: 0.70 (0.23)
						• Depression
						  • With: 0.62 (0.22)
						  • Without: 0.70 (0.23)
						• Atherosclerosis
						  • With: 0.63 (0.25)
						  • Without: 0.69 (0.23)
						The differences for these comorbidities were
							additional countries to the UK and so may not directly align with the preferences of the UK general public.
							
							Relevance to the decision problem: Overall utility value estimates are provided for patients with T2DM with chronic comorbidities which represent relevant health states for the current cost-effectiveness evaluation.

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation

	here: COPD, asthma, Parkinson's disease and chronic pain.
	
	The mean age of patients was 67.80 (SD 10.78).
	
	182 patients were female (45.05%).
	
	The mean number of additional chronic conditions was 2.90 (SD 1.02).
						statistically significant.
						
						• **Mean EQ-5D utilities of T2DM patients with and without specific combinations of comorbidities, mean (SD):**
						• CHF and depression:
						  • With: 0.57 (0.21)
						  • Without: 0.69 (0.23)
						The differences for these comorbidities were not statistically significant.	

Kiadaliri et al. 2015[192]	Data used in the study were collected through a cross-sectional survey conducted by the Swedish National Diabetes Register in 2008 (the IQ3 project). All participants had T2DM. Mean (SD) age of the subjects: 66.1	Sweden	Total: 1,757 patients Response rate: NR	Utility value estimate at one point in time for patients with T2DM. Utility value estimates for the following complications: • Micro-vascular compli-cations • Macro-vascular	Patients completed the Swedish version of the EQ-5D-3L assessment by self-report. The UK-specific tariff reflecting the values of a representative sample of	All results relate to the EQ-5D-3L index scores. Utility estimates of overall population: • **Mean:** 0.77 • **95% CI:** 0.76–0.78 • **Median (IQR):** 0.80 (0.71–1) • **Range:** -0.59–1 • **Mean EQ-5D utilities**	**Consistency with NICE reference case:** EQ-5D-3L health state descriptions were elicited directly from patients, and the UK-specific value set (reflecting the values of a representative sample of the UK general population)

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation

	(8.8) years
	
	% female: 43%
	
	% with BMI >25 kg/m^2: 82%
	
	Prevalence of microvascular complications: 5%
	
	Prevalence of macrovascular complications: 24%
				complications
				• Myocardial infarction
				• Stroke
				• Heart failure
				• Non-acute ischemic heart disease
				• Kidney disorders
				• Retinopathy
					the UK general population was used to convert the EQ-5D health state descriptions collected from Swedish patients into EQ-5D-3L index scores.	**of T2DM patients with and without specific comorbidities, mean:**
						• Microvascular complications:
						  • With: 0.66
						  • Without: 0.77
						• Macrovascular complications:
						  • With: 0.70
						  • Without: 0.79
						• Myocardial infarction:
						  • With: 0.71
						  • Without: 0.77
						• Stroke:
						  • With: 0.66
						  • Without: 0.77
						• Heart failure:
						  • With: 0.65
						  • Without: 0.77
						• Non-acute ischemic heart disease:
						  • With: 0.70
						  • Without: 0.78
						• Kidney
							was used to derive the index scores.
							
							Relevance to the decision problem: Overall utility value estimates are provided for patients with T2DM with specific comorbidities which represent relevant health states for the current cost-effectiveness evaluation.

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
						disorders: • With: 0.61 • Without: 0.77 The differences for these comorbidities were statistically significant. • Retinopathy: • With: 0.69 • Without: 0.77 The difference for this comorbidity was not statistically significant.	
O'Shea et al. 2015[193]	Patients with T2DM aged between 25–80 and who had attended the Diabetes Day Centre at St James's Hospital on at least one occasion between August 2011 and July 2012 were randomly selected for inclusion in the study using a list of random numbers. % aged ≥55 years old: 78% % male: 60%	Ireland	Sample size: 498. Response rate: 32%.	Patients with T2DM stratified by treatment including: diet alone, OAH therapy, insulin, OAH and insulin and OAH and other injectable. Patients with T2DM stratified by comorbidity type including: diabetes alone, concordant comorbidity only, discordant comorbidity only, both concordant and	Patients completed the EQ-5D assessment by self-report. The UK-specific value set was used to convert EQ-5D health state descriptions to EQ-5D index scores.	• **Median (IQR) EQ-5D index score (n=141) in entire cohort:** 0.80 (0.69–1.00) Stratified by treatment • **Median (IQR) EQ-5D index score for:** • Diet alone (n=14): 1.00 (0.73–1.00) • OAH therapy (n=85): 0.80 (0.69–1.00) • Insulin	**Consistency with NICE reference case:** EQ-5D was used and the UK-specific value set was used to derive index scores representative of the preferences of the UK general population. **Relevance to the decision problem:** Utilities are provided for health states that are potentially relevant to the cost-

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
				discordant comorbidity. Concordant comorbidities included those associated with diabetes: heart disease, kidney disease and hypertension. Discordant comorbidities were those not associated with diabetes: lung disease, ulcer, stomach disease, liver disease, anaemia or other blood disease, cancer, depression, osteoarthritis, back pain and rheumatoid arthritis. Patients with T2DM stratified by the number of comorbid conditions. Other utility values reported but not extracted include stratificatio		(n=2): 0.85 (0.85–0.85) • OAH and insulin (n=29): 0.76 (0.67–0.90) • OAH and other injectable (n=6): 0.77 (0.19–0.85) Stratified by comorbidity type • **Median (IQR) EQ-5D index score for:** • Diabetes alone (n=31): 1.00 (0.85–1.00) • Concordant comorbidity only (n=36): 0.87 (0.80–1.00) • Discordant comorbidity only (n=19): 0.73 (0.62–0.85) • Both concordant and discordant comorbidity (n=52):	effectiveness model for ertugliflozin.

Source (study/ publications)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Results	Appropriateness of study for cost-effectiveness evaluation
				ns of the cohort by: sex, age group, marital status, formal education, diabetes duration, diabetes-related complications, and diabetes education.		0.71 (0.52–0.80) Stratified by number of comorbidities • **Median (IQR) EQ-5D index score for:** • 0 comorbidities (n=31): 1.00 (0.85–1.00) • 1 comorbidity (n=40): 0.85 (0.78–1.00) • 2 comorbidities (n=30): 0.76 (0.66–0.85) • 3 comorbidities (n=23): 0.69 (0.52–0.80) • ≥4 comorbidities (n=14): 0.35 (0.00–0.69)	

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CHF: chronic heart failure; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EQ-5D(-3L): EuroQol five dimensions questionnaire (3 levels); HRQoL: health-related quality of life; IQR: interquartile range; MR: modified release; n: number; NR: not reported; OAH, oral anti-hyperglycaemic; PBO: placebo; PCN: primary care network; PCP: primary care practice; SD: standard deviation; SE: standard error; T2DM: type 2 diabetes mellitus; UK: United Kingdom.

Appendix I: Cost and healthcare resource identification, measurement and valuation

A single review was performed to identify studies in type 2 diabetes that included published economic evaluations, studies reporting utility values and studies reporting cost and resource use data. Details of the search strategy and results of the economic SLR can be found in Appendix G. **Error! Reference source not found.**A summary of the included cost and resource use studies is provided in Table G.25. The table below presents only original cost and resource use data obtained directly in the included primary publications, therefore HTA reports and/or economic evaluations that obtained cost and resource use data from elsewhere in the literature have not been included in this element of the systematic review e.g. TA390.

Table G.25: Summary of cost and resource use studies included in the economic systematic literature review

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr>
<td>NICE Technology appraisal guidance TA336[70]</td>
<td>Objectives: to assess the cost-effectiveness of empagliflozin as a combination therapy in the treatment of T2DM.

Population: T2DM patients with insufficient glycaemic control enrolled in trials within the empagliflozin clinical trials programme.</td>
<td>Country: Unclear

Cost year: NR</td>
<td>Resource use was captured during the treatment period (the first 24 weeks) of all patients (in the full analysis set) enrolled in trials within the empagliflozin clinical trials programme.

Resource use was categorised into three types: emergency room visits, hospitalisations and outpatient visits.

For each type of resource use, data were separated into diabetes-related use and non-diabetes-related use.</td>
<td>Diabetes-related resource use during the treatment period (pooled data, full analysis set):
<table>
<tr><th>Resource type</th><th>Statistic</th><th>EMPA 25 mg (n=1,332)</th><th>EMPA 10 mg (n=1,114)</th><th>EMPA 25 mg + 10 mg (n=2,446)</th><th>PBO (n=1,332)</th></tr>
<tr><td rowspan="5">Outpatient nurse visits</td><td>n (%)</td><td>6 (0.5%)</td><td>2 (0.2%)</td><td>8 (0.3%)</td><td>6 (0.5%)</td></tr>
<tr><td>Average visits, n (SD)</td><td>9.3 (16.1)</td><td>3.0 (0.0)</td><td>7.8 (13.9)</td><td>1.2 (0.4)</td></tr>
<tr><td>Median</td><td>3</td><td>3</td><td>3</td><td>1</td></tr>
<tr><td>IQR</td><td>1–6</td><td>3–3</td><td>2–5</td><td>1–1</td></tr>
<tr><td>Range</td><td>1–42</td><td>3–3</td><td>1–42</td><td>1–2</td></tr>
</table>
</td>
<td>Resource use data have been collected directly from large clinical trials so may not reflect resource use in the real-world. Furthermore, the countries these trials were conducted in were not reported so the data may not reflect cinical practice in England, however some data potentially relevant to the economic model have been presented.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td></td><td></td><td>For the purposes of this review, only diabetes-related resource use in the outpatient setting was considered relevant and so data in other categories have not been presented here.</td><td></td><td></td></tr>
<tr><td>Chapman et al. 2016[194]</td><td>Objectives: to provide accurate measurements of the real-world healthcare utilisation and economic burden of managing diabetes patients with hypoglycaemia, stroke or heart failure using the cross-care-setting ‘Insights for Care’ diabetes dataset.

Population: T2DM patients diagnosed with hypoglycaemia (n=1,091), heart failure (n=2,637) or stroke (n=912) between 1st January 2010 and 31st December 2014 with a medical claim during inpatient admission.</td><td>UK

Cost year: NR</td><td>Patients’ demographic/clinical characteristics, readmission rates and healthcare resource usage including number of inpatient, outpatient and A&E events at a large secondary/tertiary care hospital were calculated.

Admissions were grouped by diagnosis, procedure and HRG codes.

Estimated Economic Impact was calculated using the cost of inpatient, outpatient and A&E services to the payer.</td><td><table><tr><th></th><th colspan="3">Number of interactions resulting from complication (cost of interactions, £)</th></tr><tr><th>Complication</th><th>Inpatient</th><th>Outpatient</th><th>A&E</th></tr><tr><td>Hypoglycaemia</td><td>5.2 (6,858)</td><td>6.3 (681)</td><td>1.6 (470)</td></tr><tr><td>Stroke</td><td>3.4 (6,447)</td><td>5.2 (525)</td><td>1.4 (431)</td></tr><tr><td>Heart failure</td><td>3.9 (6,849)</td><td>6.1 (639)</td><td>1.4 (401)</td></tr></table></td><td>Data were collected from a large, real-world, UK diabetes dataset, and costs have been presented in GBP.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr>
<td>Frier et al. 2015[195]</td>
<td>Objectives: to quantify the self-reported frequency of non-severe hypoglycaemic events (NSHEs, with "non-severe" events defined as those that do not require external assistance to effect recovery) and its effects in adults with insulin-treated diabetes in the UK.

Population: 1,038 respondents (466 T1DM, 572 T2DM) completed 3,528 questionnaires between September and December 2013. Recruitment was through an online consumer panel (>99%) or via telephone interviews and referral sampling from general practitioners and patients (all <1%). Individuals over 15 years of age with T1/T2DM receiving insulin therapy were included; T2DM patients were characterised by their insulin regimen: basal-only, basal-bolus and other forms.</td>
<td>UK

Cost year: N/A</td>
<td>Respondents completed 4 online questionnaires, one every 7 days. All questionnaires covered the frequency of NSHEs and the impact of the respondent’s most recent event on their use of healthcare resources.</td>
<td>Proportion of NSHEs where last NSHE resulted in contact with healthcare professionals:
<table>
<tr><th rowspan="2">Last NSHE across all respondents</th><th rowspan="2">T2DM – all patients, n/N (%)</th><th colspan="3">T2DM treatment subgroups</th></tr>
<tr><th>Basal-only therapy</th><th>Basal-bolus therapy/short- and long-acting insulin</th><th>Other therapy</th></tr>
<tr><td>Overall</td><td>61/884 (7)</td><td>14/194 (7)</td><td>39/536 (7)</td><td>8/154 (5)</td></tr>
<tr><td>Diurnal</td><td>40/674 (6)</td><td>7/150 (5)</td><td>27/399 (7)</td><td>6/125 (5)</td></tr>
<tr><td>Nocturnal</td><td>21/210 (10)</td><td>7/44 (16)</td><td>12/137 (9)</td><td>2/29 (7)</td></tr>
</table>
</td>
<td>Data were collected from respondents in the UK, which likely included some English patients. In addition, the data provided could be useful in an economic model.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr>
<td>Hammer et al. 2009[146]</td>
<td>Objective: To assess the costs of SHEs in diabetes patients in Germany, Spain and the UK.

Population: For the purposes of this review, only UK T2DM patients were relevant and so results for these patients only have been reported here (n=100). Patients were recruited predominantly by HCPs using a non-random selection process. The patients were aged ≥16 years and receiving insulin alone or in combination with OAD agents and had experienced at least one SHE in the previous 12 months. Patients were categorised according to the setting in which the SHE was managed:
• "Family/ domestic", where patients were treated by a family member or friend (n=50)
• "Community HCP", where</td>
<td>UK

Cost year: 2007</td>
<td>Healthcare resource use was collected via a questionnaire delivered at patient interviews conducted between February and March 2007.

Unit costs were derived from online sources, official statistics, local tariffs and national formularies. Costs were inflated to 2007 values to account for inflation where necessary using the UK Hospital & Community Health Services Pay and Prices Index.

If surveyed patients had experienced more than 1 SHE, resource use was recorded only for the single most recent event.

The cost per SHE for each treatment setting was calculated by dividing the total costs in each group by the number of patients.</td>
<td>Direct costs of treatment for SHEs in the UK survey sample:
<table>
<tr><th colspan="2">Treatment</th><th>Family/ Domestic, £ (% of group total cost) (n=50)</th><th>Community HCP, £ (% of group total cost) (n=25)</th><th>Hospital HCP, £ (% of group total cost) (n=25)</th></tr>
<tr><td rowspan="2">Outside hospital (attendance by HCP, ambulance service, glucose/drugs administered)</td><td>Subtotal</td><td>61 (3.7%)</td><td>4,216 (70.8%)</td><td>4,508 (20.2%)</td></tr>
<tr><td>Cost per SHE</td><td>1</td><td>169</td><td>180</td></tr>
<tr><td rowspan="2">Hospital treatment (transport [non-ambulance], admission, care and treatment [first 24 hours], follow-up care [beyond 24 hours])</td><td>Subtotal</td><td>0 (0%)</td><td>0 (0%)</td><td>15,022 (67.4%)</td></tr>
<tr><td>Cost per SHE</td><td>0</td><td>0</td><td>£601</td></tr>
<tr><td rowspan="2">Follow-up treatment (visits and calls to PCP, extra blood glucose tests, training for patient and family members)</td><td>Subtotal</td><td>1,596 (96.3%)</td><td>1,548 (26.0%)</td><td>2,008 (9.0%)</td></tr>
<tr><td>Cost per SHE</td><td>£32</td><td>£62</td><td>£80</td></tr>
<tr><td>Subtotal</td><td>Total</td><td>1,657</td><td>5,764</td><td>21,538</td></tr>
<tr><td>Cost per SHE</td><td>Cost per SHE</td><td>33</td><td>231</td><td>862</td></tr>
</table>
</td>
<td>Cost data were derived from UK sources and resource use was derived from UK T2DM patients. Average costs for SHEs were reported in GBP.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td>patients received emergency treatment from a paramedic or other HCP without requirement for hospital treatment (n=25)
• "Hospital HCP", where patients were treated in a hospital (n=25)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hex et al. 2012[196]</td><td>Objective: to estimate the current and future economic burdens of T1/T2DM in the UK.

Population: cost data were generated for UK T1/T2DM patients (adults and children) from aggregated data sets and literature.</td><td>UK

Cost year: 2010/2011</td><td>Incidence and cost data were obtained from either literature or national data sources such as NHS Reference Costs, Hospital Episode Statistics (HES) and registries such as the UK Renal Registry. Where appropriate, historic costs were projected forward to 2010 using the Hospital and Community Health Services index of inflation.

For all complications, the incidence among the general population was discounted from the diabetes cost estimate.</td><td>Relevant estimated UK costs attributable to T2DM for 2010/2011, based on a total population prevalence of 3,419,727 adults and children:<table><tr><th>Screening</th><th>Cost, £</th></tr><tr><td>Retinopathy screening</td><td>2,414,554</td></tr><tr><th>Treatment and management</th><th>Cost, £</th></tr><tr><td>Primary care</td><td>950,713,826</td></tr><tr><td>Prescriptions</td><td>701,792,008</td></tr><tr><th>Complications</th><th>Cost, £</th></tr><tr><td>Hypoglycaemia (moderate)</td><td>22,614,644</td></tr><tr><td>Hypoglycaemia (severe)</td><td>16,433,734</td></tr><tr><td>Neuropathy</td><td>266,628,248</td></tr><tr><td>Ketoacidosis</td><td>0</td></tr><tr><td>Ischaemic heart disease</td><td>458,690,699</td></tr><tr><td>Myocardial infarction</td><td>573,797,013</td></tr><tr><td>Heart failure</td><td>277,342,025</td></tr><tr><td>Stroke</td><td>273,998,966</td></tr><tr><td>Kidney failure</td><td>379,004,594</td></tr></table></td><td>All costs and incidence data were taken from UK sources with costs provided in GBP. However, the data generated are at a population-level as opposed to per event, which would have been more useful for the purposes of an economic model (individual unit cost data are not provided).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Other renal costs</td><td>374,838,822</td></tr>
<tr><td>Retinopathy</td><td>51,967,658</td></tr>
<tr><td>Foot ulcers and amputations</td><td>874,005,362</td></tr>
<tr><td>Other cardiovascular disease</td><td>1,489,369,602</td></tr>
<tr><td>Excess inpatient days</td><td>1,805,472,271</td></tr>
</table>
</td><td></td></tr>
<tr><td>Holbrook et al. 2016[197] (Tunceli et al. 2015)[198]</td><td>Objective: To describe, during 2008–2014:
• Rate and cost of hospitalised hypoglycaemic events for patients in subgroups based on drug classes and regimens
• Number and length of secondary care admissions for hypoglycaemia

Population: UK T2DM patients were identified from primary care Clinical Practice Research Datalink (CPRD) data based on clinical and therapeutic history.</td><td>UK

Cost year: 2013/2014</td><td>The HES dataset was used to obtain data on inpatient and outpatient contacts with NHS trusts.

Hospitalisations for hypoglycaemic events were identified using HRGs. Rates of admissions for hypoglycaemic events were calculated using a pooled count of events over the number of pooled days of exposure.

The cost of hospitalised hypoglycaemic events was calculated via linkage of HRGs to the 2013–2014 National Tariff, adjusted for nature of the admission (elective admission vs emergency) and excess length of stay.</td><td>Holbrook 2016
Hospitalisations for hypoglycaemic events by treatment regimen:
<table>
<tr><th>Therapy</th><th>Patients admitted</th><th>Episodes</th><th>Mean (SD) length of stay</th><th>Mean (SD) cost excluding excess bed days, £</th></tr>
<tr><td colspan="5">Monotherapy</td></tr>
<tr><td>MET</td><td>11</td><td>11</td><td>5.5 (9)</td><td>1,148 (824)</td></tr>
<tr><td>SU</td><td>81</td><td>89</td><td>7.3 (8.8)</td><td>1,576 (785)</td></tr>
<tr><td>DPP4i</td><td>0</td><td>0</td><td>N/A</td><td>N/A</td></tr>
<tr><td>SITA</td><td>0</td><td>0</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Insulin</td><td>125</td><td>151</td><td>7.1 (12.8)</td><td>1,319 (743)</td></tr>
<tr><td>Other</td><td>2</td><td>2</td><td>0</td><td>547 (0)</td></tr>
<tr><td colspan="5">Insulin-containing</td></tr>
<tr><td>Insulin + SU ± 1 other AHA</td><td>13</td><td>13</td><td>4.8 (8.1)</td><td>1,289 (782)</td></tr>
<tr><td>Insulin + SU alone</td><td>5</td><td>5</td><td>6 (12.9)</td><td>875 (733)</td></tr>
<tr><td>Insulin + SU + 1 other AHA</td><td>8</td><td>8</td><td>4 (3.9)</td><td>1,548 (736)</td></tr>
<tr><td>Insulin + 1 or 2</td><td>60</td><td>65</td><td>3.2 (6.1)</td><td>1,045 (697)</td></tr>
</table>
</td><td>Study conducted using data from the CPRD, which is derived from nearly 700 UK primary care practices, costs derived from 2013/2014 National Tariffs and all costs have been reported in GBP.</td></tr>
</table>

Study	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis

non-SU AHAs				
Non-insulin-containing				
SU + 1 or 2 non-insulin AHAs	102	108	6.8 (14.8)	1,437 (786)
Non-insulin non-SU regimen	13	13	4.7 (8.5)	1,055 (785)
Dual therapy				
MET + SU	76	80	6.2 (13.3)	1,381 (789)
MET + DPP4i	0	0	N/A	N/A
MET + SITA	0	0	N/A	N/A

Tunceli 2015

Number/cost of hospital admissions for hypoglycaemia by treatment regimen:

Subgroup	Patients admitted	Exposures	Hospital admissions	Length of stay, mean days	Cost per event excluding excess bed days, mean £	Cost per event, mean £
Mono-therapy	225	82,398	260	8.4	1,758	2,089
Dual therapy	153	32,012	164	6.3	1,635	1,906
Triple therapy	23	6,703	23	11.1	1,885	2,776

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th colspan="7">Treatment class</th></tr>
<tr><td>SU</td><td>204</td><td>37,172</td><td>218</td><td>8.4</td><td>1,831</td><td>2,186</td></tr>
<tr><td>Insulin</td><td>195</td><td>16,925</td><td>226</td><td>7.2</td><td>1,593</td><td>1,918</td></tr>
</table>
</td><td></td></tr>
<tr><td>Holden et al. 2017[199]</td><td>Objectives: using UK primary and secondary care data, to estimate NHS resource use and related costs in patients receiving regimens that include exenatide in its once-weekly (EQW) or twice-daily formulation (EBID), compared with regimens such as basal insulin (BI).

Population: T2DM patients who were naïve to injectable therapies, registered in the UK CPRD, and received their first recorded prescription for EQW (n=218), EBID (n=2,180) or BI (n=8,723) between 1st January 2009 and 31st December 2014.</td><td>UK

Cost year: 2014</td><td>Primary care consultations were classified by consultation type and staff type and assigned a unit cost as listed in the Unit Costs of Health and Social Care 2015 from the Personal Social Services Research Unit (PSSRU).

Prescriptions were identified in the CPRD, matched to the corresponding product listed in the 2014 Prescription Cost Analysis report, and attributed a net ingredient cost per quantity. This was multiplied by the quantity of medication entered in each prescription to determine the cost of each prescription.

Data from inpatient admissions recorded in HES were processed into HRGs using HRG-4 grouper. These allocated HRGs were linked to the 2013 to 2014 National Tariff.</td><td>Primary and secondary care contacts and costs after treatment with exenatide (EQW or EBID) or BI:*
<table>
<tr><th>Healthcare resource</th><th>EQW total (rate per patient-year) [n=218]</th><th>EBID total (rate per patient-year) [n=2,180]</th><th>BI total (rate per patient-year) [n=8,723]</th></tr>
<tr><td colspan="4">Primary care contacts</td></tr>
<tr><td>Number of contacts</td><td>5,413 (29.1)</td><td>48,052 (24)</td><td>230,172 (35.4)</td></tr>
<tr><td>Cost of contacts, £</td><td>181,661 (976)</td><td>1,591,677 (787)</td><td>7,664,456 (1,178)</td></tr>
<tr><td colspan="4">Primary care prescriptions</td></tr>
<tr><td>Glucose-lowering therapies, £</td><td>170,589 (914)</td><td>1,686,164 (832)</td><td>3,309,968 (507)</td></tr>
<tr><td>Lipid-lowering therapy, £</td><td>4,970 (27)</td><td>65,657 (32)</td><td>204,442 (31)</td></tr>
<tr><td>Antihypertensives, £</td><td>6,587 (35)</td><td>78,381 (39)</td><td>220,087 (34)</td></tr>
<tr><td>Antiplatelets, £</td><td>1,560 (8)</td><td>10,561 (5)</td><td>47,336 (7)</td></tr>
<tr><td colspan="4">Secondary care admissions</td></tr>
<tr><td>Number of admissions</td><td>109 (0.6)</td><td>854 (0)</td><td>8,466 (1.3)</td></tr>
<tr><td>Number of emergency admissions</td><td>45 (0.2)</td><td>301 (0)</td><td>3,573 (0.5)</td></tr>
<tr><td>Total length of stay, days</td><td>184 (1.0)</td><td>2,557 (1)</td><td>39,760 (6.1)</td></tr>
</table>
</td><td>Costs derived from Unit Costs of Health and Social Care 2015 from PSSRU, costs have been presented in GBP. Some data potentially relevant to the economic model have been presented.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td></td><td></td><td>Frequency and costs were compared between cohorts before and after matching by propensity score using Poisson regression.</td><td><table><tr><td>Total cost of hospital admissions, £</td><td>141,403 (760)</td><td>1,444,848 (715)</td><td>13,637,849 (2,096)</td></tr></table>
*Data extracted here are for unmatched cohorts; data were also presented in the publication but not extracted here for cohorts matched by propensity score.</td><td></td></tr>
<tr><td>Huan et al. 2016[200]</td><td>Objective: to identify the frequency of hypoglycaemia in T1/T2DM patients requiring emergency care input.

Patients: a population-based study investigated all patients with diabetes in Tayside, Scotland, from 2009 to 2012 inclusive.</td><td>UK

Cost year: NR</td><td>Using unique patient identifiers, diabetes registry data were linked to hospital admission, emergency department attendance and ambulance emergency calls. Rates of hypoglycaemia were calculated.</td><td>Average bed stay for hypoglycaemia in T2DM patients: 6.8 days.

Estimated annual cost of hypoglycaemia in T2DM patients: £421,271 (£19 per patient).</td><td>Data were collected in Scotland and costs reported in GBP; cost year and tariffs used to calculate costs not specified.</td></tr>
<tr><td>Mitchell et al. 2013[201]</td><td>Objective: to assess the link between hypoglycaemic events, HbA1c, patient-reported outcomes, and healthcare resource use among patients with T2DM in the UK.

Patients: potential respondents were identified through the 2011 5EU National Health and Wellness Survey and the diabetes chronic ailment panel of</td><td>UK

Cost year: N/A</td><td>All measures were by self-report. Respondents were asked whether they had ever experienced a hypoglycaemic event, and also to indicate the number of times that they visited different healthcare providers in the preceding four weeks to ascertain their healthcare resource use. These included the physician who normally manages their T2DM (primary/secondary care), and other providers</td><td>Diabetes-related healthcare resource use in the preceding 4 weeks reported at the baseline survey for patients reporting hypoglycaemia and patients not experiencing hypoglycaemia:<table><tr><th rowspan="2">Resource Use</th><th colspan="2">Mean (SD)</th><th rowspan="2">p-value</th></tr><tr><th>Hypoglycaemia (n=365)</th><th>No hypoglycaemia (n=964)</th></tr><tr><td>4-week primary care physician visits</td><td>0.73 (1.05)</td><td>0.38 (0.66)</td><td><0.0001</td></tr><tr><td>4-week total visits</td><td>1.82 (2.50)</td><td>0.92 (1.51)</td><td><0.0001</td></tr><tr><td>4-week hospitalisations</td><td>0.16 (0.16)</td><td>0.06 (0.31)</td><td>0.0006</td></tr></table></td><td>Data were collected from UK patients for outcomes potentially of relevance to an economic model of ertugliflozin.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective and patient population</th><th>Country and cost year</th><th>Valuation methods</th><th>Cost and resource use data presented</th><th>Applicability to clinical practice in England and for cost-effectiveness analysis</th></tr>
<tr><td></td><td>Light Speed Research in the UK. Those who gave consent (n=3,224) were screened for a physician diagnosis of T2DM and current use of a prescription medicine for T2DM. Remaining patients (n=1,776) were directed to the first (baseline) of 6 questionnaires provided between February and July 2012, each separated by 4 weeks. 34% of patients (n=451) reported at the last follow-up and 12% (n=155) completed all follow-ups.</td><td></td><td>(nurses, dieticians, podiatrists).</td><td>Diabetes-related healthcare resource use in the preceding 4 weeks for patients reporting hypoglycaemia who completed all study surveys:<table><tr><th rowspan="2">Resource Use</th><th colspan="2">Mean (SD)</th><th rowspan="2">p-value</th></tr><tr><th>Hypoglycaemia (n=83)</th><th>No hypoglycaemia (n=72)</th></tr><tr><td>4-week primary care physician visits</td><td>0.43 (0.48)</td><td>0.31 (0.41)</td><td>0.0948</td></tr><tr><td>4-week total visits</td><td>1.07 (1.24)</td><td>0.69 (0.88)</td><td>0.0286</td></tr><tr><td>4-week hospitalisations</td><td>0.05 (0.15)</td><td>0.06 (0.24)</td><td>0.9661</td></tr></table></td><td></td></tr>
<tr><td>Willis et al. 2013[202]</td><td>Objectives: to collect information from patients with diabetes in three European countries, to outline the possible implications of hypoglycaemia on healthcare expenditure, and to highlight how this expenditure may be reduced through self-monitoring of blood glucose and prevention of both hyperglycaemia and hypoglycaemia.

Population: patients</td><td>UK, France, Germany (only UK data extracted here)

Cost year: N/A</td><td>Respondents completed a 10-minute questionnaire containing 11 key questions about their understanding, perceptions and daily experiences of hypoglycaemia, including questions that could ascertain healthcare resource use.

The approximate healthcare burden of hypoglycaemia was estimated assuming 460,000 T2DM insulin-</td><td>Mean number of pharmacist consultations about hypoglycaemia per insulin-treated T2DM patient in the UK during the previous 12 months: 1.0

Estimated number of emergency room visits due to hypoglycaemia by T2DM patients in the UK over 12 months: 9,000 (2% of 460,000 T2DM patients in the UK).</td><td>Data were collected from UK patients for outcomes potentially of relevance to an economic model of ertugliflozin.</td></tr>
</table>

Study	Objective and patient population	Country and cost year	Valuation methods	Cost and resource use data presented	Applicability to clinical practice in England and for cost-effectiveness analysis
	diagnosed with T1/T2DM in the LifeScan patient database were selected for inclusion in an online market-research survey. All patients had to be receiving insulin treatment (included oral therapy and insulin). 480 patients were selected from the UK.		treated patients in the UK.		

Abbreviations: A&E: accident and emergency; ALO: alogliptin; BI: basal insulin; CPRD: Clinical Practice Research Datalink; DPP4i: dipiptidyl peptidase 4 inhibitor; EBID: exenatide twice-daily; EMPA: empagliflozin; EQW: exenatide once-weekly; GBP: Great British Pound; GP: general practitioner; HCP: healthcare professional; HES: hospital episode statistics; HRG: Healthcare Resource Group; IQR: interquartile range; MET: metformin; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; NSHE: non-severe hypoglycaemic event; OAD: oral antidiabetic agent; PBO: placebo; PCP: primary care physician; PSSRU: Personal Social Services Research Unit; SHE: severe hypoglycaemic event; SITA: sitagliptin; SU: sulfonylurea; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; UK: United Kingdom.

Appendix J: Clinical outcomes and disaggregated results from the model

J.1 Clinical outcomes from the model

As the NMA in section 2.9 revealed that ertugliflozin provides similar health outcomes to the other SGLT-2is on a background of metformin with DPP-4is a cost-minimisation analysis has been conducted. As health outcomes were not required for the analysis they were not modelled.

J.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

As a cost-minimisation analysis has been conducted disaggregated cost-effectiveness results are not available.

Appendix K: Checklist of confidential information

Appendix L: Other outcomes in VERTIS SITA2 trial

Further to the outcomes reported within the NICE scope (Table 1), presented below are additional efficacy / safety evaluations and safety laboratory parameters assessed in the VERTIS SITA2 study. Additionally, more detailed information on outcomes relevant to this submission (e.g. HDL, LDL) are also provided.

H.1 Additional efficacy evaluations in VERTI SITA2 study

Proportion of subjects with HbA1c <7.0% (<53 mmol/mol)

Table L.1 shows the analysis of the proportion of subjects with an HbA1c <7.0% (<53 mmol/mol) at week 26, excluding data after initiation of glycaemic rescue therapy. The raw proportion of subjects with an HbA1c <7.0% was almost 2-times greater in the ertugliflozin 5 mg group and was more than 2-times greater in the ertugliflozin 15 mg group relative to the placebo group. The model-based odds of having an HbA1c <7.0% at week 26, using multiple imputation for subjects with missing week 26 data, were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (p<0.001 for both comparisons).

Table L.1 Analysis of Subjects with HbA1c <7.0% (<53 mmol/mol) at week 26 (Logistic Regression Using Multiple Imputation) (FAS: Excluding Rescue Approach)

Treatment	N	Number (%) of subjects with HbA1c <6.5% (raw proportion)	Adjusted Odds Ratio relative to Placebo*		
			Point estimate	95% CI	p-Value
PBO	153	26 (17.0)			
ERT 5 mg	156	50 (32.1)	3.16	(1.74, 5.72)	<0.001
ERT 15 mg	153	61 (39.9)	4.43	(2.44, 8.02)	<0.001

Abbreviations: HbA1c=hemoglobin A1c; CI= confidence interval; cLDA =constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; N = number of subjects in FAS.
*Adjusted Odds Ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycaemic medication (metformin + DPP-4 inhibitor /metformin + SU), covariates for baseline HbA1c and baseline eGFR (continuous). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Fasting Plasma Glucose (FPG)

Table L.2 shows the results of the analysis of change from baseline in FPG at week 26, excluding data after initiation of glycaemic rescue therapy. The LS mean reductions from baseline in FPG at week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (p<0.001 for both comparisons).

LS mean changes from baseline in FPG over time, excluding data after initiation of glycaemic rescue therapy, are plotted in Figure L.1. In the ertugliflozin 15 mg group, a reduction from baseline in FPG at week 6 (first scheduled post-randomisation assessment) was followed by subsequent small reductions at each time point through week 26. A similar

pattern was observed in the ertugliflozin 5 mg group except that FPG increased slightly between weeks 18 and 26. The magnitude of the reduction in FPG was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. In the placebo group, small fluctuations from baseline in FPG occurred through week 26.

Table L.2 FPG (mg/dL): Change from baseline at week 26 (cLDA) (FAS: Excluding Rescue Approach)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
PBO	152	169.62 (37.824)	120	160.93 (36.713)	153	-1.76 (-7.70, 4.18)
ERT 5 mg	156	167.67 (37.719)	137	140.92 (31.605)	156	-26.91 (-32.58, -21.24
ERT 15 mg	152	171.72 (39.060)	138	137.18 (29.412)	153	-33.04 (-38.71, -27.36)

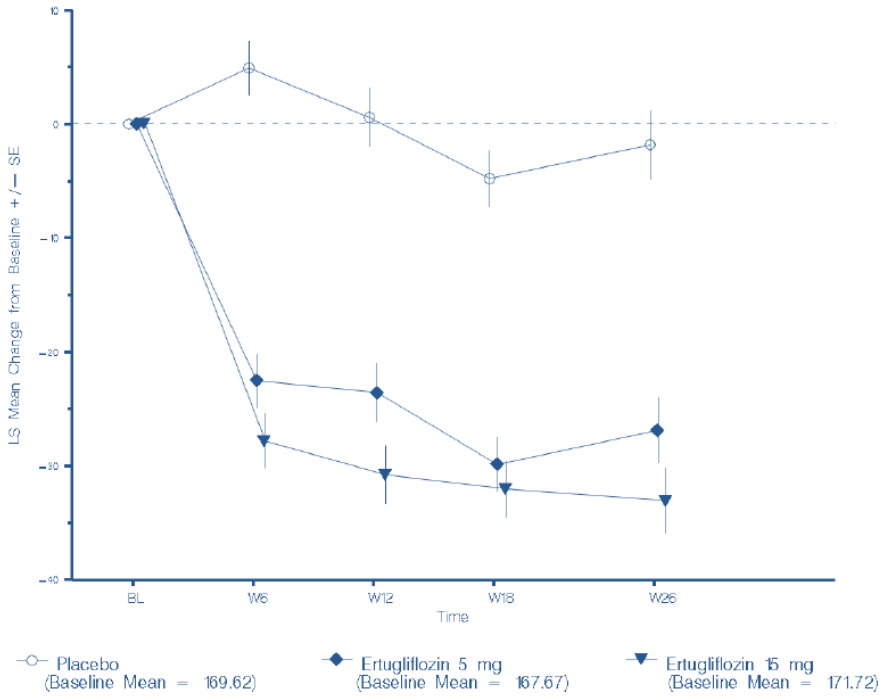
Pairwise comparison	Differences in LS means (95% CI)*	p-Value
Ertugliflozin 5 mg vs. Placebo	-25.15 (-32.76, -17.54)	<0.001
Ertugliflozin 15 mg vs. Placebo	-31.28 (-38.90, -23.66)	<0.001
Conditional pooled SD of change from baseline		31.49

Abbreviations: CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; FPG= Fasting plasma glucose

For baseline and week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at week 26, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

* Based on cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication (metformin + DPP-4 inhibitor /metformin + SU), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Figure L.1 FPG (mg/dL): LS Mean Change from baseline over Time (cLDA) (FAS: Excluding Rescue Approach)



Abbreviations: BL = baseline; cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error; W = week.

Subject receiving glycaemic rescue therapy through week 26

The analysis of the proportion of subjects who received glycaemic rescue medication is presented in Table L.3. A graphical display of the Kaplan-Meier estimates for cumulative percentage of subjects rescued is in Figure L.2. The cumulative percentage of subjects who received glycaemic rescue medication through week 26 in the ertugliflozin groups (≤2.0% in both groups) was lower than in the placebo group (16.3%) (nominal p<0.001 for both comparisons).

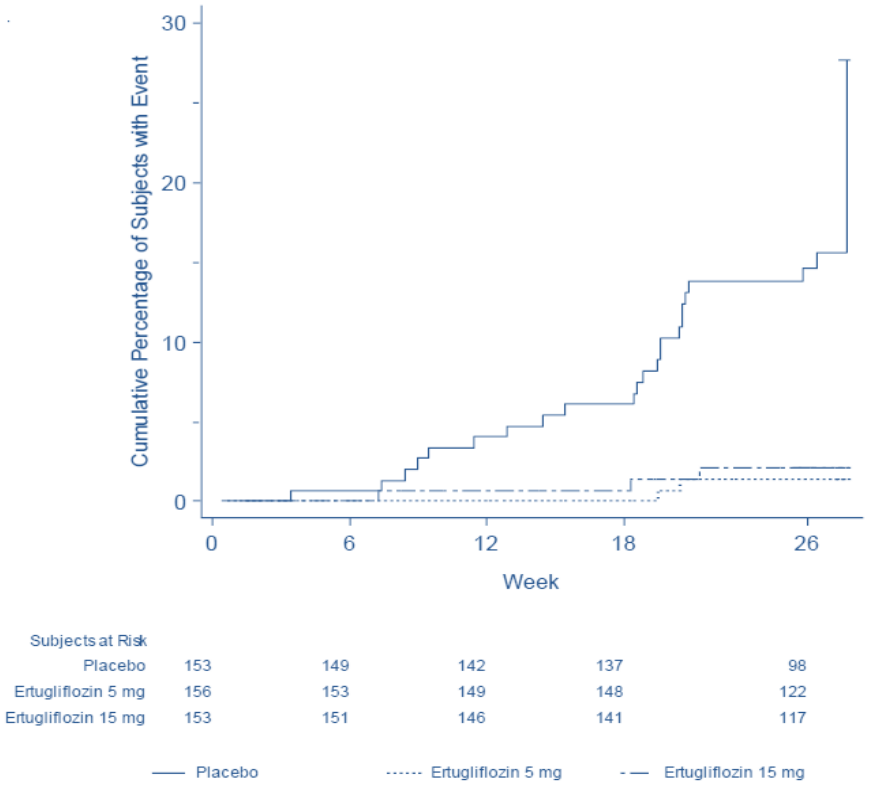
Table L.3 Analysis of subjects receiving glycaemic rescue medication at week 26 (APaT)

Treatment	N	(%)	Differences in % vs. Placebo	
			Estimate (95% CI)	p-Value*
Subjects in population				
PBO ERT 5 mg ERT 15 mg	153 156 153	-	-	-
With one or more subjects taking glycaemic rescue medication				
PBO ERT 5 mg	25 2	16.3 1.3	-15.1 (-21.9, -9.4)	<0.001

ERT 15 mg	3	2.0	- 14.4 (-21.3, -8.5)	<0.001

Abbreviations: CI = confidence interval; n = number of subjects.
*Based on Miettinen & Nurminen method.

Figure L.2 Cumulative percentage of subjects with glycaemic rescue therapy (Kaplan-Meyer Curves; APaT)



Abbreviations: BL= baseline; W= week

HOMA-β cell function

Table L.4 shows the results of the analysis of change from baseline in β-cell function assessed by HOMA-%β at week 26, excluding data after initiation of glycaemic rescue therapy. The LS mean increases from baseline at week 26 were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (nominal p<0.001 for both comparisons).

Table L.4 HOMA-β cell function (%): Change from baseline at week 26 (cLDA) (FAS: Excluding Rescue Approach)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
PBO	127	48.04 (30.733)	131	49.76 (29.299)	147	0.52 (-4.08, 5.12)
ERT 5 mg	140	47.99 (23.890)	141	161.40 (25.481)	153	13.28 (8.87, 17.68)
ERT 15 mg	131	48.54 (34.782)	138	61.19 (29.431)	151	12.43 (7.94, 16.93)
Pairwise comparison			**Differences in LS means (95% CI)***		**p-Value**	

Ertugliflozin 5 mg vs. Placebo Ertugliflozin 15 mg vs. Placebo	12.75 (6.83, 18.68) 11.91 (5.94, 17.88)	<0.001 <0.001
Conditional pooled SD of change from baseline		24.38

Abbreviations: CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation;
For baseline and week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at week 26, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.
* Based on cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication (metformin + DPP-4 inhibitor /metformin + SU), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

H.2 Additional safety / laboratory parameters information in VERTI MET study

Hypovolemia

Table L.5 presents the Tier 1 analysis of hypovolemia AEs, excluding data after initiation of glycaemic rescue therapy. The incidences of hypovolemia AEs were low and similar across the 3 treatment groups, reported for 1 subject in the ertugliflozin 5 mg group, 1 subject in the placebo group, and no subjects in the ertugliflozin 15 mg group.

Table L.5 Analysis of subjects with Tier 1 Aes (Hypovolemia) (APaT: Excluding rescue approach)

Treatment	N	(%)	Differences in % vs. Placebo	
			Estimate (95% CI)	p-Value*
Subjects in population				
PBO ERT 5 mg ERT 15 mg	153 156 153	-	-	-
With one or more subjects AEs associated with hypovolemia				
PBO ERT 5 mg ERT 15 mg	1 1 0	0.7 0.6 0.0	 -0.0 (-3.0, 3.0) -0.7 (-3.6, 1.8)	 0.989 0.317

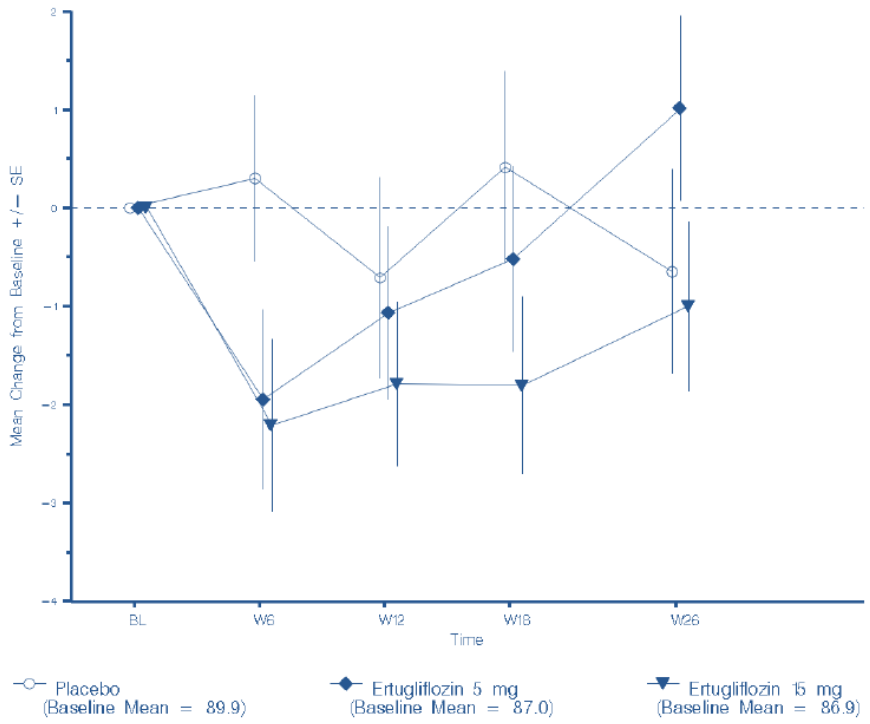
Abbreviations: AE= adverse event; CI, confidence interval; n, number of subjects: vs = versus
*Based on Miettinen & Nurminen method

Estimated Glomerular Filtration Rate (eGFR)

Mean changes over time in eGFR are presented in Figure L.3, excluding data after initiation of glycaemic rescue therapy.

The mean eGFR value decreased modestly from baseline at week 6 in the ertugliflozin 5 mg and 15 mg groups but returned to baseline in the ertugliflozin 5 mg group and increased toward baseline in the ertugliflozin 15 mg group at week 26. Small mean changes around the baseline value were observed in the placebo group through week 26.

Figure L.3 Mean change from baseline in eGFR (mL/min/1.73m^2) over time (Mean ± SE; APaT: excluding rescue approach)



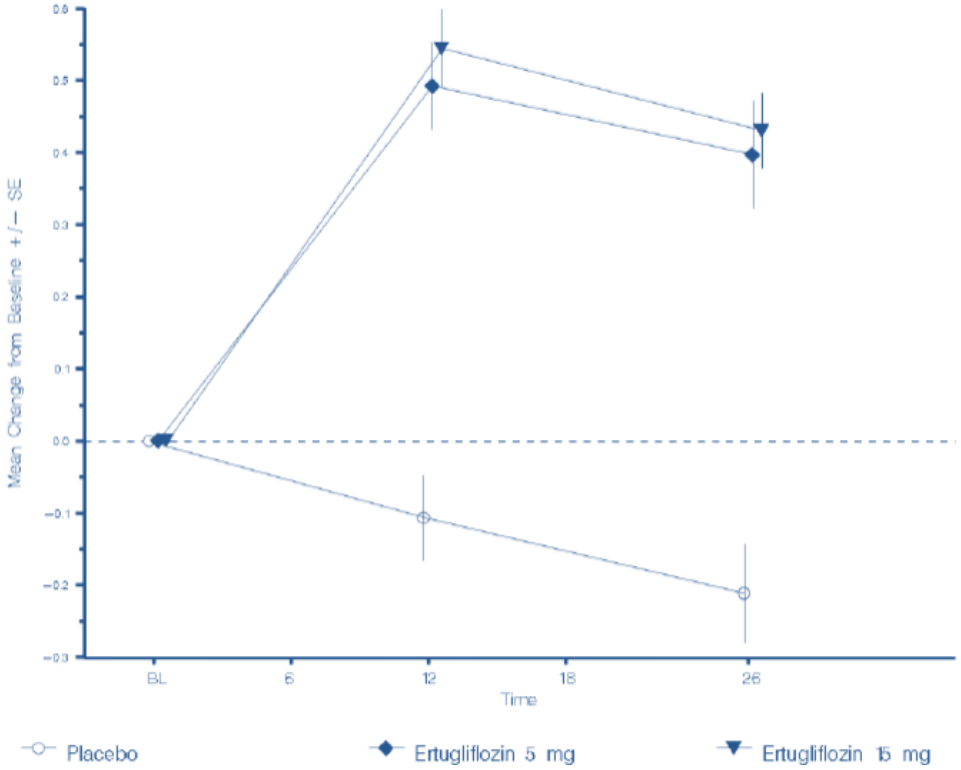
Abbreviations: BL = Baseline; eGFR = estimated glomerular filtration rate; SE = standard error; W = week.

Haemoglobin

Mean changes over time in haemoglobin are presented in Figure L.4, excluding data after initiation of glycaemic rescue therapy. A small mean increase from baseline in haemoglobin was observed in the ertugliflozin 5 mg and 15 mg groups at week 12 which persisted through week 26. A small mean decrease from baseline was observed in the placebo group at weeks 12 and 26.

No subjects across the 3 treatment groups had an AE reported that was associated with a change in haemoglobin. Six (4.0%), 2 (1.4%), and 1 (0.7%) subjects in the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups, respectively, met the PDLC criterion of an increase from baseline in haemoglobin >2 g/dL (at least 1 occurrence) (excluding data after initiation of glycaemic rescue therapy;

Figure L.4 Mean change from baseline in Haemoglobin (g/dL) over time (Mean ± SE; APaT: excluding rescue approach)



Abbreviations: BL = Baseline; SE = standard error; W = week.

LDL-C

Table L.6 presents the LS mean percent change from baseline in LDL-C at week 26, excluding data after initiation of glycaemic rescue therapy.

The LS mean percent increase from baseline in LDL-C at week 26 was small in each treatment group and not meaningfully different between the ertugliflozin groups relative to the placebo group.

Table L.6 LDL-C (mg/dL): Percent change from baseline at week 26 (cLDA) (APaT: Excluding Rescue Approach)

Treatment	Baseline		Week 26		Percent Change from baseline at week 26	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
PBO	148	94.0 (36.0)	135	92.2 (33.6)	130	4.45 (-0.43, 9.34)
ERT 5 mg	152	92.4 (31.5)	145	92.7 (31.9)	141	3.86 (-0.84, 8.56)
ERT 15 mg	147	96.2 (35.0)	139	97.3 (34.9)	133	5.77 (0.95, 10.59)
Estimated difference			**Differences in LS means (95% CI)***			
Ertugliflozin 5 mg vs. Placebo			-0.59 (-7.17, 5.98)			
Ertugliflozin 15 mg vs. Placebo			1.31 (-5.36, 7.98)			
Conditional pooled SD of change from baseline						29.58

Abbreviations: APaT = All population as treated; CI = confidence interval; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol; LS = least squares; SD = standard deviation; vs = versus.
*Based on cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication, baseline eGFR (continuous), menopausal status randomization stratum and the interaction of time by treatment. Time was treated as a categorical variable

HDL-C

Table L.7 presents the analysis of the LS mean percent change from baseline in HDL-C at week 26, excluding data after initiation of glycaemic rescue therapy. The mean percent increase from baseline in HDL-C at week 26 was higher in the ertugliflozin groups relative to the placebo group. The mean percent increase was similar in the ertugliflozin 5 and 15 mg groups.

Table L.7 HDL-C (mg/dL): Percent change from baseline at week 26 (cLDA) (APaT: Excluding Rescue Approach)

Treatment	Baseline		Week 26		Percent Change from baseline at week 26	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
PBO	148	46.3 (12.2)	136	46.4 (11.2)	131	2.67 (-0.38, 5.73)
ERT 5 mg	152	48.6 (14.0)	147	51.3 (15.7)	143	6.91 (3.99, 9.84)
ERT 15 mg	147	47.1 (12.5)	140	50.1 (13.1)	134	7.09 (4.07, 10.11)
Estimated difference			**Differences in LS means (95% CI)***			
Ertugliflozin 5 mg vs. Placebo			4.24 (0.07, 8.41)			
Ertugliflozin 15 mg vs. Placebo			4.42 (0.18, 8.65)			
Conditional pooled SD of change from baseline					18.12	

Abbreviations: APaT = All population as treated; CI = confidence interval; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; LS = least squares; SD = standard deviation; vs = versus.
*Based on cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

Appendix M: Overview on Phase B results of the VERTIS SITA2 trial

Ertugliflozin triple therapy: VERTIS SITA2 Phase A + B outcomes (0 – 52 weeks)

- **Phase A + B efficacy outcomes in VERTI SITA2 study – week 52**

Table M.1 Summary of efficacy outcomes in Phase A + B of VERTIS SITA2 study (FAS: excluding rescue approach)

Treatment	Baseline		Change from baseline at week 52
	N	Mean (SD)	LS mean (95% CI)
HbA1c (%)			
ERTU5 ERTU15	156 153	8.1 (0.9) 8.0 (0.8)	–0.7 (–0.9, –0.6) –0.8 (–1.0, –0.7)
FPG (mmol/L)			
ERTU5 ERTU15	156 153	9.3 (2.1) 9.5 (2.2)	–1.4 (–1.7, –1.1) –1.5 (–1.8, –1.2)
Body weight (kg)			
ERTU5 ERTU15	156 153	87.6 (18.6) 86.6 (19.5)	–3.5 (–4.1, –2.9) –2.8 (–3.4, –2.2)
SBP (mmHg)			
ERTU5 ERTU15	156 153	132.1 (12.5) 131.6 (13.2)	–4.2 (–6.0, –2.3) –4.1 (–6.0, –2.2)
DBP (mmHg)			
ERTU5 ERTU15	156 153	78.4 (7.3) 78.8 (7.2)	–1.5 (–2.7, –0.3) –1.4 (–2.6, –0.2)

Abbreviations:
Statistical testing was not performed at Week 52.

- **Phase A + B safety outcomes in VERTI SITA2 study – week 52**

Table M.2: Summary of safety outcomes in Phase A + B of VERTIS SITA2 study (ASaT: including rescue approach)

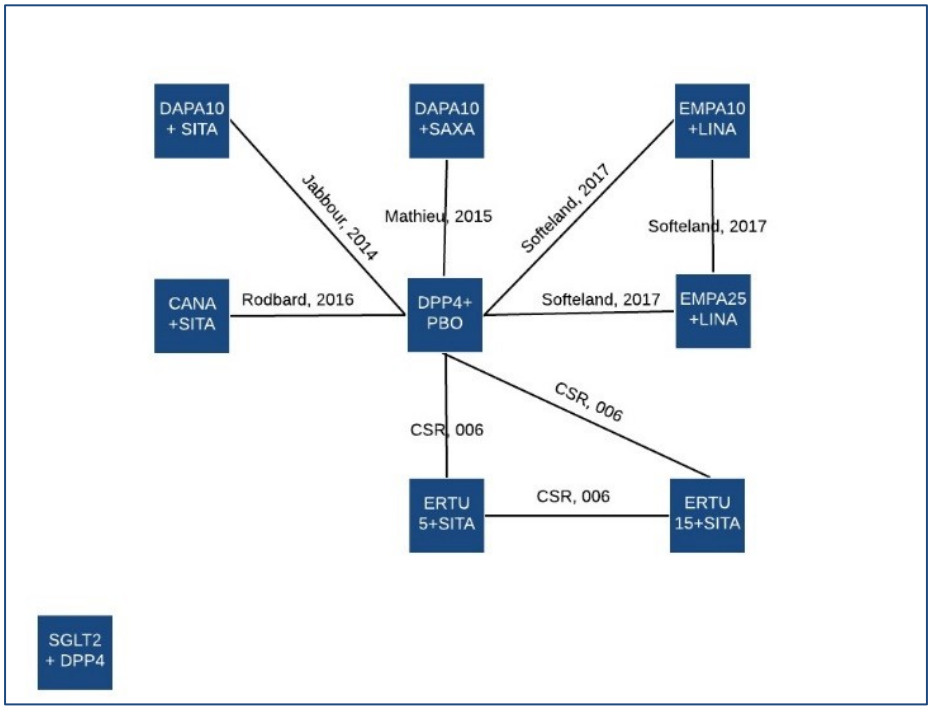
Event	ERTU5 N = 156	ERTU15 N = 153
One or more AEs	90 (57.7)	92 (60.1)
AEs related to study drug[a]	19 (12.2)	32 (20.9)
One or more SAE	13 (8.3)	3 (2.0)
AEs leading to discontinuation	7 (4.5)	6 (3.9)
Death	0 (0.0)	0 (0.0)
Tier 1 AEs		
Genital mycotic infection (women)	9 (12.0)*	10 (14.1)*
Genital mycotic infection (men)	4 (4.9)*	3 (3.7)
UTIs	5 (3.2)	11 (7.2)
Symptomatic hypoglycaemia	7 (4.5)	3 (2.0)
Hypovolemia	1 (0.6)	0 (0.0)

Abbreviations:
* p-value < 0.05 vs. PBO
[a] As reported by the investigator

Appendix N: NMA – outcome-specific network diagrams

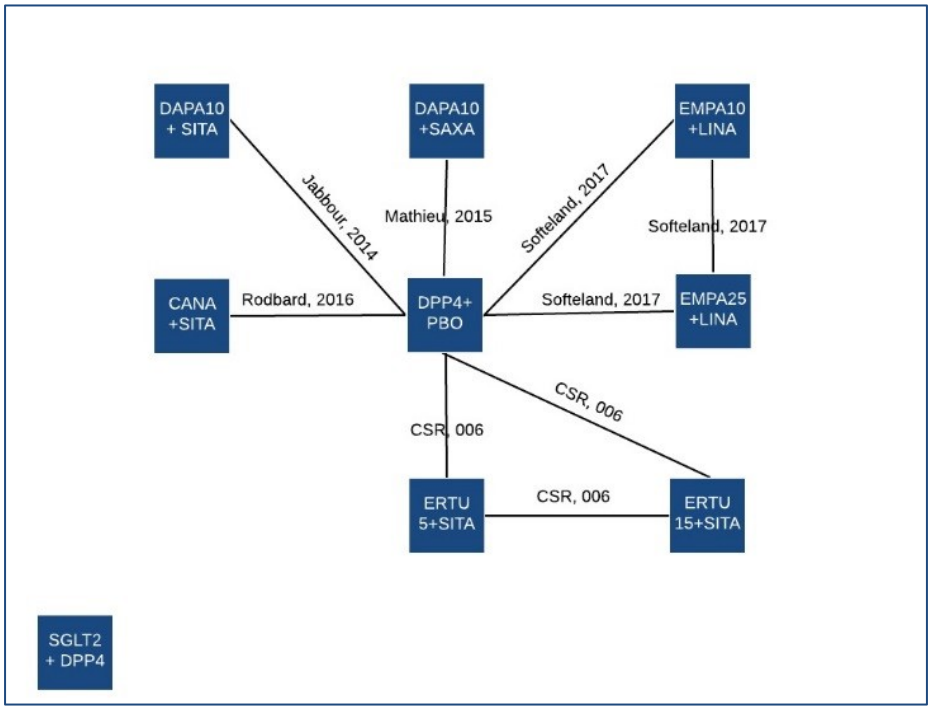
Ertugliflozin triple therapy

Figure N.1: Triple therapy - HbA1c Change (%) Network Diagram



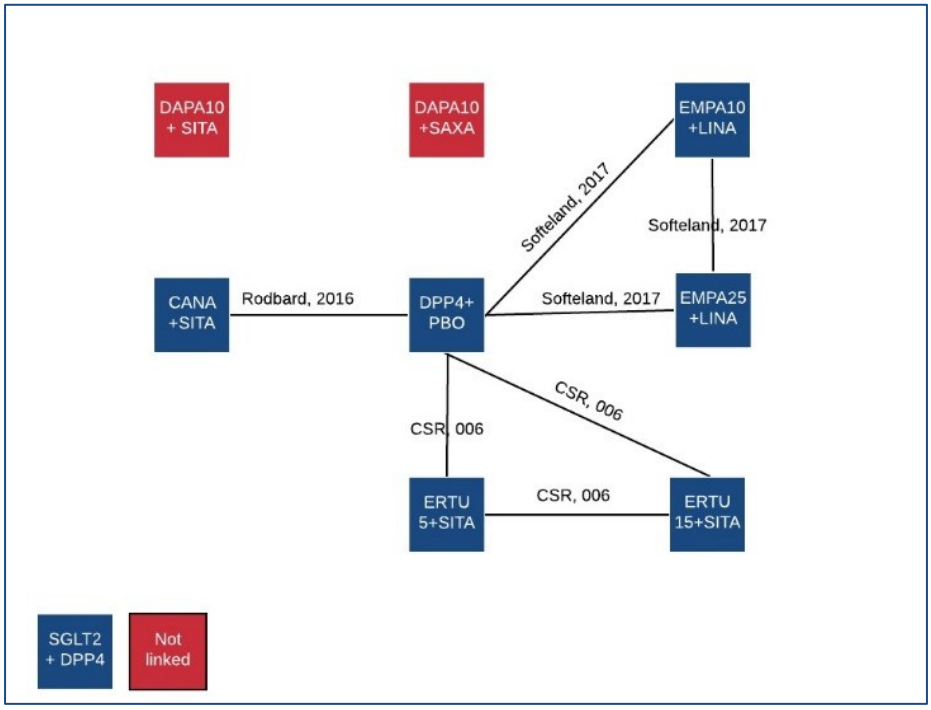
Note: All treatment arms included metformin

Figure N.2: Triple therapy - Weight Change (kgs) Network Diagram



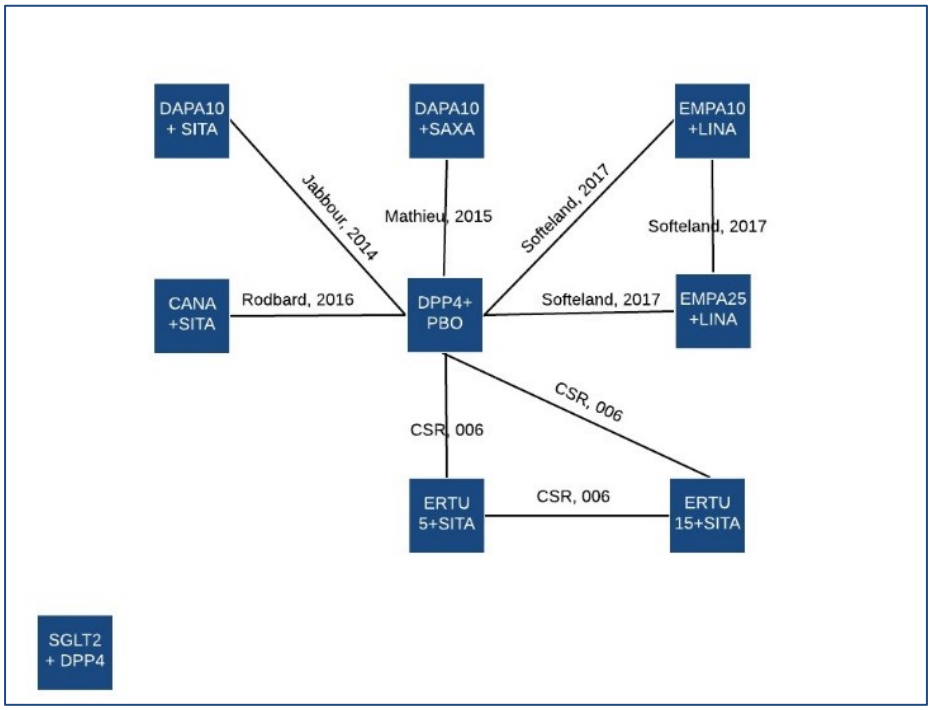
Note: All treatment arms included metformin

Figure N.3: Triple Therapy - SBP Change (mmHg) Network Diagram



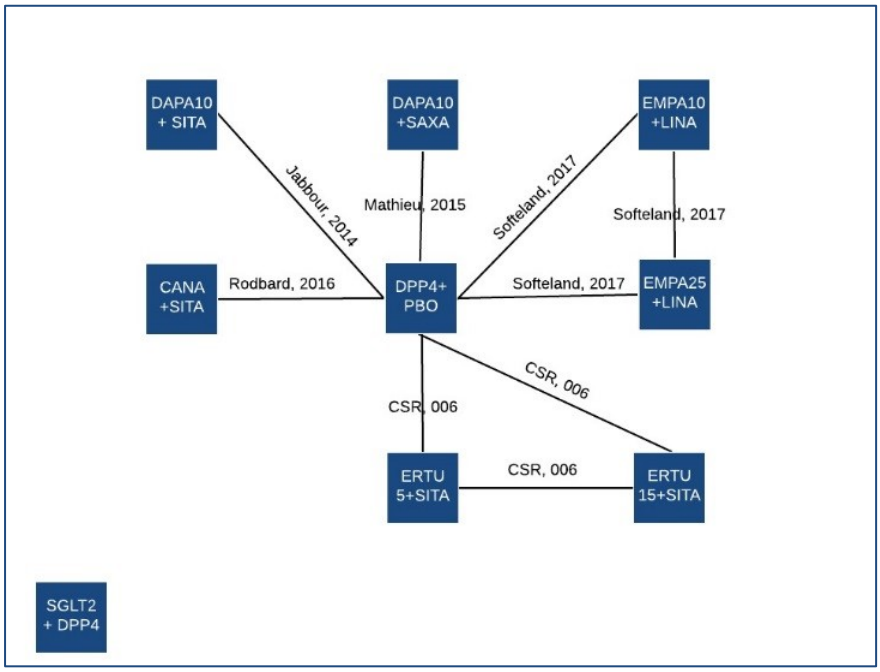
Note: All treatment arms included metformin

Figure N.4: Triple therapy - HbA1c in target (<7.0%) Network Diagram



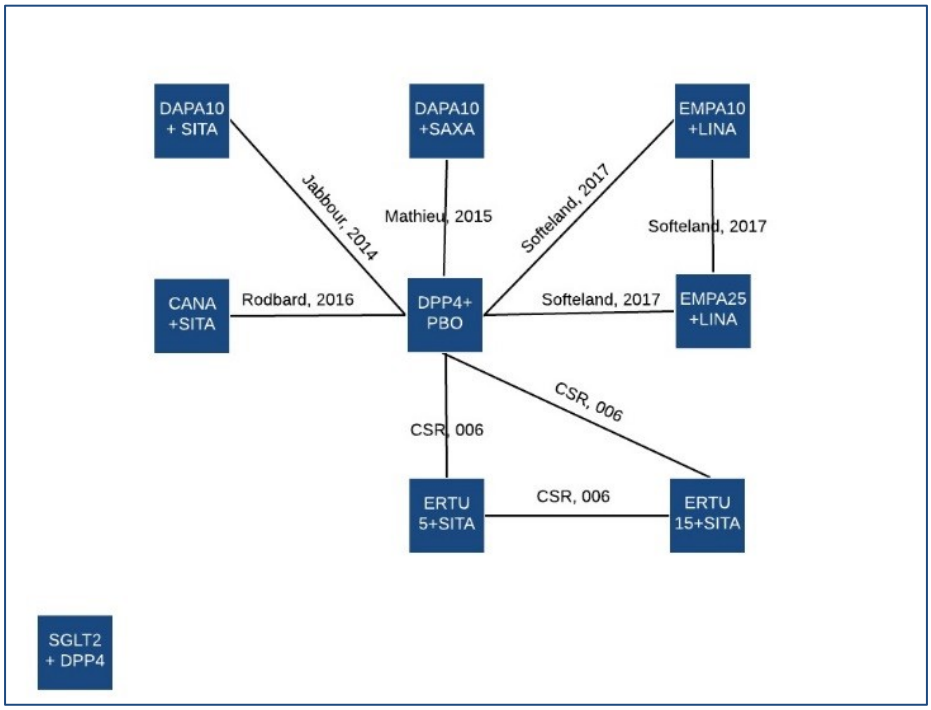
Note: All treatment arms included metformin

Figure N.5: Triple therapy - UTIs Network Diagram



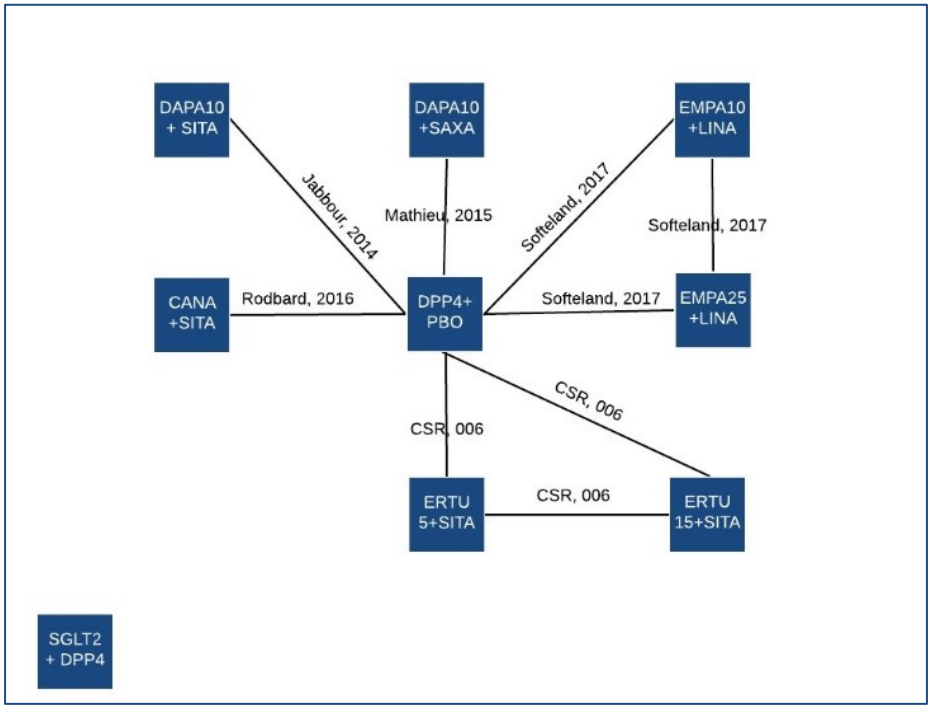
Note: All treatment arms included metformin

Figure N.6: Triple therapy - AEs Network Diagram



Note: All treatment arms included metformin

Figure N.7: Triple therapy - GTIs Network Diagram



Note: All treatment arms included metformin

Appendix O: Effect modifiers

Baseline HbA1c varied for triple therapy, from a low of 7.9% to a high of 8.5%. All included studies were multinational, which was reflected in the reduced variation in weight and BMI (where available) compared to mono and dual therapy. Only 3 of 5 studies reported baseline SBP, making interpretation of this outcome difficult. There was limited variation in age. Mathieu 2015 reported 54% females, compared to 41%-43% for the remaining studies, which may adversely increase rates of UTIs and GTIs all else being equal versus the other studies.

Figure O.1: Triple therapy – Pooled study baseline HbA1c (%)

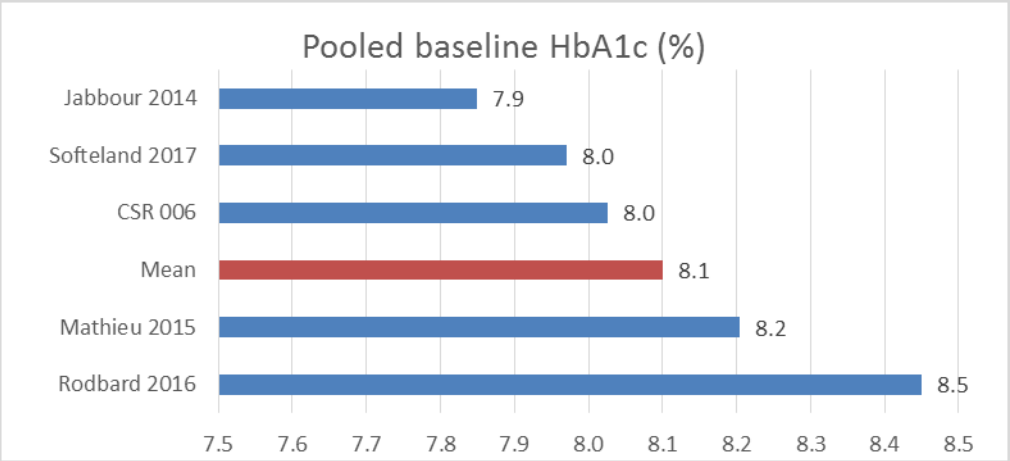


Figure O.2: Triple therapy – Pooled study baseline weight (kgs)

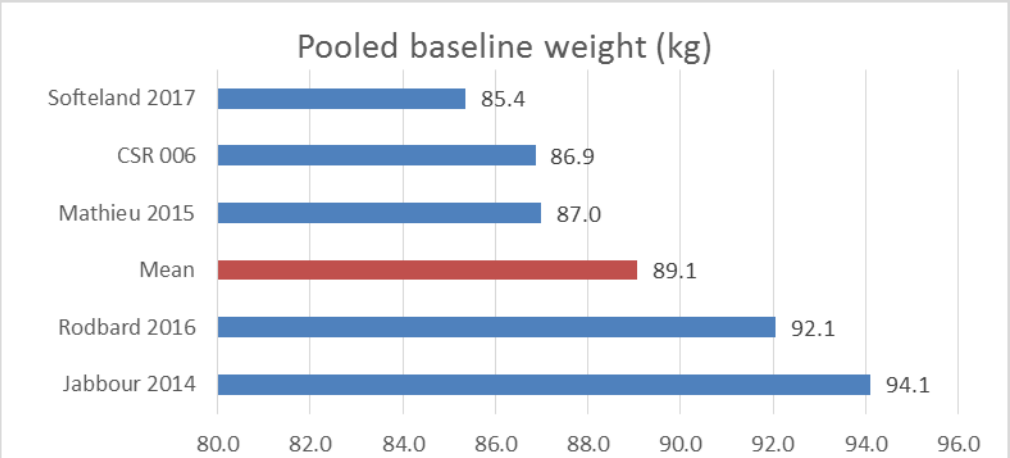
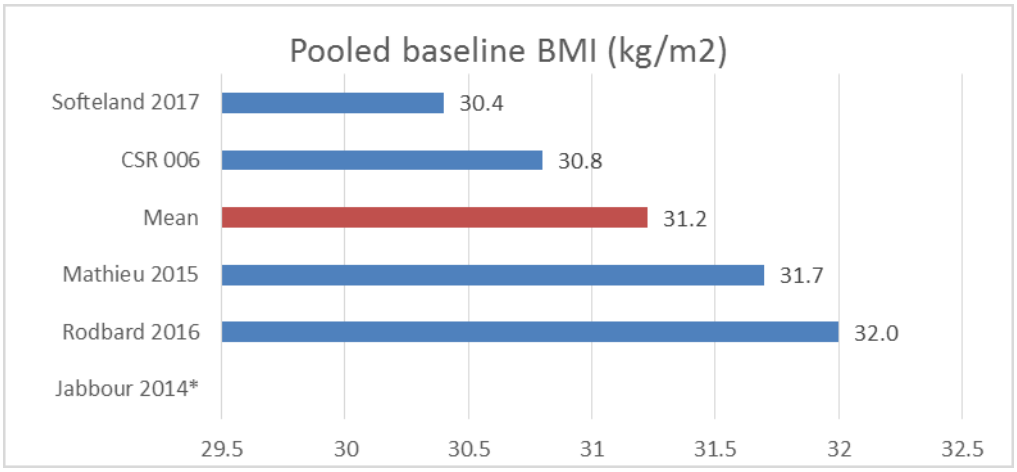
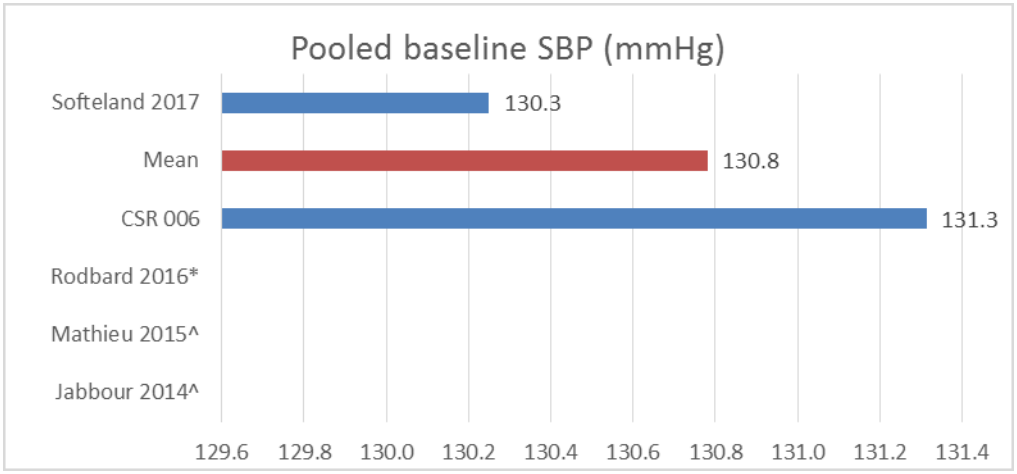


Figure O.3: Triple therapy – Pooled study baseline BMI (kg/m2)



* Baseline NR

Figure O.4: Triple therapy – Pooled study baseline SBP (mmHg)



^ Outcome and baseline NR, * Baseline NR

Figure O.5: Triple therapy – Pooled study baseline age (years)

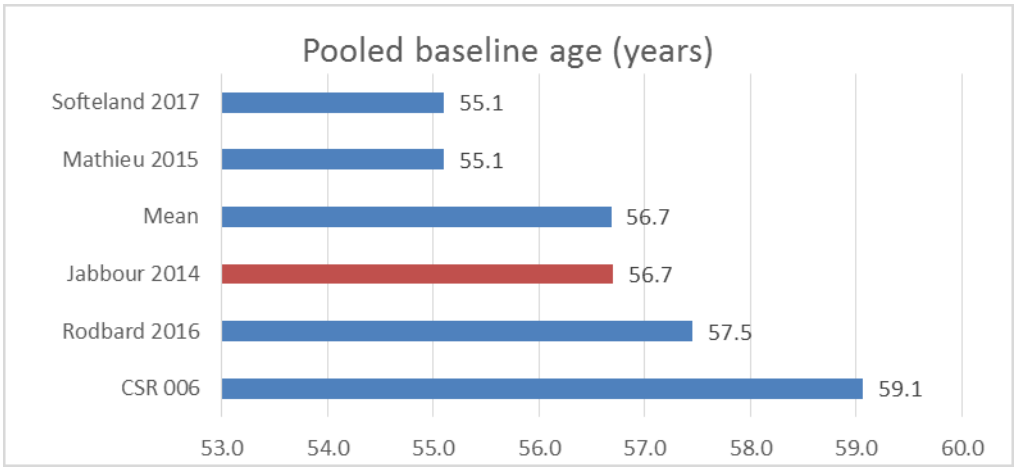
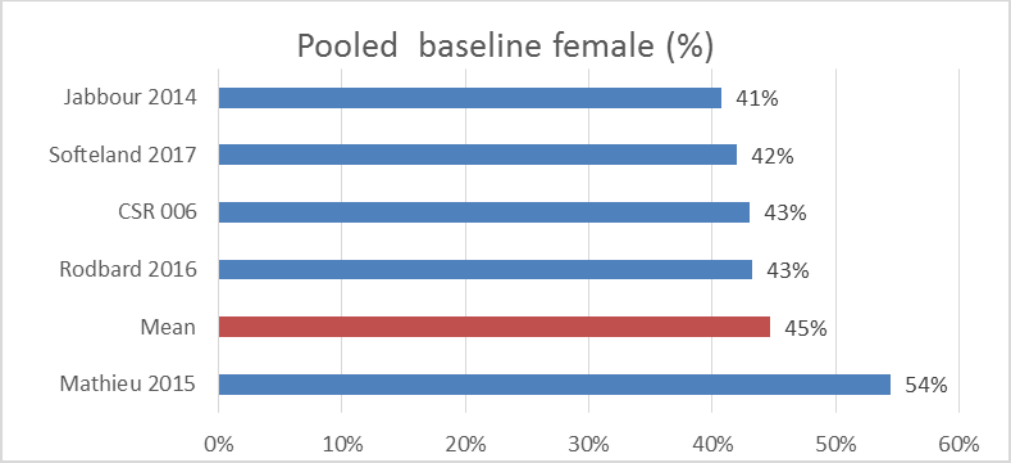


Figure O.6: Triple therapy – Pooled study baseline female (%)



Appendix P: NMA – additional base case results

- **Triple therapy**

Table P.1: HbA1c Change (%) Median difference (95% CrI): Random Effects

	PBO+DPP4+MET	Ertu5+Sita+MET	Ertu15+Sita+MET	Dapa10+Sita+MET	Dapa10+Saxa+MET	Cana+Sita+MET	Empa10+Lina+MET	Empa25+Lina+MET
PBO+DPP4+MET		-0.69 (-6.97 to 5.56)	-0.77 (-7.05 to 5.53)	-0.4 (-6.66 to 5.88)	-0.72 (-7.01 to 5.58)	-0.9 (-7.16 to 5.39)	-0.79 (-7.08 to 5.51)	-0.7 (-7 to 5.59)
Ertu5+Sita+MET	0.69 (-5.56 to 6.97)		-0.08 (-6.35 to 6.21)	0.29 (-8.55 to 9.13)	-0.02 (-8.89 to 8.86)	-0.21 (-9.08 to 8.67)	-0.1 (-8.99 to 8.82)	-0.01 (-8.89 to 8.89)
Ertu15+Sita+MET	0.77 (-5.53 to 7.05)	0.08 (-6.21 to 6.35)		0.37 (-8.51 to 9.26)	0.05 (-8.81 to 8.95)	-0.13 (-9 to 8.78)	-0.02 (-8.94 to 8.89)	0.07 (-8.84 to 8.95)
Dapa10+Sita+MET	0.4 (-5.88 to 6.66)	-0.29 (-9.13 to 8.55)	-0.37 (-9.26 to 8.51)		-0.32 (-9.21 to 8.56)	-0.5 (-9.39 to 8.34)	-0.38 (-9.27 to 8.49)	-0.3 (-9.19 to 8.6)
Dapa10+Saxa+MET	0.72 (-5.58 to 7.01)	0.02 (-8.86 to 8.89)	-0.05 (-8.94 to 8.81)	0.32 (-8.56 to 9.21)		-0.18 (-9.08 to 8.69)	-0.07 (-8.99 to 8.82)	0.02 (-8.89 to 8.92)
Cana+Sita+MET	0.9 (-5.39 to 7.16)	0.21 (-8.67 to 9.08)	0.13 (-8.78 to 9)	0.5 (-8.34 to 9.39)	0.18 (-8.69 to 9.08)		0.11 (-8.75 to 9.01)	0.2 (-8.7 to 9.06)
Empa10+Lina+MET	0.79 (-5.51 to 7.08)	0.1 (-8.82 to 8.99)	0.02 (-8.89 to 8.94)	0.38 (-8.49 to 9.27)	0.07 (-8.82 to 8.99)	-0.11 (-9.01 to 8.75)		0.09 (-6.21 to 6.39)
Empa25+Lina+MET	0.7 (-5.59 to 7)	0.01 (-8.89 to 8.89)	-0.07 (-8.95 to 8.84)	0.3 (-8.6 to 9.19)	-0.02 (-8.92 to 8.89)	-0.2 (-9.06 to 8.7)	-0.09 (-6.39 to 6.21)	

Bold values indicate significant results.

Table P.2: Weight Change (kgs) Median difference (95% CrI): Random Effects

	PBO+DPP4+MET	Ertu5+Sita+MET	Ertu15+Sita+MET	Dapa10+Sita+MET	Dapa10+Saxa+MET	Cana+Sita+MET	Empa10+Lina+MET	Empa25+Lina+MET
PBO+DPP4+MET		-2.03 (-8.31 to 4.27)	-1.72 (-8.03 to 4.59)	-2.1 (-8.44 to 4.24)	-1.5 (-7.83 to 4.83)	-1.75 (-8.07 to 4.56)	-2.76 (-9.04 to 3.56)	-2.22 (-8.53 to 4.11)
Ertu5+Sita+MET	2.03 (-4.27 to 8.31)		0.31 (-5.99 to 6.63)	-0.07 (-9.01 to 8.87)	0.53 (-8.39 to 9.47)	0.28 (-8.68 to 9.2)	-0.73 (-9.64 to 8.19)	-0.18 (-9.13 to 8.74)
Ertu15+Sita+MET	1.72 (-4.59 to 8.03)	-0.31 (-6.63 to 5.99)		-0.38 (-9.31 to 8.53)	0.22 (-8.73 to 9.17)	-0.03 (-9.02 to 8.9)	-1.04 (-9.97 to 7.9)	-0.49 (-9.45 to 8.43)
Dapa10+Sita+MET	2.1 (-4.24 to 8.44)	0.07 (-8.87 to 9.01)	0.38 (-8.53 to 9.31)		0.6 (-8.39 to 9.56)	0.35 (-8.6 to 9.27)	-0.65 (-9.56 to 8.3)	-0.12 (-9.02 to 8.84)
Dapa10+Saxa+MET	1.5 (-4.83 to 7.83)	-0.53 (-9.47 to 8.39)	-0.22 (-9.17 to 8.73)	-0.6 (-9.56 to 8.39)		-0.25 (-9.22 to 8.7)	-1.26 (-10.21 to 7.66)	-0.71 (-9.68 to 8.25)
Cana+Sita+MET	1.75 (-4.56 to 8.07)	-0.28 (-9.2 to 8.68)	0.03 (-8.9 to 9.02)	-0.35 (-9.27 to 8.6)	0.25 (-8.7 to 9.22)		-1.01 (-9.95 to 7.96)	-0.46 (-9.43 to 8.5)
Empa10+Lina+MET	2.76 (-3.56 to 9.04)	0.73 (-8.19 to 9.64)	1.04 (-7.9 to 9.97)	0.65 (-8.3 to 9.56)	1.26 (-7.66 to 10.21)	1.01 (-7.96 to 9.95)		0.54 (-5.79 to 6.85)

Empa25+ Lina+MET	2.22 (-4.11 to 8.53)	0.18 (-8.74 to 9.13)	0.49 (-8.43 to 9.45)	0.12 (-8.84 to 9.02)	0.71 (-8.25 to 9.68)	0.46 (-8.49 to 9.43)	-0.54 (-6.85 to 5.79)	

Bold values indicate significant results.

Table P.3: SBP change (mmHg) Median difference (95% CrI): Random Effects

	PBO+DPP 4+MET	Ertu5+ Sita+MET	Ertu15+ Sita+MET	Cana+ Sita+MET	Empa10+ Lina+MET	Empa25+ Lina+MET
PBO+DPP 4+MET		-2.92 (-9.57 to 3.7)	-3.92 (-10.57 to 2.73)	-5.84 (-12.67 to 0.99)	-1.31 (-8.1 to 5.46)	-2.62 (-9.42 to 4.17)
Ertu5+ Sita+MET	2.92 (-3.7 to 9.57)		-1.01 (-7.65 to 5.61)	-2.93 (-12.4 to 6.61)	1.61 (-7.88 to 11.1)	0.3 (-9.18 to 9.79)
Ertu15+ Sita+MET	3.92 (-2.73 to 10.57)	1.01 (-5.61 to 7.65)		-1.91 (-11.47 to 7.65)	2.61 (-6.9 to 12.14)	1.31 (-8.19 to 10.85)
Cana+ Sita+MET	5.84 (-0.99 to 12.67)	2.93 (-6.61 to 12.4)	1.91 (-7.65 to 11.47)		4.53 (-5.1 to 14.15)	3.22 (-6.47 to 12.86)
Empa10+ Lina+MET	1.31 (-5.46 to 8.1)	-1.61 (-11.1 to 7.88)	-2.61 (-12.14 to 6.9)	-4.53 (-14.15 to 5.1)		-1.31 (-8.03 to 5.43)
Empa25+ Lina+MET	2.62 (-4.17 to 9.42)	-0.3 (-9.79 to 9.18)	-1.31 (-10.85 to 8.19)	-3.22 (-12.86 to 6.47)	1.31 (-5.43 to 8.03)	

Bold values indicate significant results.

Appendix Q: NMA – non-converged analyses

- Triple therapy

Table Q.1: GTI NMA summary statistics

	Fixed-effects model
DIC	58.87
Total residual deviance (95% CrI)	13.05 (4.81 to 25.25)
Data points	12

Table Q.2: GTIs Median Odds Ratio (CrI): Fixed Effects

	PBO+DPP 4+MET	Ertu5+ Sita+MET	Ertu15+ Sita+MET	Dapa10+ Sita+MET	Dapa10+ Saxa+MET	Cana+ Sita+MET	Empa10+ Lina+MET	Empa25+ Lina+MET
PBO+DPP 4+MET		18.18 (1.24 to 8235)	13.99 (0.87 to 6290)	0.03 (0 to 0.18)	11.51 (1.76 to 332.9)	8.59 (1.21 to 250.9)	0.98 (0.1 to 9.55)	2.87 (0.56 to 23.21)
Ertu5+ Sita+MET	0.06 (0 to 0.81)		0.77 (0.16 to 3.37)	0 (0 to 0.05)	0.64 (0 to 45.09)	0.47 (0 to 34.2)	0.05 (0 to 1.91)	0.15 (0 to 4.89)
Ertu15+ Sita+MET	0.07 (0 to 1.15)	1.3 (0.3 to 6.18)		0 (0 to 0.07)	0.83 (0 to 62.49)	0.61 (0 to 46.87)	0.06 (0 to 2.65)	0.2 (0 to 6.79)
Dapa10+ Sita+MET	32.14 (5.42 to 899.4)	750.6 (20.87 to 561100)	576 (15.13 to 429800)		442.7 (25.37 to 38960)	329 (18.05 to 29640)	34.3 (1.72 to 1683)	102.2 (7.86 to 4429)
Dapa10+ Saxa+MET	0.09 (0 to 0.57)	1.57 (0.02 to 868.7)	1.2 (0.02 to 676.9)	0 (0 to 0.04)		0.74 (0.02 to 34.23)	0.08 (0 to 1.66)	0.24 (0.01 to 4.16)
Cana+ Sita+MET	0.12 (0 to 0.83)	2.13 (0.03 to 1157)	1.63 (0.02 to 899.3)	0 (0 to 0.06)	1.35 (0.03 to 62.88)		0.11 (0 to 2.33)	0.33 (0.01 to 5.84)
Empa10+ Lina+MET	1.02 (0.1 to 9.99)	20.58 (0.52 to 11750)	15.77 (0.38 to 9021)	0.03 (0 to 0.58)	12.7 (0.6 to 642.1)	9.39 (0.43 to 482.5)		2.92 (0.57 to 23.64)
Empa25+ Lina+MET	0.35 (0.04 to 1.78)	6.55 (0.2 to 3311)	5.04 (0.15 to 2553)	0.01 (0 to 0.13)	4.13 (0.24 to 161.6)	3.05 (0.17 to 123.5)	0.34 (0.04 to 1.74)	

Bold values indicate significant results.

Appendix R: WinBUGS code

- **FEM binary outcomes**


```
# Binomial likelihood, logit link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

for (c in 1:(nt-1)) {

 for (k in (c+1):nt) {
      lor[c,k] <- (d[k]-d[c])
       lor[k,c] <- (d[c]-d[k])
       or[c,k] <- exp((d[k]-d[c]))
       or[k,c] <- exp((d[c]-d[k]))
                                                          }
 }
}                                   # *** PROGRAM ENDS
```

Data

Initial Values

Results

- **FEM continuous outcomes**


```
# Normal likelihood, identity link
# Fixed effects model
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)      # calculate variances
        prec[i,k] <- 1/var[i,k]         # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
        theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])              #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

for (c in 1:(nt-1)) {
 for (k in (c+1):nt) {
      diff[c,k] <- (d[k]-d[c])
       diff[k,c] <- (d[c]-d[k])
                                                              }
 }
}                                       # *** PROGRAM ENDS
```

Data

Initial Values

Results

- **REM binary outcomes**


```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))          }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])              # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)      # vague prior for between-trial SD
tau <- pow(sd,-2)    # between-trial precision = (1/between-trial variance)

for (c in 1:(nt-1)) {

 for (k in (c+1):nt) {
      lor[c,k] <- (d[k]-d[c])
       lor[k,c] <- (d[c]-d[k])
       or[c,k] <- exp((d[k]-d[c]))
       or[k,c] <- exp((d[c]-d[k]))
                                                          }
 }
}                                       # *** PROGRAM ENDS
```

Data

Initial Values

Results

- **REM continuous outcomes**


```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])              #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)      # vague prior for between-trial SD
tau <- pow(sd,-2)    # between-trial precision = (1/between-trial variance)

for (c in 1:(nt-1)) {

 for (k in (c+1):nt) {
      diff[c,k] <- (d[k]-d[c])
       diff[k,c] <- (d[c]-d[k])
                                                          }
 }

}                                       # *** PROGRAM ENDS
```

Data

Initial Values

Results

Appendix S: References – full PDFs

Please note this appendix has been sent as a separate folder to this document.

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Single technology appraisal

Ertugliflozin in triple therapy for treating type 2 diabetes [ID1160]

Dear [redacted],

The Evidence Review Group, Warwick Evidence and the technical team at NICE have looked at the submission received on 25 September 2018 from MSD. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Monday 5 November 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted]. Any procedural questions should be addressed to [redacted].

Yours sincerely

[redacted]
HTA Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Prescribing data

A1. Table 3 on page 14 of the company submission reports that 11.4% of people with type 2 diabetes on triple therapy in the UK in 2017 were on triple therapy with metformin + a DPP4 inhibitor + a SGLT2 inhibitor. Please explain the source(s) of the prescribing data in the IQVIA report.

VERTIS SITA2 analysis

A2. Please confirm how the median odds ratios in the company submission, Table 25 (page 46) have been calculated. The ERG has been unable to replicate these figures.

A3. Please provide details on the methods of model/covariate specification for the models presented in B.2.6.

A4. Please provide detailed model output for the final adjusted models (e.g. covariate effect estimates and confidence intervals).

A5. Please reproduce company submission, Table 7 for baseline characteristics (page 23) for the FAS population.

A6. Please provide information on the hierarchical structure used in the cLDA (i.e. details of the random effects).

Network meta-analysis

A7. Please check the data in the company submission, Table 14 (page 37). The ERG notes that the third row, starting SITA + PBO with 153 patients in the next column, belongs with Dagogo 2018, not Jabbour. Please confirm that the correct figures were used in the NMA for these trials.

A8. The Jabbour trial had two groups, on dual and triple therapy. Please consider the effect of using mixed dual and triple results from Jabbour for the adverse effect and HbA1c target (Figure 11, page 43) analyses in the NMA. Please consider whether it would be safer to remove the Jabbour trial from the adverse effects section of the NMA.

The results that we only have for the whole group include:

- The proportions with HbA1c in target. The figures 12% and 22% relate to the whole group.

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- The figures for NHSE (of 4% and 5%) and SHE.
- UTI frequency
- Genital tract infections

In addition, please check the figures in Table 14 (1% and 17% for the dapaglifozin and placebo respectively) as these are the reverse of what might be expected. GTIs are rare for people on placebo, but common on SGLT2 inhibitors. They don't match the figures in the Jabbour article, which the ERG understands reports that by 48 weeks, 9.8% had had a GTI in the dapagliflozin arm, compared to 0.4% in the placebo arm.(i.e. the 48 week incidence includes the 24 week incidence). Please confirm which figures were used in the NMA.

A9. Please check the figures in the company submission for Figure 12 relating to adverse events (page 44) and Figure 13 relating to UTIs (page 45). The odds ratios (ORs) do not appear to reflect the direction of effect expected given the data from these studies, for example the ERG wonders if the correct OR for AEs from Matthieu should be in the region of 0.90 (0.58, 1.4) and 0.79 (0.3, 2.1) for UTIs?

A10. Please confirm how the median ORs in the company submission, Table 25 (page 45) have been calculated. The ERG has been unable to replicate these figures.

A11. Please provide the complete code and inputs enabling the ERG to reproduce the NMAs presented in section B.2.9.3, and to verify each NMA's input and output.

A12. The ERG has not been able to identify some of the necessary information from the published trial papers. Please provide sources of data and explain how CIs or SE for changes from baseline were obtained when papers (for example Rodbard and Softelund) only provide CI or SE for incremental effect.

A13. Please check the confidential marking (academic in confidence) in Tables 15, 17 and 19 as only some cells are shaded, whereas in, for example, Tables 21,23 and 25, all cells are shaded.

MSD Response to Clarification Questions on Single Technology Appraisal: ertugliflozin in triple therapy for treating type 2 diabetes [ID1160]

Section A: Clarification on effectiveness data

Prescribing data

A1. Table 3 on page 14 of the company submission reports that 11.4% of people with type 2 diabetes on triple therapy in the UK in 2017 were on triple therapy with metformin + a DPP4 inhibitor + a SGLT2 inhibitor. Please explain the source(s) of the prescribing data in the IQVIA report.

Response

The prescribing data is comprised of electronic medical records collected from a nationally representative standard panel of 150 practices/800 GPs across the UK; collated over 12 months, from January 2017 to December 2017.

VERTIS SITA2 analysis

A2. Please confirm how the median odds ratios in the company submission, Table 25 (page 46) have been calculated. The ERG has been unable to replicate these figures.

Response

Question A2 is a duplicate of question A10. Please see question A10 for the response.

A3. Please provide details on the methods of model/covariate specification for the models presented in B.2.6.

Response

The statistical models and covariates were pre-specified in the Statistical Analysis Plan. The following covariates were included in the model:

- Treatment (3 levels: placebo, ertugliflozin 5mg, ertugliflozin 15 mg).
- Prior anti-hyperglycaemic agent (AHAs) (2 levels: yes, no).
- Baseline estimated glomerular filtration rate (eGFR) (continuous).

A4. Please provide detailed model output for the final adjusted models (e.g. covariate effect estimates and confidence intervals).

Response

The detailed model outputs for HbA1c (change from baseline and proportion of patients at HbA1c target [7.0%]), body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and EQ-5D are provided in the appendices.

- Appendix A - HbA1c change from baseline Stat Output.
- Appendix B - HbA1c at target (7.0%) Stat Output.
- Appendix C - Body Weight Stat Output.
- Appendix D - SBP Stat Output.
- Appendix E - DBP Stat Output.
- Appendix F - EQ-5D Stat Output.

The final estimates for the proportion of patients with an HbA1c at target are only provided in the table output; the model output shows the 10 imputation results (Appendix B).

A5. Please reproduce company submission, Table 7 for baseline characteristics (page 23) for the FAS population.

Response

In the VERTIS SITA2 study the FAS population is the same as the ASaT population and the tables would be the same.

A6. Please provide information on the hierarchical structure used in the cLDA (i.e. details of the random effects).

Response

Subject ID is the only random effect in the model. An unstructured variance/covariance matrix was specified to model random effects within subjects across timepoints.

Network meta-analysis

A7. Please check the data in the company submission, Table 14 (page 37). The ERG notes that the third row, starting SITA + PBO with 153 patients in the next column, belongs with Dagogo 2018, not Jabbour. Please confirm that the correct figures were used in the NMA for these trials.

Response

MSD agrees that there was a formatting error in Table 14 (page 37) of the submissions and the third row starting with SITA + PBO with 153 patients belongs to Dagogo et al., 2018. We can confirm that the correct figures were used in the NMA.

A8. The Jabbour trial had two groups, on dual and triple therapy. Please consider the effect of using mixed dual and triple results from Jabbour for the adverse effect and HbA1c target (Figure 11, page 43) analyses in the NMA. Please consider whether it would be safer to remove the Jabbour trial from the adverse effects section of the NMA.

- The results that we only have for the whole group include:

- The proportions with HbA1c in target. The figures 12% and 22% relate to the whole group.
- The figures for NHSE (of 4% and 5%) and SHE.
- UTI frequency
- Genital tract infections

In addition, please check the figures in Table 14 (1% and 17% for the dapaglifozin and placebo respectively) as these are the reverse of what might be expected. GTIs are rare for people on placebo, but common on SGLT2 inhibitors. They don't match the figures in the Jabbour article, which the ERG understands reports that by 48 weeks, 9.8% had had a GTI in the dapagliflozin arm, compared to 0.4% in the placebo arm (i.e. the 48 week incidence includes the 24 week incidence). Please confirm which figures were used in the NMA.

Response

An error was made in the data extraction for the Jabbour et al (2014) Study. HbA1c within target (HbA1c ≥ 7%) was not reported in the manuscript and the safety outcomes (NSHE, SHE, UTIs, GMIs, AEs) were not available separately for patients on a background of sitagliptin and metformin. Table 14 below has been updated with the correct data (bold red font has been used to highlight changes).

The networks with HbA1c in target and UTIs were re-run excluding Jabbour et al (2014). There were no changes to base case findings (i.e. no difference between SGLT2s), except for sitagliptin with dapagliflozin being excluded from the network.

Table 14 - Outcomes reported by included studies informing the NMA

Reference	Arms	N	HbA1c change (%)	Weight change (kg)	SBP (mm/hg)	DBP (mm/hg)	HbA1c in target (%)	NSHE (%)	SHE (%)	UTIs (%)	Genital mycotic infection (%)	AEs (%)
Triple therapy												
Dagogo 2018 [7-10]	SITA+ERTU5	156	-0.78	-3.4	-3.8	/	32%	4%	0.0%	3%	3%	42%
	SITA+ERTU15	153	-0.86	-3.0	-4.8	/	40%	2%	0.0%	5%	2%	44%
	SITA+PBO	153	-0.09	-1.3	-0.9	/	17%	3%	0.6%	2%	0%	48%
Jabbour 2014 [11, 12]	SITA+PBO	113	0.00	-0.4	NR	/	**NR**	**NR**	**NR**	**NR**	**NR**	NR
	SITA+DAPA10	113	-0.40	-2.5	NR	/	**NR**	**NR**	**NR**	**NR**	**NR**	NR
Mathieu 2015 [13, 14]	SAXA+PBO	129	-0.10	-0.4^	2.0**	/	13%	0%	NR	6%	1%	59%
	SAXA+DAPA10	146	-0.82	-1.9^	-1.9**	/	37%	0%	NR	5%	5%	56%
Rodbard 2016 [15, 16]	SITA+PBO	94	-0.01	-1.6^	0.1^	/	12%	2%	0.0%	2%	1%	40%
	SITA+CANA	99	-0.91	-3.4^	-5.8^	/	32%	4%	0.0%	2%	6%	44%
Softeland 2017 [17, 18]	LINA+PBO	108	0.14	-0.3^	-1.7	/	17%	1%	0.0%	7%	2%	68%
	LINA+EMPA10	109	-0.65	-3.1^	-3.0	/	37%	0%	0.0%	7%	2%	55%
	LINA+EMPA25	110	-0.56	-2.5^	-4.3	/	33%	3%	0.0%	4%	5%	52%

Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; NSHE, non-severe hypoglycaemic event; SHE, severe hypoglycaemic event; UTI, urinary tract infection; GTI, genital tract infections; AE, adverse event; ERTU, ertugliflozin; MET, metformin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; SITA, sitagliptin; LINA, linagliptin; SAXA, saxagliptin; NR, not reported

^ Data sourced from clinicaltrials.gov ** SE not able to be imputed, therefore the study is unable to be included in the network

A9. Please check the figures in the company submission for Figure 12 relating to adverse events (page 44) and Figure 13 relating to UTIs (page 45). The odds ratios (ORs) do not appear to reflect the direction of effect expected given the data from these studies, for example the ERG wonders if the correct OR for AEs from Matthieu should be in the region of 0.90 (0.58, 1.4) and 0.79 (0.3, 2.1) for UTIs?

Response

An error was made when selecting the data to generate the forest plots. The forest plots have been updated with the correct data and the exclusion of the Jabbour et al (2014) data, as per question A8. Please see the revised figures 12 (AEs) and 13 (UTIs) below.

Figure 12 Base case – AEs at week 24 - 26 (binary outcome, FEM)

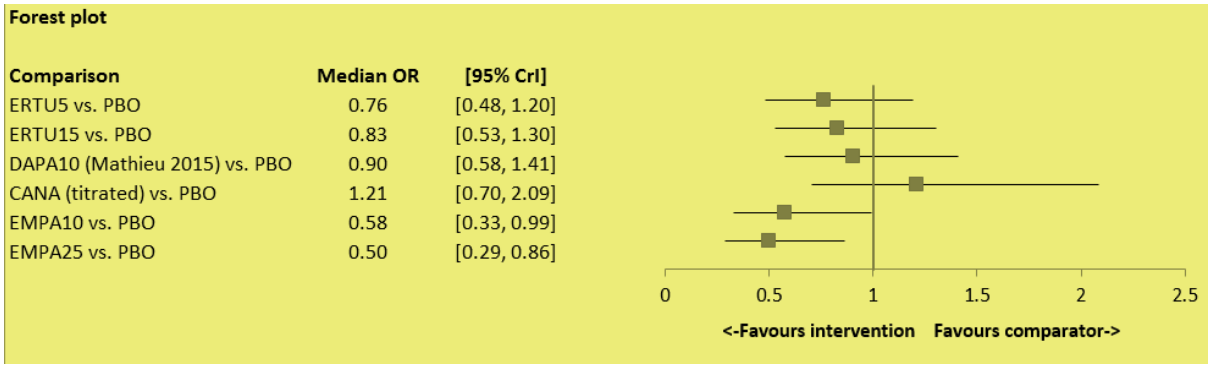
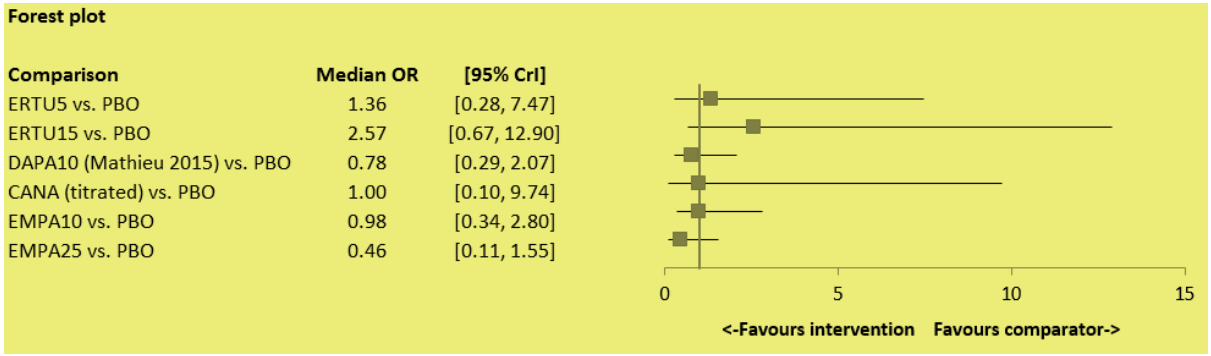


Figure 13 Base case – UTIs at week 24 - 26 (binary outcome – FEM)



A10. Please confirm how the median ORs in the company submission, Table 25 (page 45) have been calculated. The ERG has been unable to replicate these figures.

Response

Unfortunately, there was an error in the UTI odds ratio entered within Table 25 of the dossier. In accordance with question A8, the network has been re-run with the Jabbour et al (2014) data excluded. The overall conclusions do not change in light of the revised results in Table 25 below.

Table 25 - UTIs median odds ratio (CrI): FEM **Updated**

	ERTU5	ERTU15
DAPA10 (Mathieu 2015)	*1.74 [0.27,12.37]*	*3.32 [0.62,21.70]*
CANA (titrated)	*1.37 [0.09,22.81]*	*2.62 [0.18,40.82]*
EMPA10	*1.39 [0.21,10.27]*	*2.65 [0.47,17.77]*
EMPA25	*3.00 [0.40,26.21]*	*5.72 [0.90,45.90]*

A11. Please provide the complete code and inputs enabling the ERG to reproduce the NMAs presented in section B.2.9.3, and to verify each NMA's input and output.

Response

The complete code and inputs are included in an accompanying Zip file called "Winbugs.zip".

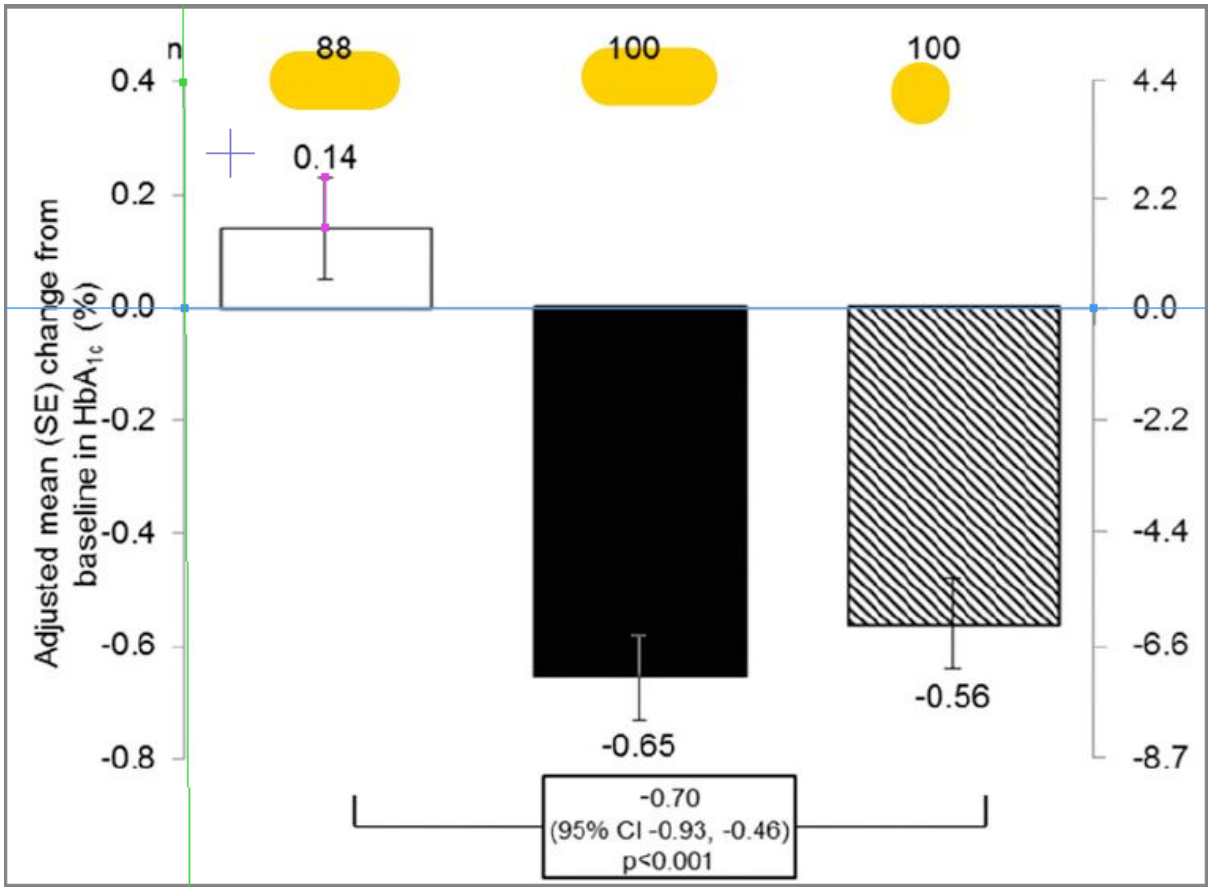
A12. The ERG has not been able to identify some of the necessary information from the published trial papers. Please provide sources of data and explain how CIs or SE for changes from baseline were obtained when papers (for example Rodbard and Softelund) only provide CI or SE for incremental effect.

Response

Whilst Rodbard et al. (2016) and Softerland et al. (2014) did not provide the actual CIs and SEs for change from baseline as numbers, they did provide figures that graphically presented the data. For papers where the data was graphically presented, the software "Graphic Digitizer" was used to first create the correct scale (per the published axis) and then estimate the value for a given line or data point. For example, Figure 2A from Softeland 2017 is presented below. The pink line is the standard error and is estimated to be 0.09.

We used the same procedure for weight loss (figure 4B) and SBP (supplementary figure 1C) in Softeland 2017 and for HbA1c (figure 2A), SBP (figure 2E) and weight (figure 2D, subsequently converted from percentage change to kg) in Rodbard 2016.

Figure 2A- Efficacy Parameters



A13. Please check the confidential marking (academic in confidence) in Tables 15, 17 and 19 as only some cells are shaded, whereas in, for example, Tables 21,23 and 25, all cells are shaded.

The confidential marking (academic in confidence) in tables 15, 17, 19, 21, 23 and 25 is correct. The unshaded cells contain data that has been presented at the American Diabetes Association (ADA) in July 2018.

Appendix A – HbA1c change from baseline Stat Output

Statistical Output for Tables 14.2.1.1.2 & 16.2.6.1.1.1 (Ertugliflozin Protocol MK-8835-006/B1521015)

The Mixed Procedure

Model Information

Data Set	WORK._DS
Dependent Variable	AVAL
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Estimated R Matrix for USUBJID 8835-006_000800001

Row	Col1	Col2	Col3	Col4	Col5
1	0.7317	0.5765	0.4745	0.3975	0.3767
2	0.5765	0.7004	0.6056	0.5048	0.4903
3	0.4745	0.6056	0.7559	0.6375	0.6083
4	0.3975	0.5048	0.6375	0.7574	0.6835
5	0.3767	0.4903	0.6083	0.6835	0.7988

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P1: Week 26; TRT: 2	-0.7806	0.06729	446	-11.60	<.0001	0.05	-0.9128	-0.6483
P1: Week 26; TRT: 3	-0.8568	0.06781	444	-12.64	<.0001	0.05	-0.9901	-0.7236
P1: Week 26; TRT: 99	-0.09388	0.06974	469	-1.35	0.1789	0.05	-0.2309	0.04317

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P2: Week 26; TRT: 2 - 3	0.07627	0.09158	387	0.83	0.4055	0.05	-0.1038	0.2563
P2: Week 26; TRT: 2 - 99	-0.6867	0.09305	400	-7.38	<.0001	0.05	-0.8696	-0.5038
P2: Week 26; TRT: 3 - 99	-0.7630	0.09342	400	-8.17	<.0001	0.05	-0.9466	-0.5793

Appendix B – HbA1c at target Stat Output

```
Statistical Output for Table  (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS: Multiple Imputation
(_IMPUTATION_=1)                    1

The GENMOD Procedure

      Model Information

Data Set              WORK._DS
Distribution          Binomial
Link Function            Logit
Dependent Variable        AVAL



    Class Level Information

Class         Levels    Values

AVAL               2    1 0
TRT01PN            3    3 2 1
ASULSTFL           2    Yes No


       Response Profile

 Ordered                Total
   Value    AVAL     Frequency

       1    1              153
       2    0              306
```

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=1) 2

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.3772	1.3054	2.8187	7.9356	16.97	<.0001
TRT01PN	3	1	1.4516	0.2851	0.8927	2.0104	25.92	<.0001
TRT01PN	2	1	1.1654	0.2853	0.6062	1.7247	16.68	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0112	0.0070	-0.0026	0.0250	2.54	0.1113
ASULSTFL	Yes	1	-0.3427	0.2378	-0.8087	0.1233	2.08	0.1495
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-0.9961	0.1595	-1.3086	-0.6835	39.01	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Lower	Exponentiated Estimate	Exponentiated Upper
3	-0.3619	0.1805	-2.01	0.0449	0.05	-0.7156	-0.00815	0.6964	0.4889	0.9919
2	-0.6480	0.1859	-3.49	0.0005	0.05	-1.0123	-0.2836	0.5231	0.3634	0.7530
1	-1.8134	0.2349	-7.72	<.0001	0.05	-2.2738	-1.3530	0.1631	0.1029	0.2585

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.2861	0.2500	1.14	0.2524	0.05	-0.2039	0.7761	1.3312	0.8156	2.1730
3	1	1.4516	0.2851	5.09	<.0001	0.05	0.8927	2.0104	4.2697	2.4418	7.4661
2	1	1.1654	0.2853	4.08	<.0001	0.05	0.6062	1.7247	3.2073	1.8335	5.6106

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=2) 1

The GENMOD Procedure

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	6.1117	1.3479	3.4699	8.7535	20.56	<.0001
TRT01PN	3	1	1.5979	0.2924	1.0249	2.1709	29.87	<.0001
TRT01PN	2	1	1.2724	0.2919	0.7003	1.8444	19.00	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0078	0.0071	-0.0061	0.0218	1.21	0.2719
ASULSTFL	Yes	1	-0.4348	0.2424	-0.9098	0.0402	3.22	0.0728
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0628	0.1647	-1.3857	-0.7400	41.63	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.3580	0.1825	-1.96	0.0497	0.05	-0.7156	-0.00044	0.6990	0.4889	0.9996
2	-0.6836	0.1885	-3.63	0.0003	0.05	-1.0530	-0.3141	0.5048	0.3489	0.7304
1	-1.9559	0.2443	-8.01	<.0001	0.05	-2.4348	-1.4771	0.1414	0.08762	0.2283

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.3255	0.2521	1.29	0.1967	0.05	-0.1686	0.8196	1.3847	0.8448	2.2697
3	1	1.5979	0.2924	5.47	<.0001	0.05	1.0249	2.1709	4.9426	2.7868	8.7661
2	1	1.2724	0.2919	4.36	<.0001	0.05	0.7003	1.8444	3.5693	2.0144	6.3246

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=3) 1

The GENMOD Procedure

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	6.1252	1.3323	3.5139	8.7366	21.14	<.0001
TRT01PN	3	1	1.4038	0.2838	0.8475	1.9601	24.46	<.0001
TRT01PN	2	1	1.0448	0.2840	0.4881	1.6014	13.53	0.0002
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0052	0.0070	-0.0086	0.0189	0.54	0.4632
ASULSTFL	Yes	1	-0.4857	0.2409	-0.9578	-0.0136	4.07	0.0438
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0126	0.1615	-1.3291	-0.6961	39.32	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.3932	0.1821	-2.16	0.0308	0.05	-0.7501	-0.03627	0.6749	0.4723	0.9644
2	-0.7522	0.1892	-3.98	<.0001	0.05	-1.1231	-0.3814	0.4713	0.3253	0.6829
1	-1.7970	0.2340	-7.68	<.0001	0.05	-2.2557	-1.3383	0.1658	0.1048	0.2623

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.3590	0.2520	1.42	0.1542	0.05	-0.1349	0.8529	1.4320	0.8738	2.3466
3	1	1.4038	0.2838	4.95	<.0001	0.05	0.8475	1.9601	4.0706	2.3338	7.0999
2	1	1.0448	0.2840	3.68	0.0002	0.05	0.4881	1.6014	2.8427	1.6292	4.9600

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=4) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.8075	1.3079	3.2440	8.3710	19.72	<.0001
TRT01PN	3	1	1.4816	0.2816	0.9296	2.0335	27.68	<.0001
TRT01PN	2	1	1.0046	0.2817	0.4525	1.5566	12.72	0.0004
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0085	0.0070	-0.0052	0.0222	1.46	0.2261
ASULSTFL	Yes	1	-0.4095	0.2377	-0.8753	0.0563	2.97	0.0849
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0061	0.1593	-1.3183	-0.6939	39.90	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.2534	0.1799	-1.41	0.1591	0.05	-0.6060	0.09929	0.7762	0.5455	1.1044
2	-0.7304	0.1881	-3.88	0.0001	0.05	-1.0990	-0.3618	0.4817	0.3332	0.6964
1	-1.7349	0.2301	-7.54	<.0001	0.05	-2.1860	-1.2839	0.1764	0.1124	0.2770

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.4770	0.2512	1.90	0.0576	0.05	-0.01536	0.9694	1.6112	0.9848	2.6363
3	1	1.4816	0.2816	5.26	<.0001	0.05	0.9296	2.0335	4.3998	2.5335	7.6411
2	1	1.0046	0.2817	3.57	0.0004	0.05	0.4525	1.5566	2.7307	1.5723	4.7427

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=5) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.4952	1.3110	2.9256	8.0647	17.57	<.0001
TRT01PN	3	1	1.5466	0.2868	0.9844	2.1087	29.08	<.0001
TRT01PN	2	1	1.1385	0.2872	0.5757	1.7013	15.72	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0087	0.0070	-0.0051	0.0225	1.52	0.2174
ASULSTFL	Yes	1	-0.2744	0.2377	-0.7402	0.1914	1.33	0.2482
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-0.9906	0.1596	-1.3035	-0.6777	38.50	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.2909	0.1794	-1.62	0.1049	0.05	-0.6425	0.06074	0.7476	0.5260	1.0626
2	-0.6989	0.1866	-3.75	0.0002	0.05	-1.0646	-0.3333	0.4971	0.3449	0.7166
1	-1.8374	0.2367	-7.76	<.0001	0.05	-2.3013	-1.3735	0.1592	0.1001	0.2532

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.4081	0.2500	1.63	0.1027	0.05	-0.08203	0.8981	1.5039	0.9212	2.4550
3	1	1.5466	0.2868	5.39	<.0001	0.05	0.9844	2.1087	4.6952	2.6763	8.2373
2	1	1.1385	0.2872	3.96	<.0001	0.05	0.5757	1.7013	3.1221	1.7783	5.4812

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=6) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.9477	1.3278	3.3452	8.5501	20.06	<.0001
TRT01PN	3	1	1.3566	0.2845	0.7990	1.9142	22.74	<.0001
TRT01PN	2	1	1.1582	0.2844	0.6008	1.7156	16.59	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0094	0.0070	-0.0044	0.0232	1.78	0.1827
ASULSTFL	Yes	1	-0.4412	0.2399	-0.9113	0.0290	3.38	0.0659
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0403	0.1622	-1.3582	-0.7224	41.14	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.4483	0.1830	-2.45	0.0143	0.05	-0.8070	-0.08965	0.6387	0.4462	0.9143
2	-0.6468	0.1872	-3.46	0.0005	0.05	-1.0136	-0.2799	0.5237	0.3629	0.7559
1	-1.8050	0.2346	-7.69	<.0001	0.05	-2.2647	-1.3452	0.1645	0.1039	0.2605

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.1984	0.2515	0.79	0.4302	0.05	-0.2946	0.6914	1.2195	0.7448	1.9965
3	1	1.3566	0.2845	4.77	<.0001	0.05	0.7990	1.9142	3.8830	2.2234	6.7815
2	1	1.1582	0.2844	4.07	<.0001	0.05	0.6008	1.7156	3.1842	1.8236	5.5600

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=7) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.7438	1.3096	3.1771	8.3104	19.24	<.0001
TRT01PN	3	1	1.5122	0.2856	0.9525	2.0719	28.04	<.0001
TRT01PN	2	1	1.2256	0.2852	0.6666	1.7846	18.46	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0088	0.0070	-0.0049	0.0225	1.58	0.2094
ASULSTFL	Yes	1	-0.3516	0.2373	-0.8167	0.1136	2.19	0.1385
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0158	0.1596	-1.3286	-0.7029	40.49	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Lower	Exponentiated Estimate	Exponentiated Upper
3	-0.3063	0.1803	-1.70	0.0894	0.05	-0.6597	0.04710	0.7362	0.5170	1.0482
2	-0.5929	0.1850	-3.20	0.0014	0.05	-0.9556	-0.2302	0.5527	0.3846	0.7944
1	-1.8185	0.2352	-7.73	<.0001	0.05	-2.2795	-1.3575	0.1623	0.1023	0.2573

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.2866	0.2496	1.15	0.2508	0.05	-0.2026	0.7757	1.3319	0.8166	2.1722
3	1	1.5122	0.2856	5.30	<.0001	0.05	0.9525	2.0719	4.5366	2.5921	7.9398
2	1	1.2256	0.2852	4.30	<.0001	0.05	0.6666	1.7846	3.4062	1.9476	5.9572

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=8) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	6.4074	1.3638	3.7345	9.0803	22.07	<.0001
TRT01PN	3	1	1.6052	0.2932	1.0306	2.1799	29.97	<.0001
TRT01PN	2	1	1.2462	0.2927	0.6726	1.8198	18.13	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0073	0.0071	-0.0067	0.0213	1.05	0.3044
ASULSTFL	Yes	1	-0.4138	0.2432	-0.8904	0.0629	2.90	0.0889
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0968	0.1670	-1.4241	-0.7695	43.14	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.3597	0.1832	-1.96	0.0496	0.05	-0.7187	-0.00071	0.6979	0.4874	0.9993
2	-0.7188	0.1899	-3.79	0.0002	0.05	-1.0909	-0.3466	0.4874	0.3359	0.7071
1	-1.9650	0.2452	-8.01	<.0001	0.05	-2.4456	-1.4843	0.1402	0.08667	0.2267

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.3590	0.2533	1.42	0.1564	0.05	-0.1374	0.8555	1.4319	0.8716	2.3525
3	1	1.6052	0.2932	5.47	<.0001	0.05	1.0306	2.1799	4.9790	2.8026	8.8455
2	1	1.2462	0.2927	4.26	<.0001	0.05	0.6726	1.8198	3.4771	1.9593	6.1709

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=9) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.9307	1.3163	3.3508	8.5106	20.30	<.0001
TRT01PN	3	1	1.3569	0.2812	0.8057	1.9081	23.28	<.0001
TRT01PN	2	1	1.0347	0.2815	0.4830	1.5863	13.51	0.0002
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0075	0.0070	-0.0062	0.0212	1.16	0.2810
ASULSTFL	Yes	1	-0.4046	0.2381	-0.8712	0.0620	2.89	0.0892
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0115	0.1601	-1.3252	-0.6978	39.94	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.3773	0.1813	-2.08	0.0374	0.05	-0.7326	-0.02194	0.6857	0.4806	0.9783
2	-0.6995	0.1874	-3.73	0.0002	0.05	-1.0669	-0.3321	0.4968	0.3441	0.7174
1	-1.7342	0.2302	-7.53	<.0001	0.05	-2.1854	-1.2830	0.1765	0.1124	0.2772

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.3222	0.2510	1.28	0.1993	0.05	-0.1698	0.8142	1.3802	0.8439	2.2573
3	1	1.3569	0.2812	4.82	<.0001	0.05	0.8057	1.9081	3.8841	2.2382	6.7404
2	1	1.0347	0.2815	3.68	0.0002	0.05	0.4830	1.5863	2.8142	1.6210	4.8858

Statistical Output for Table (Ertugliflozin Protocol MK-8835-006/B1521015) - FAS:Multiple Imputation (_IMPUTATION_=10) 1

The GENMOD Procedure

PROC GENMOD is modeling the probability that AVAL='1'.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.9355	1.3461	3.2973	8.5738	19.44	<.0001
TRT01PN	3	1	1.5615	0.2917	0.9899	2.1332	28.66	<.0001
TRT01PN	2	1	1.2082	0.2917	0.6364	1.7800	17.15	<.0001
TRT01PN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
BASEGFR		1	0.0094	0.0071	-0.0046	0.0233	1.73	0.1889
ASULSTFL	Yes	1	-0.3257	0.2413	-0.7987	0.1472	1.82	0.1771
ASULSTFL	No	0	0.0000	0.0000	0.0000	0.0000	.	.
BASE		1	-1.0614	0.1650	-1.3847	-0.7380	41.39	<.0001
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

TRT01PN Least Squares Means

TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	-0.3696	0.1820	-2.03	0.0423	0.05	-0.7264	-0.01283	0.6910	0.4837	0.9873
2	-0.7229	0.1889	-3.83	0.0001	0.05	-1.0931	-0.3527	0.4853	0.3352	0.7028
1	-1.9311	0.2431	-7.94	<.0001	0.05	-2.4076	-1.4547	0.1450	0.09003	0.2335

Differences of TRT01PN Least Squares Means

TRT01PN	_TRT01PN	Estimate	Standard Error	z Value	Pr > |z|	Alpha	Lower	Upper	Exponentiated Estimate	Exponentiated Lower	Exponentiated Upper
3	2	0.3533	0.2524	1.40	0.1615	0.05	-0.1413	0.8479	1.4238	0.8682	2.3347
3	1	1.5615	0.2917	5.35	<.0001	0.05	0.9899	2.1332	4.7662	2.6909	8.4418
2	1	1.2082	0.2917	4.14	<.0001	0.05	0.6364	1.7800	3.3476	1.8897	5.9301

Appendix C – body weight Stat Output

Weight Stat OutStatistical Output for Tables 14.2.2.1.2 & 16.2.6.1.2 (Ertugliflozin Protocol MK-8835-006/B1521015)

Model Information

Data Set	WORK._DS
Dependent Variable	AVAL
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Estimated R Matrix for USUBJID 8835-006_000800001

Row	Col1	Col2	Col3	Col4	Col5
1	385.20	383.54	382.55	382.65	381.01
2	383.54	384.16	383.06	383.15	381.45
3	382.55	383.06	383.86	383.75	382.11
4	382.65	383.15	383.75	385.50	383.73
5	381.01	381.45	382.11	383.73	384.02

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P1: Week 26; TRT: 2	-3.3456	0.2205	425	-15.17	<.0001	0.05	-3.7790	-2.9122
P1: Week 26; TRT: 3	-3.0412	0.2233	425	-13.62	<.0001	0.05	-3.4801	-2.6022
P1: Week 26; TRT: 99	-1.3184	0.2294	446	-5.75	<.0001	0.05	-1.7693	-0.8675

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P2: Week 26; TRT: 2 - 3	-0.3044	0.3137	424	-0.97	0.3324	0.05	-0.9211	0.3123
P2: Week 26; TRT: 2 - 99	-2.0272	0.3181	434	-6.37	<.0001	0.05	-2.6525	-1.4019
P2: Week 26; TRT: 3 - 99	-1.7228	0.3201	434	-5.38	<.0001	0.05	-2.3519	-1.0937

Appendix D – SBP Stat Output

Statistical Output for Tables 14.2.2.3.2 & 16.2.6.1.4.1 (Ertugliflozin Protocol MK-8835-006/B1521015)

Model Information

Data Set	WORK._DS
Dependent Variable	AVAL
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Estimated R Matrix for USUBJID 8835-006_000800001

Row	Col1	Col2	Col3	Col4	Col5
1	164.74	114.60	104.43	108.25	108.22
2	114.60	172.13	116.88	110.89	106.56
3	104.43	116.88	167.08	121.67	106.35
4	108.25	110.89	121.67	166.26	104.40
5	108.22	106.56	106.35	104.40	173.02

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P1: Week 26; TRT: 2	-3.8051	0.8708	436	-4.37	<.0001	0.05	-5.5166	-2.0936
P1: Week 26; TRT: 3	-4.8200	0.8798	436	-5.48	<.0001	0.05	-6.5492	-3.0909
P1: Week 26; TRT: 99	-0.8774	0.9256	445	-0.95	0.3436	0.05	-2.6965	0.9416

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P2: Week 26; TRT: 2 - 3	1.0149	1.2043	402	0.84	0.3999	0.05	-1.3526	3.3825
P2: Week 26; TRT: 2 - 99	-2.9277	1.2384	408	-2.36	0.0185	0.05	-5.3621	-0.4933
P2: Week 26; TRT: 3 - 99	-3.9426	1.2447	408	-3.17	0.0017	0.05	-6.3894	-1.4958

Appendix E – DBP Stat Output

Statistical Output for Tables 14.2.2.4.2 & 16.2.6.1.4.2 (Ertugliflozin Protocol MK-8835-006/B1521015)

Model Information

Data Set	WORK._DS
Dependent Variable	AVAL
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Estimated R Matrix for USUBJID 8835-006_000800001

Row	Col1	Col2	Col3	Col4	Col5
1	54.0983	37.8995	34.3728	35.1375	37.0081
2	37.8995	64.5904	42.6306	39.3847	42.3792
3	34.3728	42.6306	61.5949	43.1657	40.1391
4	35.1375	39.3847	43.1657	60.9116	42.3595
5	37.0081	42.3792	40.1391	42.3595	76.7542

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P1: Week 26; TRT: 2	-1.6771	0.6100	425	-2.75	0.0062	0.05	-2.8761	-0.4781
P1: Week 26; TRT: 3	-1.8112	0.6165	425	-2.94	0.0035	0.05	-3.0230	-0.5994
P1: Week 26; TRT: 99	-0.4348	0.6478	437	-0.67	0.5025	0.05	-1.7080	0.8385

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P2: Week 26; TRT: 2 - 3	0.1341	0.8544	407	0.16	0.8754	0.05	-1.5454	1.8136
P2: Week 26; TRT: 2 - 99	-1.2424	0.8773	414	-1.42	0.1575	0.05	-2.9669	0.4822
P2: Week 26; TRT: 3 - 99	-1.3764	0.8818	414	-1.56	0.1193	0.05	-3.1099	0.3570

Appendix F – EQ 5D Stat Output

Statistical Output for Table 14.2.2.6.2 (Ertugliflozin Protocol MK-8835-006/B1521015)

Model Information

Data Set	WORK._DS
Dependent Variable	AVAL
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

Estimated R Matrix for USUBJID 8835-006_000800001

Row	Col1	Col2
1	0.02672	0.01233
2	0.01233	0.02090

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P1: Week 26; TRT: 2	0.004041	0.01136	469	0.36	0.7221	0.05	-0.01827	0.02636
P1: Week 26; TRT: 3	0.01873	0.01149	461	1.63	0.1036	0.05	-0.00384	0.04130
P1: Week 26; TRT: 99	0.01220	0.01204	456	1.01	0.3116	0.05	-0.01147	0.03587

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
P2: Week 26; TRT: 2 - 3	-0.01469	0.01503	391	-0.98	0.3290	0.05	-0.04424	0.01486
P2: Week 26; TRT: 2 - 99	-0.00816	0.01547	391	-0.53	0.5981	0.05	-0.03857	0.02225
P2: Week 26; TRT: 3 - 99	0.006531	0.01558	389	0.42	0.6754	0.05	-0.02410	0.03717

NICE National Institute for Health and Care Excellence

Professional organisation submission

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Chair of Clinical Biochemistry SAC, RCPath. Consultant Chemical Pathologist**
4. Are you (please tick all that apply):	☒ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ x a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The College is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates and trainees, supported by the staff who are based at the College's London offices. As such it is funded by subscription from its members. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 19 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology. (adapted from RCPath website https://www.rcpath.org/about-the-college.html)
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To gain and maintain control of blood glucose levels so that Hba1c is 53 mmol/mol or less. Treatment should reduce the incidence of complications of diabetes.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant treatment response is a reduction in Hba1c to target levels – usually 53 mmol/mol.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	yes
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline 28 on the management of Type 2 diabetes in adults provides clinical guidelines to manage this condition.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is quite well defined – the treatment options after metformin and before insulin is required can vary depending on the clinical condition of the patient and co-morbidities.
• What impact would the technology have on the current pathway of care?	It would add another option for the sodium glucose transporter inhibitor medications current available.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes

• How does healthcare resource use differ between the technology and current care?	There are similar treatments available and in routine use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Mainly in primary care but some in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional resource
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It is likely to be similar to other SGLT2 inhibitors
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Like other medication in the same class it is particularly useful in patients with type 2 diabetes who have normal kidney function but elevated hba1c and are overweight or obese.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It will be similar to current care in terms of ease of use.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is stopped when eGFR falls below 30 mls/min. eGFR is routinely monitored in patients with diabetes so additional monitoring is unlikely to be required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	No- similar to other products currently available.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects are polyuria and UTIs / genital infections. These are unpleasant but not usually severe.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in Hba1c, weight reduction, reduction in CV events / deaths Yes - first two were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	A cardiovascular event study is underway and will provide information on this outcome.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any initially unreported adverse effects.
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA288, TA315, TA336, TA390, TA418]?	No
21. How do data on real-world experience compare with the trial data?	Not known
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- This treatment appears similar to other SGLT2 inhibitors.
- These are a very useful class of drugs in the management of type 2 diabetes.
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160] and

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**University of Liverpool and Aintree University Hospital NHS Foundation Trust**

3. Job title or position	**Professor of Medicine**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms of hyperglycaemia, to reduce development and progression of complications, whilst minimising adverse events.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in HbA1c by at least 5mmol/mol (0.5%) that is sustained for at least one year Reduction in the development of micro and macrovsacular complications of diabetes
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Initially with lifestyle (diet and exercise), metformin 1st line drug and sequential addition of additional drugs and insulin as outlined in NICE TA 288 and others. Active management of risk factors for cardiovascular disease. Treatment of complications if they arise.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes NICE CG87; however ADA / EASD guidelines are more up to date.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Would fit as 2nd or 3rd line treatment or as 1st line if metformin not tolerated or contraindicated. Three other drugs in SGLT2i class with very similar effects are already in the guidelines.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes would fit in same place as other SGLT2 inhibitors.

• How does healthcare resource use differ between the technology and current care?	Similar as drugs in class already in use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care and specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil specific
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Similar to other drugs in the class.
• Do you expect the technology to increase length of life more than current care?	Possible, but we don't yet have CV outcomes data for ertugliflozin that we do for the other SGLT2i so currently unknown.

• Do you expect the technology to increase health-related quality of life more than current care?	Possible but no data available
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Less effective in people with renal impairment (eGFR < 45ml/min due to mode of action in kidneys
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Similar to other SGTL2 inhibitors

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	N/A
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possible when CV outcome trial data is available. Weight loss might provide some addition benefit
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	The class as a whole is innovative, but this is 4th drug in class – no clear differences from others.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The class provides new benefits (reduced heart failure, CV death, major adverse cardiovascular events and probably reduced progression of renal disease) that has not yet been shown for ertugliflozin.
• Does the use of the technology address any particular unmet need of the patient population?	Yes as other drugs in class reduce risk of important outcomes as outlined above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main adverse event is risk of fungal genetic infections which can be problematic for some people. Rarely patients can develop diabetic ketoacidosis Lower limb amputations emerged as a possible risk in CANVAS trial with canagliflozin
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Lowering of HbA1c predicts reduced micro and macrovascular adverse events in diabetes. However beneficial effects of SGLT2i on CV and renal disease seems independent of reductions in glycaemia.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Rare adverse events such as DKA were not seen in the trials
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA418, TA390, TA336, TA315, TA288]?	Yes 3 major trials have reported EMPA-REG outcome CANVAS DECLARE TIMI-58 1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373(22): 2117-28. 2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377(7): 644-57. 3. Stephen D. Wiviott, Itamar Raz, Marc P. Bonaca et al Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes New England Journal of Medicine 2018 DOI: 10.1056/NEJMoa1812389

	These show reduced heart failure hospitalisation, mortality and in some cases reduce major adverse CV events. This seems to be a class effect (see meta-analysis below) but the results of the VERTIS trial with ertugliflozin are not yet reported. Thomas A. Zelniker, Stephen D. Wiviott, Itamar Raz, Kyungah Im, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo HM Furtado, Deepak L Bhatt, Lawrence A. Leiter, Darren K. McGuire, John PH Wilding, Marc S. Sabatine SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcomes Trials Lancet 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X Secondary analysis of these trials also suggests renoprotective events definitive trials are underway
22. How do data on real-world experience compare with the trial data?	Extensive Real World evidence with other drugs in class shows clinical effects and improved CV outcomes that are consistent with the clinical trial data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Ertugliflozin is an effective SGLT2 inhibitor; glucose lowering, weight loss and blood pressure reduction are similar to other drugs in the class
- Favourable CV outcome data are present for empagliflozin, canagliflozin and dapagliflozin. This is probably a class effect but no data yet available for ertugliflozin
- Current NICE guidelines do not reflect new CV outcome data with SGLT2i that has led to changes in most other international guidelines that support use of the class in patients with pre-existing cardiovascular disease
- Emerging data also suggest SGLT2i are renoprotective in diabetes
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160] and

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Swansea University & ABMU Health Board, South West Wales**

3. Job title or position	**Professor of Medicine (Diabetes) & Honorary Consultant Physician**
4. Are you (please tick all that apply):	☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology?
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (I have not had sight of this document – I have been told that this is the 'norm')
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ertugliflozin is a selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor, which reduces hyperglycaemia in people with type 2 diabetes (T2DM) by reducing the renal reabsorption of filtered glucose. This leads to a reduction in glycosylated haemoglobin (HbA1c) along with secondary benefits of weight reduction and blood pressure lowering. There is a presumption that the fall in HbA1c will reduce the long-term risk of specific microvascular complications of T2DM such as retinopathy, neuropathy and nephropathy although there is currently no evidence that the progression of the underlying pathogenesis of T2DM is slowed. For other agents in the SGLT-2 inhibitor class, trials have shown a reduction in cardiovascular disease (compared with standard glucose lowering therapies) as well fewer hospitalisations for heart failure and improved preservation of renal function.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in HbA1c of 0.4% (~4 mmol/mol) is generally regarded as indicating a clinically significant glucose-lowering effect. Medicines in the SGLT-2 inhibitor class typically provide much bigger falls in HbA1c than this.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The management of T2DM in the UK is sub-optimal with huge numbers of people having poor glucose control, as assessed by HbA1c and as recommended by the current NICE guidelines (NG28). Modern therapies offer the potential for potent glucose lowering but without the adverse effects of hypoglycaemia and weight gain. Two of the newer classes of glucose-lowering agents (SGLT-2 inhibitors and GLP-1 mimetics) also provide cardiovascular protection.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE produced a new guideline for the management of T2DM in 2015 (NG28), which was updated in 2016. This forms the basis for the management of T2DM across England & Wales.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway allows for choice between second and third-line agents but is seen as out-of-date as it does not include data from positive cardiovascular outcome trials (CVOTs) of the SGLT-2 inhibitors and GLP-1 mimetics, which have been published since September 2015 (i.e. before the publication of NG28). These results have been incorporated into over 25 diabetes guidelines around the world and recently consolidated in the publication (October 2018) of a consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). The ADA/EASD document recommends that after metformin failure, the presence of atherosclerotic cardiovascular disease (ASCVD), heart failure and/or chronic kidney disease should influence the choice of glucose-lowering class (with preference for SGLT-2 inhibitors and GLP-1 mimetics). My experience relates to Wales but applies equally to England.
• What impact would the technology have on the current pathway of care?	Ertugliflozin would provide an additional (forth) choice of SGLT-2 inhibitor, whenever this class is thought the most appropriate for managing a person with T2DM.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ertugliflozin, used according to licence, would have similar indications to other medicines in the SGLT-2 inhibitor class.

• How does healthcare resource use differ between the technology and current care?	No. It may be that ertugliflozin has advantages over other members of the SGLT-2 inhibitor class but direct head-to-head studies have yet to be performed.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	SGLT-2 inhibitors can (and should) be initiated and monitored in primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional resources, given that we already have three SGLT-2 inhibitors available in the UK. It is possible (and actually desirable) that the use of this class of glucose-lowering medications will increase but this will apply equally in the current situation where three drugs recommended by the guidelines.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as per the SGLT-2 inhibitor class.
• Do you expect the technology to increase length of life more than current care?	The use of SGLT-2 inhibitors in appropriate patients with T2DM has been shown to extend life in CVOTs.
• Do you expect the	I would expect ertugliflozin to have similar benefits on health-related quality of life as the other agents in the

technology to increase health-related quality of life more than current care?	SGLT-2 inhibitor class.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Currently the trial data from CVOTs in people with T2DM suggest that most benefit accrues in those cases with pre-existing cardiovascular disease.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	The use of ertugliflozin should not pose any additional difficulties or issues over the use of the three currently available SGLT-2 inhibitors.

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Any rules would be that those that apply to the currently available SGLT-2 inhibitors. Currently this means stopping drug when the estimated glomerular filtration rate (eGFR) drops below 45mL/min. Since people with T2DM should have their kidney function checked on a regular basis, no additional testing is required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In addition to the benefit of glucose-lowering, the technology assessment needs to take into account mortality, CV morbidity, heart failure, renal, weight and blood pressure lowering effects of the SGLT-2 inhibitors.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	No, this is an addition to the currently available SGLT-2 inhibitors.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, this is an addition to the currently available SGLT-2 inhibitors.
• Does the use of the technology address any particular unmet need of the patient population?	No more (or less) than any of the currently available SGLT-2 inhibitors.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The major side-effect of the SGLT-2 inhibitors is genital mycotic infections, which are usually easily treated with over-the-counter anti-fungal creams. Urinary frequency and infection may be reported (there is still debate about the latter) and diabetic ketoacidosis (DKA) has been included in the SGLT2-inhibitor class label, but is rare. Fournier's gangrene is now also included as adverse side-effect but is extremely rare.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Given our knowledge about the SGLT-2 inhibitor class, I feel that there can be some extrapolation from studies of the other three agents.

• If not, how could the results be extrapolated to the UK setting?	Not applicable.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Cardiovascular, heart failure and mortality outcomes are hard end-points which will be reported for ertugliflozin in due course. The surrogate markers of HbA1c, weight and blood pressure reduction have been measured and published.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, HbA1c reduction is a well-established surrogate (as are weight and blood pressure).
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The post-licence observation of DKA for the SGLT-2 inhibitor class was not anticipated (although there are several hypotheses which might explain it); I am not aware of any specific issues with ertugliflozin.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No, although studies of the use of SGLT-2 inhibitors and GLP-1 mimetics are beginning to be published

treatment(s) since the publication of NICE technology appraisal guidance [TA418, TA390, TA336, TA315, TA288]?	and more data will become available in the near future.
22. How do data on real-world experience compare with the trial data?	Generally the experience with the SGLT-2 inhibitor class, in terms of glucose-lowering and weight reduction, has been better than that reported in the clinical trials. This may reflect the higher HbA1c levels at treatment initiation in 'real-life' (termed 'clinical inertia') versus lower HbA1c baseline levels in clinical trials.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	Not applicable.

Key messages
24. In up to 5 bullet points, please summarise the key messages of your statement. • Ertugliflozin will be the fourth SGLT-2 inhibitor to be made available in the UK • SGLT-2 inhibitors are a highly effective class of glucose-lowering medicines • SGLT-2 inhibitors have the secondary benefits of weight reduction and blood pressure lowering • SGLT-2 inhibitors reduce cardiovascular morbidity and mortality in appropriate patients with T2DM • SGLT-2 inhibitors are generally well-tolerated

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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Ertugliflozin in triple therapy for type 2 diabetes. NICE ID 1160

25th November

ERG report

Produced by: Warwick Evidence

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Yellow shading is academic in confidence. *Acquamarine shading is commercial in confidence*.

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Abbreviations

AE	Adverse event
AHA	Anti-hyperglycaemic agents
ASaT	All subjects as treated
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
CANVAS	CANagliflozin cardioVascular Assessment Study
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CS	Company submission
CSR	Clinical study report
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DiRECT	Diabetes Remission Clinical Trial
DKA	Diabetic ketoacidosis
DPP-4i	Dipeptidyl peptidase 4 inhibitor
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
ERTUG	Ertugliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
FEM	Fixed effect model
FPG	Fasting plasma glucose
GLP-1	Glucose-dependent insulinotropic peptide
GTI	Genital tract infection
HRQoL	Health-related quality of life
ITT	Intention-to-treat population
J2R	Jump to reference analysis
LS	Least square
MET	Metformin

MG	Metformin + gliptin
MGF	Metformin + gliptin + flozin
MSD	Merck Sharp & Dohme Ltd
NMA	Network meta-analysis
OD	Once daily
OR	Odds ratio
PBO	Placebo
PIO	Pioglitazone
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
RTB	Return To Baseline
SAE	Serious adverse event
SAXA	Saxagliptin
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT-1	Sodium-glucose cotransporter-1
SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
SITA	Sitagliptin
T2DM	Type 2 Diabetes Mellitus
TA	Technology appraisal
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary tract infections
VS2	VERTIS SITA2 trial
Wks	Weeks

Executive Summary

1.1 Critique of the decision problem in the company's submission

The MSD submission addresses the same population as the NICE scope (people with type 2 diabetes with inadequate glycaemic control on dual therapy) and the same outcomes. However it focuses on a subgroup that is on triple therapy with metformin + a DPP4 inhibitor + an SGLT2 inhibitor. This is not a combination in which the use of SGLT2 inhibitors (hereafter, the "flozins") has been previously approved by NICE but MSD provide confidential prescribing data reporting that [redacted]% of patients in a panel of 150 general practices (800 GPs, so population size about 1.2 million) in the UK on triple therapy are on metformin + DPP4 inhibitor + flozin. The DPP4 inhibitors are hereafter referred to as the gliptins, so this combination is abbreviated to MGF.

Previous technology appraisals

The NICE guidances from previous appraisals of flozins for triple oral therapy are;

- Dapagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in adults, only in combination with metformin and a sulfonylurea (TA418).[1]
- Canagliflozin in a triple therapy regimen is recommended (TA315[2]) as an option for treating type 2 diabetes in combination with metformin and a sulfonylurea **or** metformin and a thiazolidinedione.
- Empagliflozin in a triple therapy regimen is recommended (TA 336)[3] as an option for treating type 2 diabetes in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione.

In practice, "a thiazolidinedione" means pioglitazone, following concerns about cardiovascular risk with rosiglitazone.

NICE type 2 diabetes guideline

The NICE clinical guideline on type 2 diabetes (NG 28)[4] includes a flowchart on drug treatment which is reproduced as Figure 1 on page 13 of the MSD submission (see Figure 1 below), with the suggestion that treatment with metformin + a gliptin + a flozin be added as an additional option in the intensification to triple therapy, in people on dual therapy whose HbA1c is 7.5% or over. We reproduce the version in the MSD submission below.

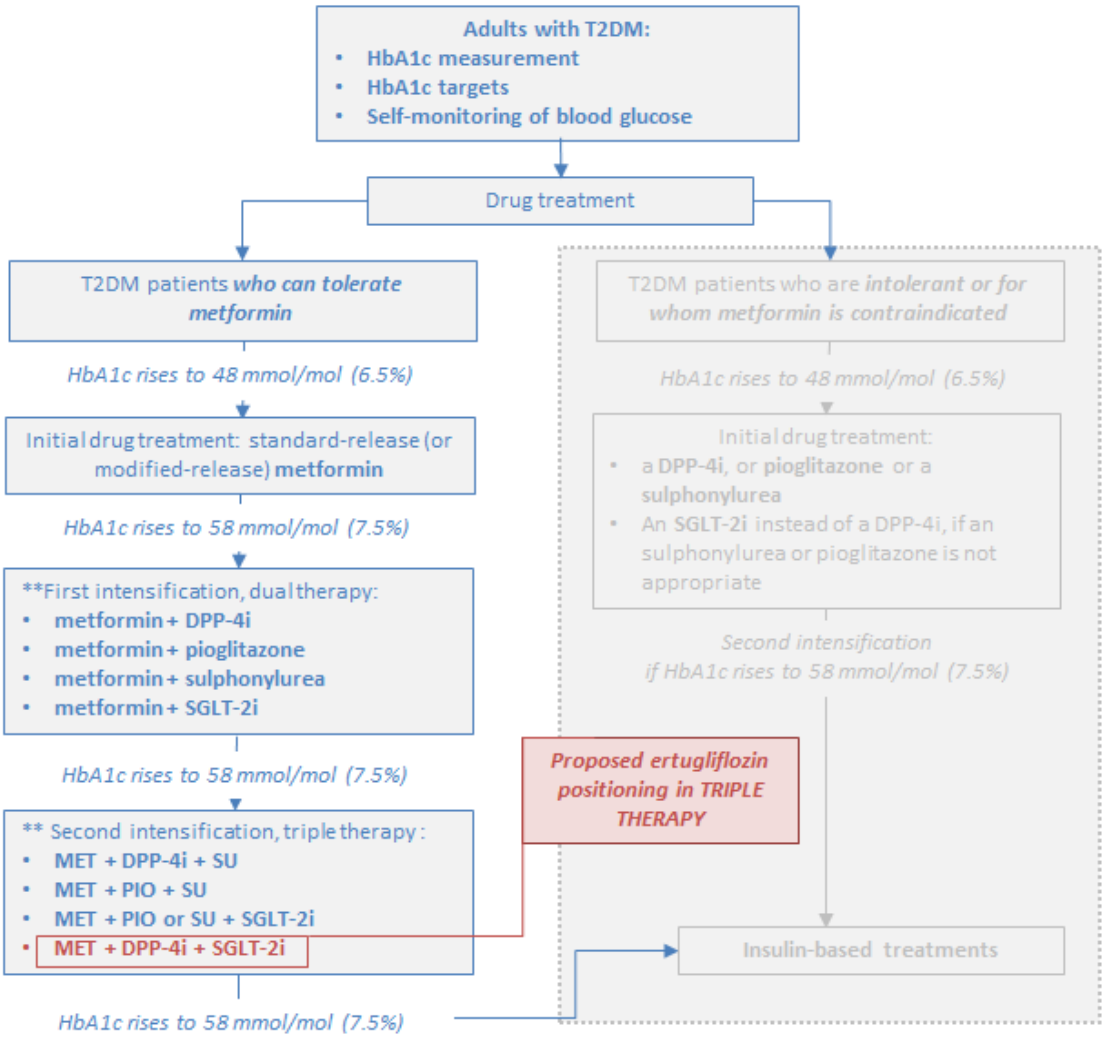

Figure 1. The NICE clinical guideline on type 2 diabetes flowchart on drug treatment

MSD have not asked for ertugliflozin to be included in the MET + PIO or SU + SGLT-2i line.

1.2 Summary of the clinical effectiveness evidence submitted by MSD

The clinical effectiveness section of the MSD submission has two elements;

- An account of VERTIS SITA2 trial (VS2)[5] which compared the MGF triple regimen with ertugliflozin as the flozin, with an MG + placebo comparator. Ertugliflozin is shown to be clinically effective compared to placebo. See section 2.1 of ERG report.

- A network meta-analysis (NMA) comparing ertugliflozin in the VS2 trial with other flozins in similar MGF trials. See section 2.2 of ERG report. The MSD submission concludes that

ertugliflozin is as effective as dapagliflozin, canagliflozin, and empagliflozin in MGF regimens.

1.3 Summary of the key issues in the cost effectiveness evidence

The MSD submission adopts a cost-comparison approach, which is approved by NICE when there is clinical effectiveness equivalence or superiority and a similar or lower price. MSD say that this is the case for ertugliflozin in triple MGF therapy.

1.4 Summary of ERG's preferred assumptions

The ERG agrees that ertugliflozin has not been shown to be significantly different in clinical effectiveness to other flozins, in triple therapy with metformin and a gliptin. In the trials in the MSD NMA, different gliptins are used, and MSD assume that all the gliptins are of similar efficacy. The ERG agrees that this assumption is reasonable. We accept the MSD costings. In a cost-comparison scenario, no cost-effectiveness modelling is required.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG checked the statistical analysis of the VS2 trial and the NMA. We had a few criticisms but none sufficient to invalidate the MSD conclusions.

The ERG thinks a simpler comparison of clinical effectiveness could have been carried out against only one of the other flozins approved by NICE in triple regimen, instead of the NMA, and has done this (Appendix 3). We conclude that clinical effectiveness equivalence is plausible.

The ERG thought that the VERTIS FACTORIAL trial provide further evidence on the effectiveness of ertugliflozin in triple therapy in the MFG combination and added data from that trial.

The main issue is that the triple therapy regimen used in the MSD submission, with metformin + gliptin + flozin, has not been approved (or rejected, or indeed considered) in the appraisals of earlier flozins.

The MSD submission has not asked for approval of ertugliflozin in the triple regimens approved by NICE for canagliflozin, dapagliflozin and empagliflozin, in triple therapy with metformin and either a sulphonylurea or pioglitazone. There are currently no trials of ertugliflozin in those combinations. However, the ERG thinks it would be reasonable to extrapolate from clinical equivalence shown in trials of triple therapy with gliptins and metformin, to triple therapy with metformin and either a sulphonylurea or pioglitazone.

2. Clinical effectiveness evidence

2.1 VERTIS SITA 2

Full details are in Appendix 1. In the VERTIS SITA2 (VS2) trial, NCT02036515[5, 6] 464 patients with type 2 diabetes who were inadequately controlled (HbA1c 7.0 to 10.5%) on dual therapy with metformin and sitagliptin were randomised to ertugliflozin 5mg or 15mg, or placebo. They came from 104 centres in 12 countries, giving an average recruitment of 4.6 patients per centre. Most centres were in Europe (49), mainly Eastern Europe, or the USA (28), with others in Korea (12), Malaysia (6) and Argentina (5). Exclusion criteria included a history of diabetic ketoacidosis, cardiovascular disease, uncontrolled hypertension, treatment with insulin, or chronic renal failure, defined as eGFR <60 ml/min. (A few patients with renal impairment were included – 2.6% in the ertugliflozin 15mg arm. We note a trivial error in Table 7 of the submission – the figures for the ertugliflozin 5mg arm exceed 100%.) The ERG assesses the trial as being of good quality. Most authors came from the manufacturers, MSD or Pfizer.

The results as presented in the MSD submission are slightly different from those in the published paper and the Clinical Study Report (CSR) because of rounding. This is of no consequence.

The trial lasted for 52 weeks, but the results from Phase 1 (to 26 weeks) are used for comparing the efficacy of ertugliflozin with other flozins. If glycaemic control deteriorated or failed to improve, patients could be started on rescue treatment with glimepiride (or insulin if glimepiride was considered inappropriate). At early visits, the threshold for rescue was based on fasting plasma glucose (11.1 mmol/l after week 12), but at week 26 an HbA1c level over 8.0% also triggered rescue.

Key results;

- At 26 weeks, 78% of the placebo group, 89% of the ertugliflozin 5mg and 91% of the ertugliflozin 15mg group remained on allocated treatment. The corresponding figures at week 52 were 48%, 77% and 76%.
- At 26 weeks, 17% of the placebo group achieved the HbA1c target of <7.0%, falling to 14% by week 52. At 26 weeks, 32% of the ertugliflozin 5 mg achieved that target, as did 40% of the ertugliflozin 15mg arm. By 52 weeks, the corresponding ertugliflozin figures were 33% and 33%. So most patients would be considered for further intensification of treatment.
- By 26 weeks, rescue treatment was required in 1.3% of the ertugliflozin 5mg group, 2% of the ertugliflozin 15mg group, and 16.3% of those on placebo.

- Of those still on allocated treatment at 26 weeks, the mean reductions in HbA1c were 0.3% on placebo, 0.9% on ertugliflozin 5mg and 0.8% on ertugliflozin 15mg. Of those still on allocated treatment at 52 weeks, the reductions in HbA1c were 0.7%, 1.0% and 1.0% on placebo, ertugliflozin 5 and 15mg respectively (but only 48% were still on placebo, so the 0.7% reduction reflects selection out of patients with poor control).
- Weight loss by 26 weeks was 1.3kg, 3.4kg and 3.0kg on placebo, ertugliflozin 5 and 15mg respectively. By week 52, weight loss was mostly maintained on ertugliflozin, 3.5Kg on 5mg and 2.8mg on ertugliflozin 15mg, whereas a little weight (0.3kg)was regained by the placebo group (perhaps partly due to weight gain with rescue glimepiride – the 52 week weight results include all patients).
- Systolic blood pressure fell by 0.9 mmHg in the placebo arm, and by 3.8 mmHg and 4.8 mmHg in the ertugliflozin arms. The fall on placebo was not maintained to 52 weeks but was in the ertugliflozin arms.
- The frequencies of genital tract infections by 52 weeks were in women, 1.9% on placebo (one case), and 12% and 14% on ertugliflozin 5mg and 15mg. In men, none on placebo, 5% and 4% on ertugliflozin 5mg and 15mg.
- Urinary tract infections showed little difference amongst arms.
- There were no ketoacidosis events.
- The higher the baseline HbA1c, the greater the reduction by week 26. For example, on ertugliflozin 5mg, the mean HbA1c reductions were 0.78% in those with baseline HbA1c < 8.0%; 0.87% in those with baseline HbA1c 8.0 to <9.0%; and 1.81% in those with baseline 9.0% or over. So ertugliflozin is still worth trying in people with a high baseline HbA1c.

Conclusion: ertugliflozin is effective in improving glycaemic control, with a third of patients achieving the target of HbA1c <7.0%, with modest weight loss and reduction in blood pressure.

Adverse events

The commonest adverse event (AE) was genital tract infections. The FDA pooled data from all placebo controlled trials of ertugliflozin, giving larger numbers than in VERTIS SITA 2 alone, as shown in Table 1.

Table 1. Adverse events in pooled trials versus placebo

	Placebo N = 515	Ertugliflozin 5mg N = 519	Ertugliflozin 15mg N = 510
Genital mycotic	1/280 0.4%	10/267 3.7%	11/265 4.2%

infections – men			
Genital mycotic infections – women	7/235 3.0%	23/252 9.1%	30/245 12.2%
Urinary tract infections	3.9%	4.0%	4.1%
Increased urination	1.0%	2.7%	2.4%

The MSD submission argues that the frequency of common adverse effects is similar amongst the flozins and the ERG accepts this.

Diabetic ketoacidosis

There have been reports of diabetic ketoacidosis (DKA) with the flozins. However rates are low in absolute terms, with the EMA (2015) reporting 101 cases over about 500,000 patient years of flozins use. The EMA[7] concludes that DKA should be regarded as a rare adverse event of flozin treatment in type 2 diabetes, affecting no more than one in 1,000 patients. It makes recommendations for reducing the occurrence of DKA, including avoiding use of the flozins in people with poor insulin production, increased insulin requirement such as due to illness, alcohol abuse or conditions that lead to dehydration.

In an FDA[8] pooled analysis of all ertugliflozin trials (whether placebo controlled or against active comparators), DKA was reported in 2 people (out of 1693) in 15mg ertugliflozin arms. There were no cases in 1716 people in the 5mg arms or in the placebo arms.

Other adverse events

Some rare adverse events have been reported with other flozins, including fractures with canagliflozin and dapagliflozin. A recent conference abstract by Hickman et al [9] reported a pooled analysis of 4859 patients from seven ertugliflozin RCTs. They found no increase in fractures in the ertugliflozin arms compared to the placebo arms. Bone mineral density (BMD) was measured in spine, radius, neck of femur and "total hip" at 2 years. A small reduction in BMD (1.17% in post-menopausal women) was reported for total hip but was not considered clinically meaningful.

The EMA[10] has noted an increase in amputations, mostly of toes, but some of lower limb, amongst people on canagliflozin in the CANVAS trial[11] which is the cardiovascular outcomes trial of canagliflozin. The EMA view is that "*the possibility that canagliflozin increases lower limb amputations is currently not confirmed".* Such events may be the result of volume depletion in patients with vulnerable micro/macrocirculations.

A rise in pulse rate has been reported with some glucose –lowering drugs such as the GLP-1 analogues.[12] The clinical significance of this is not known. A pooled analysis of three ertugliflozin trials by Liu et al[13] reported no rise with ertugliflozin.

In VS2, weight loss was 0.6 kg less at 52 weeks on the higher dose of ertugliflozin. This finding has been reported before in a review and meta-analysis by Li and colleagues[14] on 4828 patients in 14 trials of combination therapy with a flozin and a gliptin, though only four flozins were included: canagliflozin, dapagliflozin, empagliflozin and tofogliflozin.

Clarification questions and responses.

There were no serious problems with the MSD submission and the ERG had relatively few clarification questions.

In Tables 15, 17 and 19, only some cells are shaded as academic in confidence. MSD explained that some data had been presented at the American Diabetes Association meeting in July 2018.

2.2 NMA

The quality of the trials included in the NMA was assessed in the MSD submission, and cross-checked by the ERG. (See Appendix 2). We are in broad agreement that the included trials are of good quality.

Some results of the NMA have been published as a conference abstract[15] by McNeill and colleagues.

One trial by Jabbour et al[16] compared dapagliflozin with placebo in dual therapy with sitagliptin and in triple therapy with sitagliptin and metformin. Some results were not split by dual and triple therapy, including proportion achieving HbA1c target (< 7.0%) and adverse events. However it appears that some dual results were included in the MSD NMA. Only the triple therapy group is relevant. MSD re-ran the NMA without some Jabbour results but that made little difference. A few minor errors were noted in Figures 12 and 13, and Table 25, and the meta-analyses re-run. There is a formatting error in MSD submission Table 14 – the third row belongs to the Dagogo-Jack study not the Jabbour trial. MSD note that the correct data were used in the NMA.

2.3 Statistical analysis of VERTIS SITA 2 and the NMA

The clinical evidence supporting the efficacy of ertugliflozin in triple therapy in combination with metformin and sitagliptin came from the VS2 trial.

MSD state that their sample size calculation suggested recruiting 405 patients to achieve a study with 97% power to detect a difference of 0.5% in change from baseline HbA1c between ertugliflozin and placebo, assuming 19% of patients were lost to follow-up. The ERG were able to produce similar sample size estimates to those reported in the statistical analysis plan. The study recruited beyond the calculated sample size (462 patients).

For their primary statistical analysis, MSD use the Full Analysis Set (FAS) population, which was defined as patients who received at least one dose of study treatment and who had at least one measurement of the outcome. This could result in unhealthier patients being underrepresented in the FAS population. The ERG requested to see the baseline characteristics for the FAS population to ensure there were no major imbalances. In response MSD stated that the FAS population was identical to the "all subjects as treated" (ASAT) population. The ERG noted there were no major imbalances of baseline characteristics across the arms of VS2 in the FAS population.

MSD used continuous longitudinal data analysis methods to model the treatment effects for the continuous outcome measures, and logistic regression for the binary outcome measures. Upon request, they confirmed that they used a random effect to account for correlation in an individual's repeated measurements and did not account for another other hierarchical effects.

Models contained fixed effect parameters for treatment, previous treatment with glucose-lowering drugs (metformin + gliptin/ metformin + SU), baseline eGFR, time, and the interaction of time by treatment; however, MSD did not present the justification for the inclusion of these covariates. The ERG requested evidence to support their inclusion in the final analytical models. In response MSD referred to their statistical analysis plan, in which the ERG found no clear justification for the covariate inclusion. Despite this, their inclusion was generally consistent across other published analyses in this field. In addition, the ERG requested the full model output, to verify that no covariates beyond examination of the final models, but MSD only provided model output detailing the treatment effects, and not the other covariates.

The output that was provided by MSD in response to the ERG clarification questions matched the results presented in their main submission for the primary and majority of the secondary outcomes. For the secondary outcome, HbA1c at target, MSD did not provide output of the final logistic regression model, and the ERG could not verify their consistency.

Due to the multiple outcomes, MSD implemented a planned testing procedure where the 15mg arm was tested against the placebo arm, followed by the 5mg arm to the placebo arm across many of the outcome measures. MSD stated that if tests did not meet statistical significance then later subsequent tests were only performed nominally. The statistical analysis plan stated that the following outcomes were included in the ordered testing procedure: HbA1c change, fasting plasma glucose, body weight, HbA1c >7% and SBP. The order in which the variables were tested was not clearly presented, but as highly significant differences between placebo and ertugliflozin were observed for most outcomes, this was not a major concern.

The ERG was concerned about the potential bias introduced through the decision to analyse using the FAS population. These concerns were shared by the US Food and Drug Administration (FDA). Following request from the FDA, MSD performed two conservative analyses of the primary outcome (a "return to baseline" and a "jump to reference") where missing values were replaced, and the analysis repeated. In both of these analyses, a significant treatment benefit of ertugliflozin remained and the ERG were satisfied with the implementation of the statistical analysis.

NMA comment

MSD performed an NMA comparing ertugliflozin in triple therapy against other flozins used in triple therapy, using the results of VS2 and other relevant trials. A number of mistakes were noticed in the reporting of the NMA (clarification questions A7-10) and the ERG requested the WinBUGs code in order to scrutinise and verify the analysis.

The main assumptions of the NMA are consistency and homogeneity of the included trials.

MSD reported that the trials included in the NMA were broadly similar. The ERG noted the patients in VS2 were similar to those in Rodbard 2016 (canagliflozin) and Softelund 2017 (empagliflozin), however patients in the Mathieu 2015 (dapagliflozin) had a shorter average disease duration (7.6 years vs 9.5 years) and were more likely to be female (54% vs 43%) than in VS2. Neither of these factors are important in flozin trials, unlike in trials of some other drugs which rely on beta cell capacity, which declines over time in type 2 diabetes.

In Jabbour 2014 (dapagliflozin), patients had a higher average weight (94.1kg vs 86.9kg) and had a shorter average disease duration than in VS2 (6.6 years vs 9.5 years). Three different gliptins are used across the studies: sitagliptin, saxagliptin and linagliptin. The efficacy of these was assumed to be equal to allow a broader connected network. However the dapagliflozin 10mg arms from the two dapagliflozin trials were treated as distinct interventions in the NMA, without explanation, but presumably because the results at 26 weeks were rather different, as outlined below.

MSD reportedly assessed the statistical heterogeneity measuring the between study variance for each analysis. However, these did not appear to be presented or commented upon in their report, and it is unclear whether considerable statistical heterogeneity was present.

The ERG accept that MSD could not formally assess inconsistency as there was insufficient evidence to perform Bucher tests, and compare indirect and direct treatment effect estimates.

The ERG verified the data extraction for the NMAs provided by MSD against the original trial publications. The ERG ran their own NMA for the primary outcome and produced similar results to those presented by MSD, with no changes to estimates of effect size or statistical significance for the ertugliflozin comparisons.

Results

The ERG agree that no significant differences were found between ertugliflozin and the other comparators in the NMA for change in HbA1c.

Other results from the NMA:

[redacted]

This was because the reduction in HbA1c after 26 weeks with dapagliflozin in the Jabbour trial was only 0.4%, which contrasts with the higher reduction in the Mathieu trial (0.72%, placebo adjusted). There were only minor differences in baseline differences between these trials. Patients in Jabbour were more overweight (94kg versus 86kg) but had a lower baseline HbA1c (7.8% versus 8.2%) which seems insufficient to explain the difference in efficacy estimates. With longer follow-up, the reductions were more similar at 0.6% and 0.74% at 48 and 52 weeks.

In the random effects NMA presented by MSD (HbA1c % change, SBP, weight), the credible intervals on all estimates were very wide and no significant differences were found amongst the flozins.

ERG conclusion: While absolute equivalence is not proven, the NMA showed no clinically significant differences in glucose-lowering efficacy amongst the flozins. The effect on HbA1c of dapagliflozin in the Jabbour trial at 26 weeks was smaller than in the other dapagliflozin trial, but by 52 weeks, the effect had increased to close to that of ertugliflozin (appendix 4).

The trial of canagliflozin included in the NMA was by Rodbard et al. [17] It used a titration method, starting on 100mg daily and increasing if necessary – which it usually was, with 85% ending on 300mg. The titration approach may be a better guide to use in routine practice, as guided by the licence, than the results of trials where patients are randomised to 300mg from the start. Some previous studies have reported that canagliflozin 300mg is more potent than other flozins, and one study (from Janssen, the manufacture of canagliflozin) has reported that the cost of achieving a HbA1c target of <7% is lower with canagliflozin 300mg than with other flozins.[18]

2.4. Cost minimisation analysis

MSD conducted a systematic literature review to identify evidence on the evaluation of ertugliflozin as a mono, dual and triple therapy for T2DM patients. The review targeted primarily economic evaluations, but it also searched for studies reporting preference-based health-related quality of life (HRQoL) (EuroQol 5D (EQ-5D) utility values) and studies reporting relevant cost and resource use data.

MSD identified no economic evaluations for ertugliflozin in combination with metformin and a gliptin as a treatment for T2DM. Searches conducted by the ERG confirmed the lack of published economic evaluations for the MGF triple therapy combination.

Summary and critique of company's submitted economic evaluation by the ERG

In light of the lack of economic evaluations assessing the flozins on a background of metformin with a gliptin, a de novo cost-minimisation analysis was submitted by the company. The approach was justified on the basis of NMA results showing that the efficacy (HbA1c, weight change, SBP and HBA1c within target) and safety (AEs) of all the flozins were similar in triple therapy. The ERG considers this to be a valid justification for the analytic approach taken.

Type of analysis

Cost-minimisation calculations were carried out in Microsoft Excel. On the premise of no differences in testing, initiation, administration or monitoring costs amongst the flozins, only drug acquisition costs were considered by MSD. A one year time horizon, justified as being sufficiently long to reflect the difference in acquisition costs but equivalence of outcomes between the treatments, was used. Given this relatively short time horizon, discounting was appropriately not applied. The ERG

considers the employed assumptions to be reasonable and the submitted calculations to be appropriate for the purposes of this cost-minimisation analysis.

A table detailing answers to the NICE reference case checklist was submitted and is given below (Table 2), replicating Table 28 in the Company's submission.

Table 2. NICE reference case checklist

	Previous appraisals			Current appraisal	
Factor	**TA315** Canagliflozin in combinations	**TA336** Empagliflozin in combinations	**TA418** Dapagliflozin in triple therapy	**Chosen values**	Justification
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime (40 years)	1 year	It is long enough to reflect all important differences in costs or outcomes between the treatments being compared
Treatment waning effect?	HbA1c drift was assumed to be 0.14% for SGLT-2is	Not reported	Not reported.	None applied	Efficacy and safety are assumed to be equal for the treatments compared in a cost-minimisation analysis
Source of utilities	Bagust and Beale, 2005 [19] Currie et. al 2006 [20], Janssen UK Study (TA315) [21]	Utilities were sourced from numerous publications. The predominant sources were UKPDS 62 [22], Sullivan et al., 2011 [23]	Health Survey for England, 2003 [24], UKPDS 62 [22], Currie et al., 2006 [20], Barry et al., 1997 [25] (ref), Bagust and Beale, 2005 [19]	Not applicable.	Only costs are considered in a cost-minimisation.
Source of costs	Drug acquisition costs were taken from British National Formulary (BNF) [26], procedure costs were taken from the National Schedule of Reference Costs 2011-12 [27]	Drug acquisition costs were taken from the BNF. Event cost were sourced from Clarke et al., 2003 [28]	Drug acquisition costs were taken from the BNF complication were taken from UKPDS 65 [28], 84 [29], Curtis 2013 [30]	Drug acquisition costs were taken from the NHS drug tariff [31]	Reports the latest drug list prices as collated by the NHS.

Abbreviations: TA, technology appraisal; HbA1c, haemoglobin A1c; SGLT-2is, sodium-glucose co-transporter 2 inhibitor; UKPDS, United kingdom Prospective Diabetes Study; NHS, National Health Services

Justifications for deviance from the NICE reference case and previous appraisals were based on the assumption that efficacy and safety are equal for the therapies compared in this submission. Therapies and dosages were specified according to marketing authorisations and can be seen in Table 29 of the submission (replicated in Table 3 below).

Table 3. Interventions and comparators assessed in cost-minimisation analysis.

Therapy	Units
Background therapy	
Metformin	2000 mg OD
DPP-4i (Sitagliptin)	100 mg OD
Intervention	
Ertugliflozin	5 mg or 15 mg OD
Comparators	
Canagliflozin	100 mg or 300mg OD
Dapagliflozin	10 mg OD
Empagliflozin	10 mg or 25 mg OD

Inputs

The sole input in the cost-minimisation analysis is the acquisition cost of the compared therapies. As such, and on the basis of NMA results showing equivalent effectiveness and safety (number and type of AEs), the model contains no inputs on outcomes. HRQoL, collected in the VERTIS SITA2 trial for patients on ertugliflozin and placebo using the EQ-5D-3L instrument showed a negligible change at different collection points (baseline, 26 and 52 weeks). This, and the NMA results indicating that there are no statistically significant differences between the SGLT-2is in triple therapy in terms of efficacy and safety, justified the assumption of similar HRQoL across the compared treatments. Resource use and costs beyond drug acquisition were not considered.

The drug acquisition costs and drug dosages are reported in Table 30 of the MSD submission, together with the calculated annual cost of triple-therapy ertugliflozin and the comparators treatments. The employed acquisition cost values (price per pack) was obtained from NHS Drug Tariff Drug Tariff NHS Business Services Authority website: NHS; 2018.[32] The ERG confirms the accuracy of these values.

Results of cost-minimisation analysis

Given that metformin and DPP-4i acquisition costs are identical for all comparators, [redacted].

Ertugliflozin is associated with an annual cost of [redacted] (£[redacted] per day * 365.25_days), while

canagliflozin, dapagliflozin and empagliflozin have an annual cost of £478.48 (£1.31 per day * 365.25 days). This results in an overall annual [redacted] in favour of ertugliflozin.

2.5 Additional work by ERG

In Appendix 3 we provide a table comparing the VS2 trial with that by Mathieu and colleagues which used dapagliflozin in combination with sitagliptin and metformin in the triple therapy arm. We think this comparison provides reasonable evidence that ertugliflozin is at least as effective as dapagliflozin.

We also looked at extension studies (Appendix 4). In brief, the 48-52 week results in the Jabbour and the Mathieu trials of dapagliflozin were similar in terms of reductions in HbA1c (reductions of 0.7 (5mg), 0.6 and 0.8%). Weight loss was slightly higher with ertugliflozin; 3.5kg on 5mg, versus 2.1 and 1.8 kg on dapagliflozin.

3. Discussion

HbA1c changes in the VERTIS SITA 2 trial

The HbA1c results in VS2 have been reported in different ways as shown in Table 4 .

Table 4. Changes in HbA1c in VS2

All changes are % HbA1c

	Placebo	5mg	15mg
Dagogo-Jack			
baseline	8.0	8.1	8.0
26 weeks	7.7 (119)	7.2 (138)	7.2 (138)
52 weeks	7.3 (73, 48%)	7.1 (120, 72%)	7.0 (115, 76%)
"Change from baseline" 26 weeks	-0.2	-0.8	-0.9
LS mean 26 wks	-0.1	-0.8	-0.9
LS mean vs PBO		-0.7	-0.8
FDA Stats review			
J2R vs PBO		-0.50	-0.56
RTB	-0.21	-0.69	-0.79
RTB vs PBO		-0.48	-0.58

J2R = "jump to reference" data imputation method when missing data

RTB = return to baseline. The FDA documents[8] refer to the VERTIS SITA 2 trial as P006.

One issue with the MSD analysis is that patients who had to start rescue therapy were no longer followed up – the analysis is not by ITT. So any HbA1c data collected after glycaemic rescue or other discontinuation was excluded from MSD analysis. The FDA Statistical Review[8] commented on this:

"The cLDA primary analysis does not adequately address missing data.
The retrieved dropout approach is our preferred method, however there were not enough subjects who discontinued treatment and were followed up to perform this analysis.
The J2R analysis assumes subjects who discontinue on the experimental arm are represented by subjects who complete treatment on the comparator arm. This assumption is questionable. At the same time it is unclear how much worse the measurements of subjects who discontinue would have been had they been measured. It is my view that the RTB analysis most closely addresses missing data."

Nevertheless, the FDA Statistical Review accepted that the evidence showed superiority of ertugliflozin over placebo.

However, this issue applies to the changes in HbA1c. That was the primary outcome. A more useful outcome is the proportions who reached the target HbA1c of <7.0%. The FDA analysis (RTB) reported these to be 20% on placebo, 35% on ertugliflozin 5mg and 42%5 on ertugliflozin 15mg

VERTIS-FACTORIAL trial

The MSD submission did not include any data from the VERTIS FACTORIAL trial by Pratley et al 2018.

In the VERTIS-FACTORIAL trial adults with type 2 diabetes and HbA1c ≥7.5 and ≤11.0% on a stable dose of metformin were randomised to five groups: ertugliflozin 5 mg; ertugliflozin 15 mg; sitagliptin 100 mg; ertugliflozin 5 mg + sitagliptin 100 mg; ertugliflozin 15 mg + sitagliptin 100mg; all with metformin. The two triple therapy groups provide data of relevance to the present appraisal.

At weeks 26 and 52 similar reductions in key outcomes were observed in the 5mg and 15mg triple therapy groups, as shown in Table 5. The changes from baseline seen were generally consistent over the two time periods for HbA1c and weight. Systolic blood pressure changes were less marked over time and the proportion in target HbA1c also reduced.

Overall the results were comparable to those seen in the VERTIS-SITA trial at 26 (Appendix 1) and 52 weeks (Appendix 4). HbA1c reductions were somewhat greater in the VERTIS-FACTORIAL trial at both time points, but baseline HbA1c was higher (8.6% in Factorial, 8.0 in VS2). Weight and SBP changes were somewhat smaller (apart from the 15 mg dose at 52 weeks in VERTIS FACTORIAL, which had greater weight loss). The proportion of participants in target HbA1c was higher at 26 weeks for both dose arms of the VERTIS-FACTORIAL trial –see Table 5.

Table 5. Changes in key outcomes in the VERTIS-FACTORIAL trial

	Ertugliflozin 5mg[1] 26 wks, n=243	Ertugliflozin 15mg[1] 26 wks, n=244	Ertugliflozin 5mg[1] 52 wks, n=243	Ertugliflozin 15mg[1] 52 wks, n=244
Changes from baseline				
HbA1c %	−1.5 (−1.6, −1.4)	−1.5 (−1.6, −1.4)	−1.4 (−1.5, −1.2)	−1.4 (−1.5, −1.3)
Weight, kg	−2.5 (−3.0, −2.1)	−2.9 (−3.4, −2.5)	−2.4 (−3.0, −1.8)	−2.8 (−3.4, −2.2)
SBP, mmHg	−3.4 (−4.8, −2.0)	−3.7 (−5.1, −2.3)	−2.3 (−3.8, −0.8)	−2.2 (−3.7, −0.7)
Proportion with HbA1c <7.0%				
% target	52.3	49.2	40.7	39.8

[1]and metformin ≥1500 mg/d and sitagliptin 100mg

So these results provide support to the VERTIS SITA 2 results.

The NMA

In their NMA, MSD assumed that the gliptins were equivalent (page 49) and compared combinations of the four flozins with three different gliptins. If the gliptins varied in effectiveness, this could confound the NMA, if for example a weaker flozin was combined with a stronger gliptin. However the ERG considers the MSD assumption justified, since several analyses have concluded that the gliptins are broadly similar.[33-35] [36]

Comparators

Ertugliflozin in triple therapy with metformin and sitagliptin appears to be broadly as clinically effective as three other flozins in the same combination. However the other flozins have not been appraised by NICE in the MGF combination. MSD make a case, based on prescribing data, that the MGF regiment is sufficiently used in the UK for it to be regarded as a "standard therapy".

However it is a relatively expensive combination compared to others, as shown in Table 6 and Table 7.

Table 6. Annual direct drug costs

Treatment	**Annual costs**
Dapagliflozin	£477
Canagliflozin	£477
Empagliflozin	£477
Sitagliptin 100mg	£434
Saxagliptin 5mg	£412
Vildagliptin 100mg	£435
Linagliptin 5mg	£434
Alogliptin 25mg	£347
DPP-4i (average)	£424.50
Metformin	£25.29

Sulphonyureas	£29.46
Glicazide slow release	£62.18
Pioglitazone	£20.99

Table 7. Annual costs of triple therapy oral combinations

Combination	Annual cost (rounded to whole numbers)
Metformin + SU + pioglitazone	£76
Metformin + gliclazide MR +pioglitazone	£108 Note
Metformin + SU + DPP-4i	£479
Metformin + pioglitazone+DPP-4i	£471
Metformin + gliclazide + flozin	£568
Metformin + DPP-4i+ flozin	£927

Note. Based on past appraisals, gliclazide is the ERG's preferred sulphonylurea based on efficacy and adverse events. Older generation sulphonylureas such as glibenclamide cause more hypoglycaemia. There has been concern about cardiovascular risk with some sulphonylureas such as glipizide and glibenclamide, but gliclazide and glimepiride appear safe. See Khunti et al Lancet Diabetes. [37]

First treatment for type 2 diabetes is diet and activity, but compliance is poor, so drugs are usually needed, starting with metformin. Over time, type 2 diabetes is progressive unless a lot of weight is lost, so more drugs are needed. The second drug is usually a sulphonylurea (SU) such as gliclazide, but may be pioglitazone, because the SUs can cause hypoglycaemia (low blood glucose). Both SUs and pioglitazone cause weight gain.

SUs work by stimulating insulin release from the pancreas, so over time they lose effectiveness, because the beta cell capacity in the pancreas declines.

When a third drug is needed, there are several oral options;

- A gliptin with the commonest being sitagliptin.
- Pioglitazone, if drug 2 was a sulphonylurea, or vice versa.
- A flozin

The injected glucose lowering drugs including GLP-1 analogues such as long-acting exenatide, injected once a week (about £900 a year) and insulin, are usually later in the treatment pathway.

Some patients cannot tolerate some drugs, but the commonest one to not be tolerated is metformin, because of gastro-intestinal adverse effects. It is also contraindicated in patients with chronic renal failure, but so are the flozins.

Some patients have problems with sulphonylureas which can cause hypoglycaemia, and others have contra-indications to pioglitazone, such as macular oedema or heart failure.

Pioglitazone was discounted in some early appraisals of the flozins because of concern then that it might increase the risk of bladder cancer. This concern has been refuted, and pioglitazone has been shown to have cardiovascular benefits. For a review of pioglitazone and bladder cancer see Assessment Report for TA 390.[38]

It could be argued that if patients with type 2 diabetes cannot take either sulphonylureas or pioglitazone, that the MGF combination is then appropriate. The proportion unable to take both sulphonylureas and pioglitazone is not known.

This appraisal does not compare the gliptins and the flozins in triple therapy with metformin and either gliclazide or pioglitazone. Any such comparison would take note of three topics in which the flozins appear to have advantages over the gliptins;

- Weight loss, with a few kg loss with the flozins but none with the gliptins, though the average weight loss does not reach the 5% suggested as required to make a meaningful difference to type 2 diabetes[39]
- A greater reduction in SBP and to a lesser extent in DBP with the flozins than with the gliptins
- A reduction in cardiovascular events, most notably reduction in admissions for heart failure with the flozins[40, 41], compared to no effect with most gliptins, and a possible increase with saxagliptin (See Scheen 2018 for review[42])

However the gliptins are less expensive and have fewer adverse effects (GTIs) than the flozins. In routine care, improvements in HbA1c are often less than seen in trials, and adherence is a key factor in this. A less potent but more acceptable drug may achieve as good results as a more potent but less acceptable one, as shown by Edelman and Polonsky[43] with GLP-1 analogues compared to gliptins.

The reduction in cardiovascular events was first reported with empagliflozin but has also been reported with canagliflozin and dapagliflozin, and it is reasonable to assume that it is a class effect which will also be seen with ertugliflozin. A recent meta-analysis by Zelniker and colleagues[44] reported that significant but modest (14%) reductions in cardiovascular events were seen only in patients with established cardiovascular disease, but that reductions in admissions for heart failure were seen both in those with a history of heart failure (29% reduction) and those with no such history (21% reduction).

One comparator for the future will be oral semaglutide, which has been shown in the PIONEER 2 trial (not yet published in full[45]) to reduce HbA1c more than empagliflozin. Semaglutide has also been shown to reduce cardiovascular events in the SUSTAIN 6 trial.[46]

Lifestyle interventions

The average duration of diabetes in VERTIS SITA2 was over 9 years, so the findings of the weight loss trial, DiRECT [47] (mentioned as a comparator for ertugliflozin monotherapy and dual therapy in the other current STA, ID 1158) cannot be assumed to be applicable because the DiRECT trial recruited patients with shorter durations of diabetes.

However, most people with type 2 diabetes are overweight or obese, and significant (>5% body weight) weight loss can improve control. This usually requires intensive interventions.[39]

Switching to a vegetarian diets has also been reported to improve glycaemic control, with a reduction of 0.39% reported in a systematic review and meta-analysis by Yokoyama and colleagues.[48]

Research needs

We need future surveillance of ertugliflozin (and other new flozins) for adverse events. Genital tract infections are well-known, but serious rare events seen with some other flozins include DKA, amputations (canagliflozin[40, 49]), fractures (canagliflozin[49]) and Fournier's gangrene (necrotising fasciitis of the perineum). The FDA issued an alert about Fournier's gangrene in August 2018.[50]

A cardiovascular safety trial with ertugliflozin, VERTIS-CV is underway.[51]

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Appendix 1. VERTIS SITA2 results

This appendix includes cross-checking of the data in the MSD submission, Dagogo-Jack et al and CSR.

HbA1c (%)

Data in the MSD submissions are as reported in the trial publication and CSR with slight differences due to rounding in the publication. Absolute mean change is similar to the LS mean change. HbA1c in mmol/m also checked. Data in Table 14 are LS change. Data in MSD submission Fig 8 (NMA output) are similar to the difference in LS means vs placebo.

Table 8. HbA1c (%)

HbA1c (%)	**Placebo (n=153)**	**Ertugliflozin 5 mg (n=156)**	**Ertugliflozin 15 mg (n=153)**
Baseline	*(n=152)* 8.03	*(n=155)* 8.05	*(n=152)* 8.00
Week 26	*(n=119. 25 rescue treatment)* *7.7 (1.0)*	*(n=138, 2 rescued)* *7.2 (0.7)*	*(n=138, 3 rescued)* *7.2 (0.8)*
Mean change (SD)	*−0.2 (1.0)*	*−0.8 (0.8)*	*−0.9 (0.9)*
LS mean change (95% CI)	*−0.1 (−0.2, 0.0)*	*−0.8 (−0.9, −0.6)*	*−0.9 (−1.0, −0.7)*
Difference in LS means vs placebo (95% CI), P value		*-0.7 (-0.9, -0.5), p<0.001*	*-0.8 (-0.9, -0.6), p<0.001*
NMA base case Median difference vs placebo (95% CrI)		[redacted]	[redacted]

Data in italics from Dagogo 2017, otherwise from MSD submission. CI, confidence interval. LS, least squares; SD, standard deviation.

Body weight

Data in the MSD submissions are as reported in the trial publication (slight differences due to rounding). Absolute mean change and final values were not reported in the publication but are consistent with the data in the CSR.

Data in MSD submission Table 14 are LS change.

Data in submission Fig 9 (NMA output) are the same as the difference in LS means vs placebo.

Table 9. Body weight

Body weight (kg)	**Placebo (n=153)**	**Ertugliflozin 5 mg (n=156)**	**Ertugliflozin 15 mg (n=153)**
Baseline	86.46	87.64	86.60
Week 26	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

LS mean change (95% CI)	*−1.3 (−1.8, −0.9)*	*−3.4 (−3.8, −2.9)*	*−3.0 (−3.5, −2.6)*
Difference in LS means vs placebo (95% CI), P value		*-2.0 (-2.7, -1.4), p<0.001*	*-1.7 (-2.4, -1.1), p<0.001*
NMA base case Median difference vs placebo (95% CrI)		[redacted]	[redacted]

Data in italics from Dagogo 2017, otherwise from MSD submission or CSR. CI, confidence interval. LS, least squares; SD, standard deviation.

SBP (mmHg)

Data are as reported in the trial publication (slight differences due to rounding). Absolute mean change and final values were not in the publication. There were slight differences between the absolute mean change values and the LS mean change values, especially for placebo.

Data in MSD submission Fig 10 (NMA output) are the same as the difference in LS means vs placebo.

Table 10. SBP (mmHg)

SBP (mmHg)	**Placebo (n=153)**	**Ertugliflozin 5 mg (n=156)**	**Ertugliflozin 15 mg (n=153)**
Baseline	130.19	132.14	131.6
Week 26	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	−0.9 (−2.7, 0.9)	−3.8 (−5.5, −2.1)	−4.8 (−6.6, −3.1)
Difference in LS means vs placebo (95% CI), P value		-2.9 (-5.4, -0.5), p=0.019	-3.9 (-6.4, -1.5), p=0.002
NMA base case Median difference vs placebo (95% CrI)		[redacted]	[redacted]

Highlighted data from submission or CSR. CI, confidence interval. LS, least squares; SD, standard deviation.

Proportion with HbA1c <7.0%

Data are as reported in the trial publication and CSR (slight differences due to rounding

Data in Table 14 are proportions (rounded) as reported in publication.

Data in MSD submission Fig 11 (NMA output) are median ORs and differ from the adjusted OR in Table below but remain statistically significant. This data is also reported in MSD Appendix L1.

Table 11. Proportion with HbA1c <7.0%

	Placebo (n=153)	**Ertugliflozin 5 mg (n=156)**	**Ertugliflozin 15 mg (n=153)**
Proportion	17.0%	32.1%	39.9%
Adjusted odds ratio relative to placebo (95%		3.2 (1.7, 5.7), p<0.001	4.4 (2.4, 8.0), p<0.001)

CI), p value			
NMA base case Median OR vs placebo (95% CrI)		[redacted]	[redacted]

Highlighted data from MSD submission, rest from Dagogo-Jack. CI, confidence interval. LS, least squares; SD, standard deviation.

The FDA RTB analysis[8] reported 20% achieving the target on placebo, and 35% and 42% on ertugliflozin 5mg and 15mg respectively.

DBP (mmHg)

Data are as reported in the trial publication and CSR (slight differences due to rounding). Absolute mean change and final value were not reported in the publication, but are consistent with data in the CSR. DBP data are not included in the NMA

Table 12. DBP (mmHg)

DBP (mmHg)	**Placebo (n=153)**	**Ertugliflozin 5 mg (n=156)**	**Ertugliflozin 15 mg (n=153)**
Baseline	78.49	78.42	78.79
Week 26	[redacted]	[redacted]	[redacted]
Mean change (SD)			
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means vs placebo (95% CI), P value		[redacted]	[redacted]

Baseline data from Dagogo-Jack. Other data from MSD submission or CSR. CI, confidence interval. LS, least squares; SD, standard deviation.

EQ-5D-3L

EQ-5D data were not reported in the trial publication. Data in the MSD submission was checked against the CSR. An NMA was not conducted for EQ-5D-3L.

Table 13. EQ-5D-3L

	Placebo (n=152)	**Ertugliflozin 5 mg (n=150)**	**Ertugliflozin 15 mg (n=149)**
Baseline	[redacted]	[redacted]	[redacted]
Week 26			
Mean difference (SD)			
LS mean difference (95% CI)	[redacted]	[redacted]	[redacted]
Difference in LS means vs		[redacted]	[redacted]

placebo (95% CI), P value			

Data from CS or CSR. CI, confidence interval. LS, least squares; SD, standard deviation.

Non-severe hypoglycaemic event: publication reported symptomatic hypos (biochemical proof not required). Minus one severe, this would be placebo 3 (2%), 5mg 3.8%, 15mg 0.7% (CS Table 14 has 3%, 4%, 2% respectively).

[redacted] By 52 weeks. The proportions were 3.9%. 4.5% and 2.0% for placebo, 5 and 15mg respectively.
Not used in NMA.

Severe hypoglycaemic event: one event, occurred on placebo. Not used in NMA.

UTIs: MSD submission Table 27 and CSR (figures rounded) agrees with publication. By week 52, 6.5%, 3.2% and 7.2% on placebo, 5 and 15 mg.

[redacted]

Genital mycotic infection. Table 14 of the submission combines men and women for the NMA. The figures in Table 27 of the MSD submission match those in Dagogo-Jack et al.

NMA: models did not converge. Results reported in App Q, no forest plot. NMA OR< 1 suggest interventions have lower odds of GTIs, but this is not reflected by the data or by ORs calculated by reviewer OR>1)

Adverse events: data in CST Table 14 agree with publication, CS Table 27 and CSR (figures rounded).

NMA: The MSD submission, Fig 12, suggests AEs were lower with placebo, whereas they were higher with placebo. MSD noted an error and provided a new forest plot;

MSD response

An error was made when selecting the data to generate the forest plots. The forest plots have been updated with the correct data and the exclusion of the Jabbour et al (2014) data, as per question A8. Please see the revised figure 13 (UTIs) below.

Figure 13 Base case – UTIs at week 24 - 26 (binary outcome – FEM)

Forest plot

Comparison	Median OR	[95% CrI]
ERTU5 vs. PBO	1.36	[0.28, 7.47]
ERTU15 vs. PBO	2.57	[0.67, 12.90]
DAPA10 (Mathieu 2015) vs. PBO	0.78	[0.29, 2.07]
CANA (titrated) vs. PBO	1.00	[0.10, 9.74]
EMPA10 vs. PBO	0.98	[0.34, 2.80]
EMPA25 vs. PBO	0.46	[0.11, 1.55]

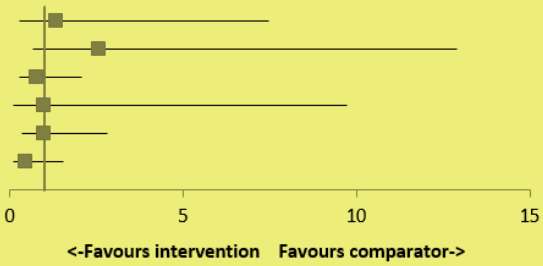

Table 14. Adverse events included in NMA, comparison with publication and NMA basecase

Source	Placebo (n=153)	Ertugliflozin 5 mg (n=156)	Ertugliflozin 15 mg (n=153)
UTIs (%)			
[redacted]			
Publication	2	2.6	4.6
OR calculated by reviewer		1.32 (0.29, 5.98)	2.40 (0.6, 9.4)
[redacted]			
GTIs (%)			
[redacted]			
Publication	0.6	6.4	7.8
OR calculated by reviewer		10.4 (1.3, 82.4)	12.9 (1.7, 100.38)
[redacted]			
AEs (%)			
[redacted]			
Publication	48.4	41.7	43.8
OR calculated by reviewer		0.76 (0.49, 1.20)	0.83 (0.53, 1.30)
[redacted]			

Appendix 2: Quality assessment of trials in NMA.

The MSD quality assessed the included VERTIS SITA2 trial and the trials included in the NMA using the York Centre for Reviews and Dissemination quality assessment tool. See Table 15 for MSD and ERG assessments of trial quality using these criteria. MSDS = MSD submission

Table 15. Trial quality assessment.

	VERTIS SITA2[5]		Jabbour 2014[16]		Matthieu 2015[52]		Rodbard 2016[17]		Softeland 2017[53]	
	MSDS	ERG	MSDS	ERG	MSDS	ERG	MSDS	ERG	MSDS	ERG
Was the randomisation method adequate?	Yes	Yes	NR	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Was the allocation adequately concealed?	Yes	Yes[1]	NR	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes	Yes[1]	Yes	Yes	Yes	Yes[1]	Yes	Yes[1]	Yes	Yes[1 2]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes[3]	Yes	Yes[3]	Yes	Unclear	Yes	Unclear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	No	No[4]	No	No	Yes	Yes (Yes)	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	Yes	Unclear[5]	No	No
Did the analysis include an intention-to-treat analysis?	No	No	No	No	NR	Yes (modified)	No	Yes (modified)	No	No

Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. There are some variations in proportions of men and women in the arm but we have seen not previously seen evidence of any gender difference in clinical effectiveness, except as regards infections as adverse events. A subgroup analysis in VERTIS SITA2 showed slightly smaller reduction in HbA1c in women – 0.78% and 0.72% on ertugliflozin 5mg and 15m g, compared to 0.88%and 0.94% in men.

2. There are slight differences in ethnic proportions, and “Asian” is undefined. Based on the centres involved, it is likely that the recruits were East Asians – from Taiwan and Korea.
3. Described as double blind but no details, NCT record states matching placebo
4. Not at the primary endpoint, higher drop-out rates in placebo during the extension study
5. Unable to identify NCT record to check, MSD submission is correct that vital signs were stated to be reported as adverse events

Appendix 3. Comparison of VERTIS SITA 2 and Mathieu trials.

Table 16. Ertugliflozin + metformin versus dapagliflozin + metformin

Ertugliflozin + metformin versus dapagliflozin + metformin

	VERTIS SITA2	**Mathieu dapagliflozin**
Trial first author and year	Dagogo-Jack 2018[5]	Mathieu 2015[52]
Inclusion criteria similar?	Adult patients with T2DM Receiving stable treatment with metformin (≥1500 mg/d, any formulation) and sitagliptin (100 mg/d) for ≥8 weeks HbA1c level of 7.0% to 10.5% (53-91 mmol/mol) at the screening visit Patients undergoing this regimen for <8 weeks, receiving metformin ≥1500 mg/d along with a sulphonylurea, or receiving lower doses of metformin and/or another DPP-4 inhibitor at screening, were eligible if they met the above criteria after the appropriate dose/medication adjustment, stabilization or washout period. Patients with adequate compliance during the placebo run-in period (≥80% based on pill count) were randomized.	Adults with T2DM. Two stratum depending on prior HbA1c and treatment which led to an open-label treatment-stabilisation period prior to randomisation. **Stratum A:** T2DM with inadequate glycemic control (HbA1c ≥ 8.0 and ≤ 11.5% at screening), on stable metformin therapy alone for at least 8 weeks prior to screening visit (≥ 1500 mg per day). Participants were switched to the nearest lower or higher multiple of metformin IR 500 mg and saxagliptin 5 mg/day for 16 weeks. **Stratum B:** T2DM with inadequate glycemic control (HbA1c ≥ 7.5 and ≤ 10.5% at screening) on stable metformin therapy (≥ 1500 mg per day) and a DPP4 inhibitor (at max approved dose) for at least 8 weeks prior to screening visit. Participants were switched to the nearest lower or higher multiple of metformin IR 500 mg and the DPP-4 inhibitor replaced by saxagliptin 5 mg/day for 8 weeks. At randomisation: HbA1c 7.0–10.5% (53–91 mmol/mol)

Key exclusion criteria	History/possible type 1 diabetes mellitus Systolic BP (SBP) >160 mm Hg and/or diastolic BP (DBP) >90 mm Hg (patients receiving BP medication must have a stable regimen for ≥4 weeks prior to randomization) Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2; serum creatinine ≥115 µmol/L (1.3 mg/dL) in men or ≥106 µmol/L (1.2 mg/dL) in women FPG >14.4 mmol/L (260 mg/dL) prior to the placebo run-in period and confirmed within 7 days. Treatment in the previous 12 weeks with insulin of any type or antihyperglycaemic agents (AHA) other than metformin, DPP-4 inhibitors or sulphonylureas History of ketoacidosis History of myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischaemic attack or functional class III-IV heart failure within 3 months of screening	Cardiovascular events within 3 months of screening Estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or a serum creatinine level of ≥1.5 mg/dL in men or ≥1.4 mg/dL in women Microscopic haematuria with no known cause in men Significant hepatic disease. Received any antidiabetes medication, other than metformin and DPP-4 inhibitors, for >14 days during the 12 weeks before screening. Pregnancy At week -10 (stratum A) and week -2 (stratum B), if FPG was >270 mg/dL, the patient was not randomized.
Duration	26-week, then 78-week extension	24 weeks then 28 weeks extension.
Number of patients	Placebo n=153 Ertug 15 mg n=153 Ertug 5 mg n=156	Dapa n=160 Placebo n=160
Number of centres and	104 centres across 12 countries (Argentina, Bulgaria, Colombia, Czech Republic, Finland, Hungary, Israel, Malaysia, Republic of	United States, Puerto Rico, Romania, Russia, Poland, Mexico, UK, Czech Republic.

countries	Korea, Romania, Slovakia, USA)	
Treatments	Ertugliflozin 5 mg, ertugliflozin 15 mg or placebo once daily, in addition to metformin (≥1500 mg/d, any formulation) and sitagliptin (100 mg/d)	After the 16 or 8 week open-label period participants received dapagliflozin 10 mg/day or placebo (in addition to saxagliptin 5mg and metformin in both groups).
Glycaemic rescue	Open-label glimepiride (or insulin glargine if glimepiride was not considered appropriate) was prescribed for patients meeting glycaemic rescue criteria: Hyperglycaemic rescue criteria were progressively more stringent over time and consisted of FPG values consistently (repeat measurement performed within 7 days): >15.0 mmol/L (270 mg/dL) after randomization through Week 6, >13.3 mmol/L (240 mg/dL) after Week 6 through Week 12, >11.1 mmol/L (200 mg/dL) after Week 12 through Week 26, >11.1 mmol/L (200 mg/dL) or HbA1c >8.0% (64 mmol/mol) after Week 26. Post-rescue efficacy data were treated as missing in all efficacy analyses.	Insulin or any other anti-diabetes medication except other DPP-4 inhibitors, SGLT-2 inhibitors,GLP-1 receptor agonists or metformin within the following criteria: FPG >270 mg/dL at week 6; FPG >240 mg/dL at weeks 6-12; FPG >200 mg/dL at weeks 12-24; HbA1c >8% at weeks 24-52. Data after the receipt of rescue medication were excluded from the analyses.
Baseline characteristics		
Mean age and range	Ertug 5 mg: 59.2 (9.3) Ertug 15 mg: 59.7 (8.6) Placebo: 58.3 (9.2)	Dapa: 55.2 (8.6) Placebo: 55.0 (9.6)
% male	Ertug 5 mg: 51.9% Ertug 15 mg: 53.6% Placebo: 65.4%	Dapa: 43.7% Placebo: 47.5%

	NB A higher proportion of males in the placebo group vs ertugliflozin groups	
Duration of diabetes (years)	Ertug 5 mg: 9.9 (6.1) Ertug 15 mg: 9.2 (5.3) Placebo: 9.4 (5.6)	Dapa: 7.2 (5.7) Placebo: 8.0 (6.6)
Ethnic groups	White: Ertug 5 mg: 73.1% Ertug 15 mg: 75.2% Placebo: 70.6% Asian: Ertug. 5 mg: 21.2% Ertug 15 mg: 18.3% Placebo: 21.6%	White: Dapa: 93.8% Placebo: 91.9% Asian: Dapa: 0.6% Placebo: 0.6%
Body weight (kg)	Ertug 5 mg: 87.6 (18.6) Ertug 15 mg: 86.6 (19.5) Placebo: 86.4 (20.8)	NR
BMI (kg/m^2)	Ertug 5 mg: 31.2 (5.5) Ertug 15 mg: 30.9 (6.1) Placebo: 30.3 (6.4)	Dapa: 31.2 (4.7) Placebo: 32.2 (5.3)
SBP, mean ± SD mmHg	Ertug 5 mg: 132.1 (12.5) Ertug. 15 mg: 131.6 (13.2) Placebo: 130.2 (13.3)	NR
HbA1c mmol/mol; %	Ertug 5 mg: 64.5 (9.4); 8.1 (0.9) Ertug 15 mg: 64.0 (9.1); 8.0 (0.8) Placebo: 64.3 (10.2); 8.0 (0.9)	Dapa: 67 (10.5); 8.24 (0.96) Placebo 66 (10.7); 8.17 (0.98)

FPG mmol/L; mg/dL	Ertug 5 mg: 9.3 (2.1); 167.7 (37.7) Ertug 15 mg: 9.5 (2.2); 171.7 (39.1) Placebo: 9.4 (2.1); 169.6 (37.8)	Dapa: 9.9 (2.7) ;179 (48.9) Placebo: 9.8 (2.6) ;177 (46.8)
One or more blood pressure medications (%)	Ertug 5 mg: 71.8% Ertug 15 mg: 71.2% Placebo: 72.5%	NR
eGFR, mL/min/1.73 m2	Ertug 5 mg: 87.0 (17.5) Ertug 15 mg: 86.9 (15.6) Placebo: 89.9 (17.5)	Dapa: 93.5 (20.8) Placebo: 91.6 (23.2)
Drop out rates: number and % with HbA1c results at 24/26 weeks	Ertug 5 mg: 143 (91.7%) Ertug 15 mg: 140 (90.9%) Placebo: 141 (92.2%)	Dapa: 148 (92.5%) Placebo: 153 (95.6%)
Results		
HbA1c Change from baseline: observed	Placebo; ertug 5mg; ertug 15mg **Change from baseline** **Week 26:** n = 153 n = 156 n = 153 Mean (SD), mmol/mol -1.7 (10.4) -8.9 (8.8) -9.4 (9.5) Mean (SD), % -0.2 (1.0) -0.8 (0.8) -0.9 (0.9) **Week 52:** n = 153 n = 156 n = 153 Mean (SD), mmol/mol -3.1 (9.3) -9.2 (10.0) -10.7 (8.7) Mean (SD), % -0.3 (0.9) -0.8 (0.9) -1.0 (0.8)	**NR**
HbA1c Change	Placebo; ertug 5mg; ertug 15mg	**Week 24:**

from baseline: reported from least squares analysis	**Week 26:** LS mean (95% CI), mmol/mol -1.0 (-2.5, 0.5) -8.5 (-1.0, -7.1) -9.4 (-10.8, -7.9) LS mean (95% CI), % -0.1 (-0.2, 0.0) -0.8 (-0.9, -0.6) -0.9 (-1.0, -0.7) **Difference in LS means vs placebo** **Week 26:** mmol/mol (95% CI) - -7.5 (-9.5, -5.5)* -8.3 (-10.3, -6.3)* % (95% CI) - -0.7 (-0.9, -0.5)* -0.8 (-0.9, -0.6)* **Week 52:** LS mean (95% CI), mmol/mol 0.2 (-1.7, 2.1) -8.1 (-9.8, -6.5) -8.9 (-10.6, -7.2) LS mean (95% CI), % 0.0 (-0.2, 0.2) -0.7 (-0.9, -0.6) -0.8 (-1.0, -0.7) **Difference in LS means vs placebo** **Week 52:** n = 153 n = 156 n = 153 mmol/mol (95% CI) - -8.3 (-10.8, -5.9) -9.1 (-11.5, -6.6) % (95% CI) - -0.8 (-1.0, -0.5) -0.8 (-1.1, -0.6) *P <.001 vs placebo	Dapa Placebo % change (95% CI) -0.82 (-0.96, -0.69) -0.10 (-0.24, 0.04) **Week 52:** % change (95% CI) –0.74 (–0.90, –0.57) 0.07 (–0.13, 0.27)
Proportion of patients achieving HbA1c target of ≤7.0%	**Week 26:** Ertug 5 mg: 32.1%; P < .001 vs placebo; Ertug 15 mg: 39.9%; P < .001 vs placebo; Placebo: 17.0% **Week 52:** Ertug 5 mg: 33.3%	**Week 24** Adjusted: Dapa: 38.0% ; p<0.0001 vs placebo; Placebo: 12.4% **Week 52**

	Ertug 15 mg: 32.7% Placebo: 13.7% NB Statistical testing was not performed at Week 52.	Adjusted: Dapa: 29.4% Placebo: 12.6%
SBP change from baseline (mmHg)	LS mean change from baseline (95% CI) **Week 26:** Ertug 5 mg: -3.8 (-5.5, -2.1). Pairwise comparison vs placebo, difference in LS means (95% CI) -2.9 (-5.4, -0.5); P = .019 vs placebo; Ertug 15 mg: -4.8 (-6.6, -3.1). Pairwise comparison vs placebo, difference in LS means (95% CI) -3.9 (-6.4, -1.5); P = .002 vs placebo. placebo: -0.9 (-2.7, 0.9) **Week 52:** Ertug 5 mg: -4.2 (-6.0, -2.3) Ertug 15 mg: -4.1 (-6.0, -2.2) Placebo: 0.8 (-1.4, 3.1)	**NR**
Weight change from baseline (kg)	**Week 26:** LS mean change from baseline (95% CI): Ertug 5 mg: -3.4 (-3.8, -2.9); Pairwise comparison vs placebo, difference in LS means (95% CI) -2.0 (-2.7, -1.4); P < .001 vs placebo Ertug 15 mg: -3.0 (-3.5, -2.6) Pairwise comparison vs placebo, difference in LS means (95% CI) -1.7 (-2.4, -1.1); P < .001 vs placebo Placebo: -1.3 (-1.8, -0.9)	**Week 24:** Adjusted mean Dapa: -1.9 (-2.34, -1.48) Placebo: -0.4 (-0.86, 0.04) **Week 52:** Adjusted mean Dapa: –2.1 kg (–2.70, –1.56) Placebo: –0.4 kg (–1.01, 0.26)

Urinary tract infections	**Week 26:** Ertug 5 mg: 4 (2.6%) Ertug 15 mg: 7 (4.6%) Placebo: 3 (2.0%) **Week 52:** Ertug 5 mg: 5 (3.2%) Ertug 15 mg: 11 (7.2%) Placebo: 10 (6.5%)	**Week 24:** Dapa: 8 (5.0%) Placebo: 10 (6.3%) **Week 52:** Dapa: 15 (9.4%) Placebo: 16 (10.0%)
Genital tract infection	**Week 26:** Genital mycotic infection (men): Ertug 5 mg: 4/81 (4.9%); P < 0.05 vs. placebo Ertug 15 mg: 3/82 (3.7%) Placebo: 0/100 (0%) Genital mycotic infection (women): Ertug 5 mg: 6/75 (8.0%) Ertug 15 mg: 9/71 (12.7%); P < 0.05 vs. placebo Placebo: 1/53 (1.9%) **Week 52:** Genital mycotic infection (men): Ertug 5 mg: 4/81 (4.9%) Ertug 15 mg: 3/82 (3.7%) Placebo: 0/100 (0%) Genital mycotic infection (women): Ertug 5 mg: 9/75 (12.0%); P < 0.05 vs. placebo Ertug 15 mg: 10/71 (14.1%); P < 0.05 vs. placebo	**Week 24:** Dapa: 8 (5.0) Placebo: 1 (0.6) **Week 52:** Dapa: 10 (6.3%) Placebo: 2 (1.3%)

	Placebo: 1/53 (1.9%)	
Discontinuation due to adverse effects	**Week 26:** Ertug 5 mg: 5/156 (3.2%) Ertug 15 mg: 1/153 (0.7%) Placebo: 1/153 (0.7%) **From week 26 to week 52, a further:** Ertug 5 mg: 7/156 (4.5%) Ertug 15 mg: 6/153 (3.9%) Placebo: 6/153 (3.9%)	**Week 24:** Dapa: 8 (5.0%) Placebo: 2 (1.3%) **Week 52:** Dapa: 9 (5.6%) Placebo: 3 (1.9%)
Trial quality	Good	Good

Appendix 4. Summary of extension studies

Ertu+met+sita[a] **VERTIS SITA 2**	**Dapa+met+sita** **(Jabbour)**	**Dapa+met+saxa** **(Mathieu)**
Change from baseline **at week 52**	**Change from baseline** **at week 48**	**Change from baseline** **at week 52**
LS mean (95% CI)	**Placebo-corrected change (95% CI)**	**Adjusted mean change (95% CI)**
HbA1c (%)		
5mg: –0.7 (–0.9, –0.6) 15 mg: –0.8 (–1.0, –0.7)	-0.6 (–0.8, –0.4)	−0.81 (−1.06, −0.55)
Body weight (kg)		
5mg: –3.5 (–4.1, –2.9) 15 mg: –2.8 (–3.4, –2.2)	-2.1 (–3.2 to –1.0)	−1.8 (−2.6, −0.9)
SBP (mmHg)		
5 mg: –4.2 (–6.0, –2.3) 15 mg: –4.1 (–6.0, –2.2)	NR	NR
DBP (mmHg)		
5 mg: –1.5 (–2.7, –0.3) 15.5mg: –1.4 (–2.6, –0.2)	NR	NR
Genital mycotic infection (women)	Total dapagliflozin group both sexes 22 (9.8%)	10 (6.3%) males and females combined
5 mg: 9 (12.0)[b] 15 mg: 10 (14.1)[b]		
Genital mycotic infection (men)		
5 mg: 4 (4.9)[b] 15 mg: 3 (3.7)		

UTIs		
5 mg: 5 (3.2) 15 mg: 11 (7.2)	Total dapagliflozin group 13 (5.8%)	15 (9.4%)
Symptomatic hypoglycaemia		
5 mg: 7 (4.5) 15 mg: 3 (2.0)	1 event, 0.4%	0

[a]From CS Table M.1 Summary of efficacy outcomes in Phase A + B of VERTIS SITA2 study (FAS: excluding rescue approach).
[b]p-value < 0.05 vs. PBO

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

Pro-forma Response

ERG report

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 7 December 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment
Page 9 line 4 of the report states that “They (patients) came from 104 centres in 14 countries”	Patient were recruited in 12 countries. Proposed amendment “They came from 104 centres in 12 countries”	Factual inaccuracy on the randomised controlled trial information

Single Technology Appraisal

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]

**By email*

Dear [redacted],

Further to our communication of the outcome of the Appraisal Committee discussion, you will be aware that the committee was unable to make a recommendation on ertugliflozin in a triple therapy regimen in combination with metformin and a DPP-4 inhibitor as an option for treating type 2 diabetes.

The committee has requested that NICE seeks further clarification from the company on the following issues:

- justification for limiting the assessment of cost effectiveness for ertugliflozin in combination with metformin and DPP-4 inhibitor to a comparison with other SGLT-2 inhibitors in combination with the same background regimen. The committee requires a detailed explanation for why the company has excluded each comparator in the scope and why a cost-utility analysis was not considered necessary.

- additional data to support the company's claim that the combination of SGLT-2 inhibitor, metformin and a DPP-4 inhibitor is a standard triple therapy regimen in the NHS, for example from sources such as the Clinical Practice Research Datalink.

- justification for not reporting some of the outcomes specified in the NICE scope such as mortality and complications of diabetes.

- the committee notes that cardiovascular outcomes data are available for the other SGLT-2is and that data for ertugliflozin are expected in due course. The committee requests to see any preliminary cardiovascular outcomes data that may be available at the present time.

Please provide the additional information by **5pm, Friday 22 February 2019**. Your response should be uploaded to NICE Docs via [redacted]

Kind regards,

[redacted]
Project Manager – Technology Appraisals (Committee A)
National Institute for Health and Care Excellence
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[redacted]
National Institute for Health and Care Excellence

22nd February 2019

Dear [redacted],

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160]
Request for additional information [AIC]

Following the NICE request for additional information on ertugliflozin in a triple therapy regimen for treating type 2 diabetes (T2D), MSD provides below key evidence and more rationale to support the combination of met + DPP-4i + SGLT-2i as an emerging standard of care (SoC) within the NHS alongside evidence that the only comparators relevant for this appraisal are other SGLT-2is.
Based on the additional information requested by NICE, the key clarification points underpinning the inability to make a recommendation, are uncertainties around the following:

1. *Limited rationale for the exclusion of each comparator in the scope, alongside the use of a cost-comparison approach rather than a cost-utility analysis*: MSD provides proper justification and evidence based on current NG28, ertugliflozin randomised controlled trial (RCT), previous NICE technology appraisals (TAs) and NMA findings.

2. *Data supporting the triple therapy combination as a SoC in the NHS*: MSD presents further evidence from global and local guidelines, clinical experts, IQVIA moving annual total (MAT) and the Clinical Practice Research Database (CPRD).

3. *Limited justification for not including mortality and complications of diabetes outcomes in the main submission:* MSD highlights the presence of these outcomes in the original submission and elaborates more on renal complications.

4. *Ertugliflozin data on cardiovascular outcomes*: MSD provides all information available pertinent to the on-going clinical trial investigating cardiovascular outcomes (VERTIS CV).

Our full response is provided below and addresses in turn, each of the above mentioned key queries. MSD has answered the Committee's concerns to the best of its ability. In MSD's opinion, this triple therapy regimen is an established prescribing behaviour within clinical practices in the NHS and it should therefore be recognised as an emerging SoC. This recognition would also reflect the widely international (EASD and ADA) and local guidelines that currently recommend the use of this combination therapy (met + DPP-4i + SGLT-2is) in T2D patients.

Should you have any questions about the content, please do not hesitate to contact me.

Kind regards

[redacted]
Associate Director, Team Leader HTA and Outcomes Research

MSD response to key queries underpinning NICE inability to recommend ertugliflozin in a triple therapy regimen in combination with metformin and a gliptin:

1. Limited rationale for the exclusion of each comparator in the scope, alongside the use of a cost-comparison approach rather than a cost-utility analysis

MSD response to this query is divided into two sections. The first one (1.a) will expand the rationale around the exclusion of each comparator in the scope, whereas the second (1.b) will provide more justification for the choice of a cost-comparison approach.

1.a Rationale for the exclusion of each comparator in the scope

NICE scope includes the following comparators in a combination regimen:

- Sulfonylureas (SUs)
- DPP-4i
- Pioglitazone (pio)
- SGLT-2is
- GLP-1 mimetics
- Insulin

In accordance with NG28 [1], the recommended triple therapy combinations with the above listed medications are:

- metformin, DPP-4 and a SU
- metformin, pio and a SU
- metformin, pio or a SU, and a SGLT-2i
- metformin, SU and a GLP-1

The reasons for the exclusion of each of the above-mentioned comparators can be easily summarised as due to:

- Decreased use of specific compounds in clinical setting (e.g. pio) or use of specific compounds later in the treatment pathway (e.g. insulin).
- Evidence and criteria used within the ertugliflozin RCT.
- Conclusions reached by the Committee in previous SGLT-2is TAs regarding appropriateness of comparators in a triple therapy regimen.

Decreasing use of specific compounds in clinical setting or use of specific compounds later in the treatment pathway

MSD excluded pio, GLP-1 and insulin from the comparison network based on the conclusions made by the Committee in the TAs 418 and 288 [2,3], whereby clinicians stated that the number of patients being newly prescribed on pio is decreasing year on year and has low use in triple therapy in clinical settings; the decrease is mainly associated to concerns around adverse effects (e.g. increase risk of CV disease, oedema and weight gain) [2-5].
For GLP-1s, it was stated that these were used less frequently and much later in the treatment pathway due to the class being injectable and therefore costly [2,3]. Likewise, insulin is used very late in the treatment pathway and usually as last option due to associated costs and mode of administration (injectable).

Evidence and criteria used within the ertugliflozin RCT

The ertugliflozin RCT (VERTIS SITA2) [6] investigated the efficacy and safety of the product in patients with T2D who had inadequate glycaemic control on dual background therapy of metformin and sitagliptin; this baseline therapy was one of the RCT inclusion criteria used to recruit patients in VERTIS SITA2 [6]. The potential inclusion of the other triple therapy combinations with a different baseline therapy other than met + DPP-4i, would have brought heterogeneity due to the use of a different population (and related baseline characteristics) and different background therapies used in other RCTs.

Based on the VERTIS SITA2 baseline dual therapy and on the above explanation, the following comparators have been excluded:

- metformin, pioglitazone and a SU
- metformin, pioglitazone or a SU, and a SGLT-2i
- metformin, SU and a GLP-1

These exclusions also ensured consistency on one crucial aspect; that is, applying the evidence gathered through the RCT to treatment practice in the real world. MSD is seeking approval for ertugliflozin in a triple therapy regimen only for patients uncontrolled on a dual therapy with metformin and a DPP-4i. This argument reflects the sequential treatment approach within NG28 [1], whereby patients are first prescribed metformin; subsequently a DPP-4i can be added if glycaemic control is not achieved. When further treatment intensification is required as add-on to metformin and a DPP-4i, clinicians could potentially prescribe a third agent, such as a SU or pio. It would be unlikely and unadvisable for the clinician to replace the second agent of the original background therapy (DPP-4i) with a pio and then add a third agent (e.g. SU) to create a triple therapy (e.g. metformin + pioglitazone + SU).

Conclusions reached by the Committee in previous SGLT-2is TAs regarding appropriateness of comparators in a triple therapy regimen

In accordance with the above, the only combination comparators left is met + DPP-4i + pio and/or met + DPP-4 + SU. As stated previously, pio is excluded as comparator due to the associated risk of CV disease, oedema and weight gain [2-5]. Therefore, the only combination comparator left for consideration is met + DPP-4 + SU. Although this combination has the baseline dual therapy used in the ertugliflozin RCT, the comparison against SUs like pio, has been excluded due to the conclusions achieved by the Committee in previous SGLT-2is TAs. In TA288 and 418 [2,3] the Committee agreed with the evidence provided by the clinical specialists which stated that most patients start on metformin and SUs are usually added-on to form a dual therapy; however, if patients are unable to use a SU due to concerns on hypoglycaemic events [7] and/or weight gain, then a pio, DPP-4i and GLP-1 may be used instead.

MSD is positioning the combination under review for use in this cohort of patients: those for whom SUs are inappropriate due to adverse events risks mentioned. This is supported by the Committee statement in TAs 288 and 418 [2,3] which concluded that dapagliflozin was more likely to be used only when a SU was not appropriate. This decision was also made in TA315 and TA336 [8,9]. The overall conclusion from these TAs is that SGLT-2is are considered

appropriate for those patients who cannot be prescribed SUs, but SGLT-2is are not a replacement of the SUs in the treatment pathway. Therefore, MSD did not consider appropriate to compare ertugliflozin against SUs. As a result, the only relevant comparator used for the appraisal was met+ DPP-4i + SGLT-2is.

1.b Rationale for a cost- comparison approach

The choice to use a cost-comparison versus a cost-utility analysis was based on the fact the NMA showed the clinical efficacy and safety of ertugliflozin to be similar to all other SGLT-2is (dapagliflozin, canagliflozin and empagliflozin) [10]. As recommended by NICE, if products in the same class shows similar efficacy and safety and have comparable costs, the most appropriate form of economic evaluation is a cost-comparison [11].
This approach was also agreed by NICE and the ERG representatives during the ertugliflozin decision problem meeting (for mono, dual and triple therapy) that occurred on the 23rd of May 2018. One of the key points of discussion by MSD was which technology appraisal process was most appropriate for ertugliflozin in a triple therapy regimen and if a cost comparison/cost-minimisation would have been an acceptable form of economic evaluation. The conclusion made by NICE and the ERG attendees was that if MSD intends to position ertugliflozin only as an alternative to other SGLT-2is on a background of metformin + DPP-4i, then a cost-comparison would be acceptable.

Summarising, MSD outlines below the rationale behind a cost-comparison over a cost-utility analysis:

- MSD assumed that pio would be an inappropriate comparator due to its associated increased risk of cardiovascular events and weight gain [2,5] and that SUs are used in a different cohort of patients when the risk of hypoglycaemic events does not exist [1,12]. On the contrary, ertugliflozin is expected to be used in patients for whom SUs or pio are not appropriate, therefore they cannot be considered comparators.
- All the triple therapy combinations with a different baseline background than met + DPP-4i are not relevant comparators.
- Based on the above, the only relevant comparators are other SGLT-2is.
- As per the NMA findings, ertugliflozin is similar in both efficacy and safety to all other SGLT-2is and it is cheaper than its comparators, therefore a cost-comparison seemed the most logical option.
- The same criteria were used for ertugliflozin in mono and dual therapy, with the only difference that MSD was not allowed to pursue a fast track appraisal (FTA) for a triple combination therapy never reviewed and approved by NICE.

2. Data supporting the triple therapy combination as an emerging SoC in the NHS

Firstly, evidence available in the public domain that supports the combination of the triple therapy regimen under consideration is presented; both globally via the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) guidelines and locally through sample formularies. The local formulary examples identified are geographically spread across England to illustrate a more generalisable representation. These local guidelines are also supported by clinical experts' statements that highlight the use of this triple therapy

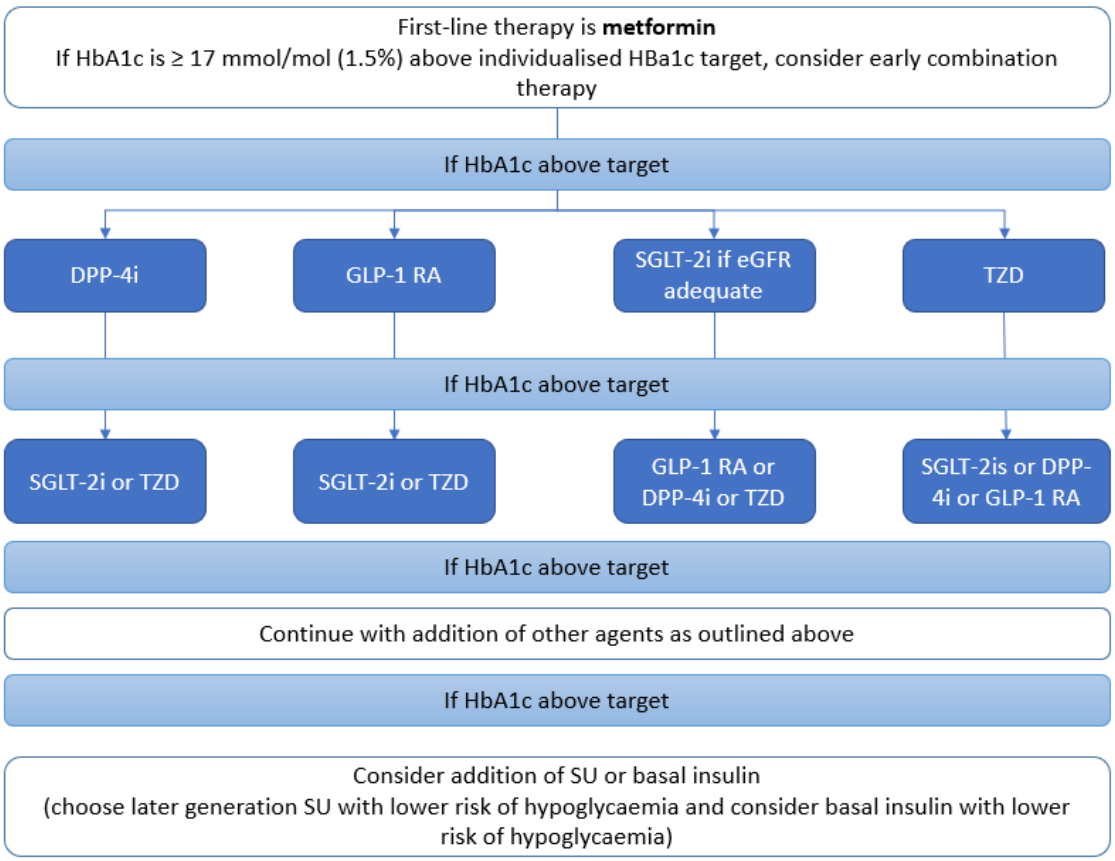
regimen in their practices. Moving annual total (MAT) data around the prescription of the triple therapy from 2016 until 2018 are then presented. Finally, CPRD data analysis has been provided to further demonstrate the prescribing behaviour established within clinical practices in England, as per the Committee's request.

2.a International guidelines on T2DM

The EASD is a highly influential non-profit, medical scientific European association. The ADA is the US equivalent; consensus guidelines on T2D were published in 2018 and have huge influence internationally. They are held as the gold-standard by the majority of diabetologists in the USA and Europe.

In accordance with the EASD-ADA consensus guidelines published in 2018 [12], the triple therapy combining met + DPP-4i + SGLT-2is is a recommended option when a compelling need to minimise hypoglycaemic events exists. This also supports MSD argument envisaging the use of this triple therapy in patients for whom SUs are not appropriate. The algorithm of the guideline has been replicated in Figure 1 below.

Figure 1: EASD-ADA T2D guidelines, 2018 [12]



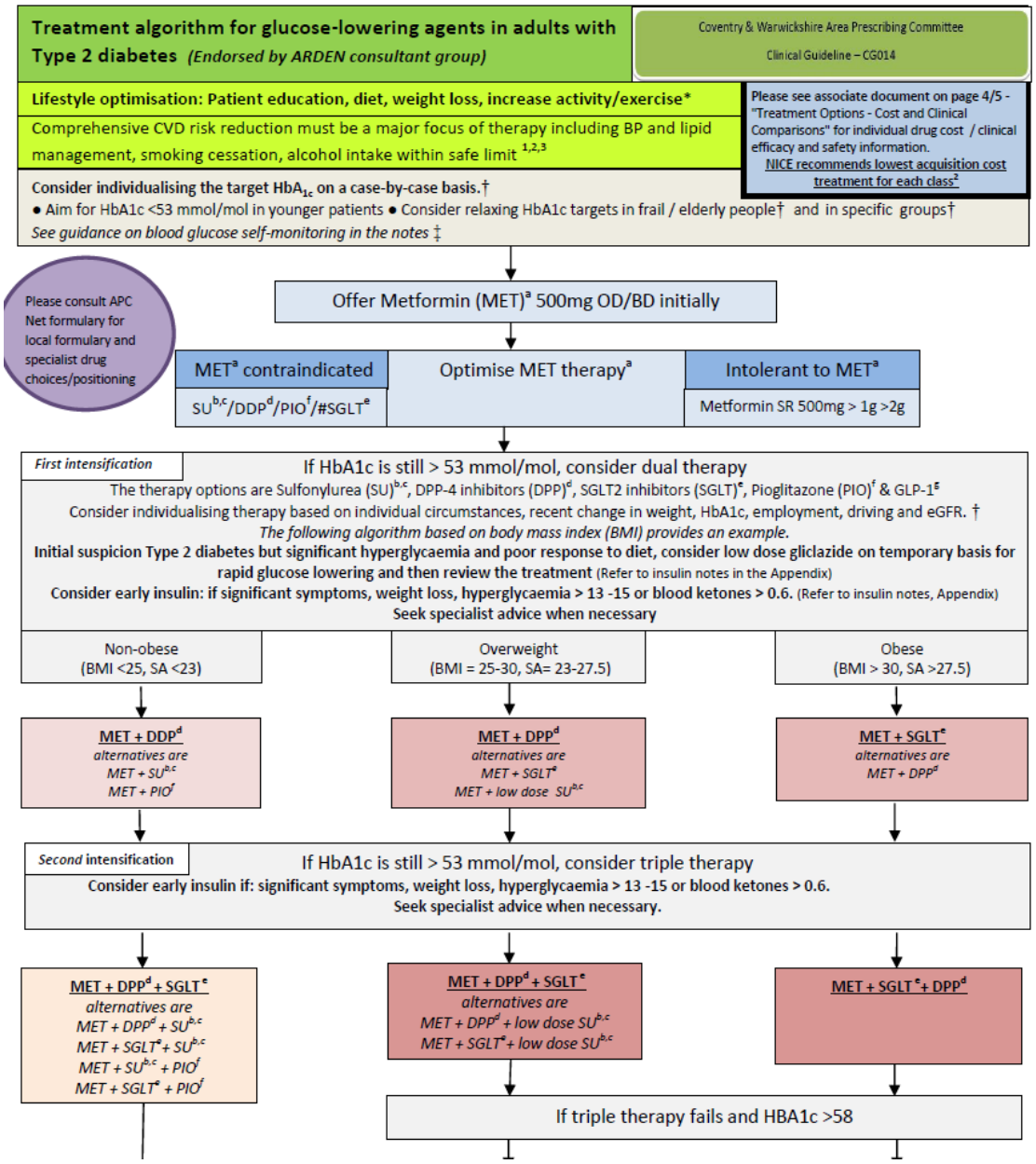
2.b Local guidelines on T2DM

There are a number of local formularies within the public domain which recommend the use of the triple therapy under consideration. To further illustrate the use of this triple therapy combination in the real-world setting, MSD has selected a few to highlight this point. Please refer to Fig. 2 for an example and here below for a list of the CCGs taken into consideration:

- *North*: Rotherham [13], Hull and East Riding [14]
- *Midlands and East*: West Suffolk [15], Coventry [16], Herts Valley [17]
- *London*: North Central London [18]
- *South West*: Royal Devon and Exeter [19], Gloucestershire [20]

Appendix 1 includes screenshots of the aforementioned local treatment pathways for T2DM.

Fig 2. Coventry and Warwickshire CCG, T2DM local guidelines [16]



2.c Clinical experts' statements

Additionally, MSD sought input from clinical experts on the use of this triple therapy combination within their practices and/or based on their expertise and knowledge. These scientific leaders provided their support in writing and agreed in sharing the information to support SGLT-2is' positioning in this triple therapy combination by NICE. Please find below the statements that MSD collated:

1) *R Ajjan (FRCP, MMed.Sci, PhD), Associate Professor/Consultant in Diabetes and Endocrinology; Regional CRN Lead for Metabolic and Endocrine Research.*

"Dear MSD/NICE,
Thank you for asking my views on triple therapy with SGLT2 in individuals with type 2 diabetes (T2D).
T2D is a progressive disease necessitating combination therapy with oral hypoglycaemic agents to achieve and maintain glycaemic targets. While reducing glucose levels is important to avoid diabetes complications, minimising the risk of hypoglycaemia, which is associated with adverse clinical outcome, is also central to patient management. Therefore, combination therapy with agents with low risk of hypoglycaemia is preferred. Metformin remains the first line hypoglycaemic agent. Agents in the sulphonylurea group were traditionally used as second line but given the precipitation of hypoglycaemia, they have been gradually replaced by newer drugs such as DPP4 and SGLT2 inhibitors. Therefore, when reaching third line treatment, there is the possibility of combining metformin, DPP4 and SGLT2 inhibitors. This combination is particularly powerful given it: i) targets different glycaemic pathways, ii) has a favourable effect on weight and iii) does not cause hypoglycaemia and iv) is cardiovascular protective and reduces heart failure risk.
A number of review articles/meta-analyses support the efficacy and safety of combining DPP4 and SGLT2 inhibitors, used as dual or triple therapies, particularly when avoidance of hypoglycaemia is important [21-23]. This combination has been used locally and was found to be well tolerated and effective at achieving glycaemic targets."

2) Prof. T. Sathyapalan, Honorary Consultant Endocrinologist, Academic Endocrinology, Diabetes and Metabolism, University of Hull/Hull and East Yorkshire Hospitals NHS Trust

"Dear MSD and NICE,
Many thanks for asking my views on the triple combination therapy with metformin, SGLT-2i and DPP-4i in the management of patients with type 2 diabetes. It is my preferred oral combination therapy in patients with type 2 diabetes needing triple therapy. It is one of the choices we have in our joint formulary with Primary Care (Hull and East Riding of Yorkshire Prescribing Committee). Both my Primary care and Secondary care colleagues prescribe this combination therapy frequently. I can confirm use of this triple therapy in Hull and East Riding of Yorkshire.
The combination is attractive since all three agents are oral agents, they all have cardiovascular safety data and two of them (metformin and SGLT-2i) have strong beneficial cardiovascular outcome data. None of these three agents can cause hypoglycaemia and there is no need for self-blood glucose monitoring while on this combination therapy. These agents

are either weight neutral (metformin and DPP-4i) and SGLT-2i promotes weight loss – weight is an important issue in patients with type 2 diabetes. In addition, all these agents have different and complimentary mechanism of action.
I am happy to use this email in support of this triple therapy combination."

3) Clifford J. Bailey, PhD, FRCP(Edin), FRCPath, Life and Health Sciences, Aston University, Birmingham, B4 7ET, UK.

"Dear Dr XX,
Thank you for a very interesting discussion this morning.
Regarding the triple oral glucose-lowering therapies, I think most type 2 patients receive metformin as initial pharmacological glucose-lowering therapy for well-established reasons. The DPP-4 inhibitors have become widely used as add-on to metformin for patients who do not achieve or maintain adequate glycaemic control. The advantages of this combination include different modes of action, low risk of weight gain (maybe some weight reduction) and especially important is the very low risk of hypoglycaemia (which is a key reason for not using an SU in the elderly, frail and other groups requiring particular attention to avoiding hypos). Potential advantages regarding CV risk and other morbidity risks associated with type 2 diabetes are also noted for the metformin + DPP-4i combination. Since the availability of SGLT-2 inhibitors we are seeing the use of triple oral therapy with metformin + DPP4i + SGLT2i, notably for those with inadequate glycaemic control and the need for improved weight control. Again, we have the advantage of agents with different modes of action, and there are accompanying benefits in blood pressure control and accumulating reports of improved CV outcomes, all encouraging evidence for use of this combination.
So, I can confirm use of such triple therapy in the locality, and indeed refer you to a recent review by Professor Tony Barnett (Heartlands, Birmingham and B'ham Univ) and an international group of authors confirming the wider use of this approach (Dipeptidyl peptidase-4 inhibitors in triple oral therapy regimens in patients with type 2 diabetes mellitus).
Hope this is useful."

4) Dr Andrew Frankel, Consultant Physician and Nephrologist, Imperial College Healthcare NHS Trust

"Dear XX (MSD) and NICE,
The combination of metformin/DPP4I/SGLT2I in my view has significant benefits compared to one with a sulphonylurea and my understanding is the forward-looking physicians are beginning to utilise combination therapies that provide benefit without the risk of hypoglycaemia.
The new Renal Association/ABCD guidelines on the management of diabetes in people with chronic kidney disease do describe the use of individual agents but do not describe a hierarchical approach to combinations. This is something that we are likely to address in future updates on the guidelines. I am certain that these guidelines will reflect the approach that treatments should ideally be those that have proven cardiovascular benefit combined with those that have proven cardiovascular safety and that agents that carry the greatest risk of

complications should be moved down any algorithm for combination treatments. I'm sure you're going to see more patients on this triple combination and indeed the bold will be considering metformin/sglt2i/GLP1RA!"

5) Richard IG Holt, Professor in Diabetes & Endocrinology, Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton

"Dear MSD and NICE,
XXXX asked me to comment on the appropriateness of using triple oral therapy with metformin, DPP4 inhibitors and SGLT2 inhibitors.
There are undoubtedly some people with type 2 diabetes for whom this would be the optimal combination for triple oral therapy. This combination is endorsed in the recent EASD/ADA position statement when avoidance of hypoglycaemia or weight gain is a priority."

It is worth of note again that the clinicians who provided advice to MSD came from different geographical locations. This is a further indicator that this prescribing behaviour or, built knowledge in the use of SGLT-2i in this combination therapy, is not a random and confined attitude but it is shared across CCGs in England.

Please bear in mind that some of the above clinicians' statements contain clear reference to CV benefits for the currently used SGLT-2is (canagliflozin, dapagliflozin and empagliflozin). Whilst MSD cannot speculate on any CV benefits for ertugliflozin, more details on ertugliflozin CV outcome data are provided here.

2.d IQVIA data - MAT

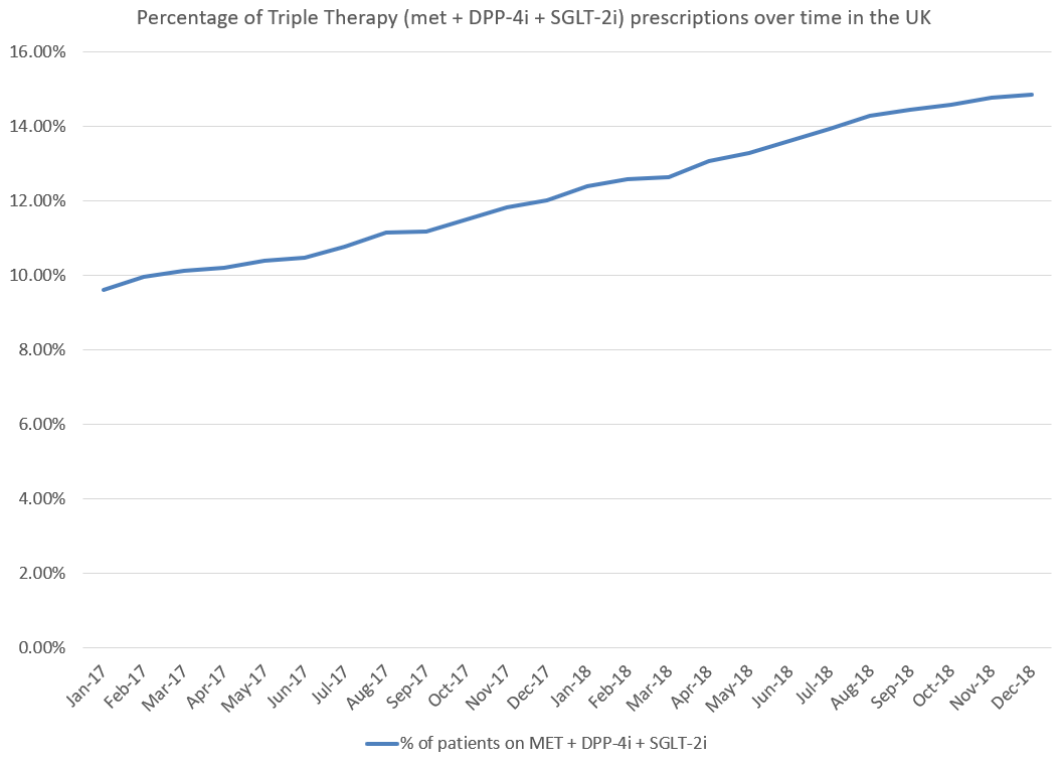
In the original submission, MSD presented MAT data for the year up to December 2017 (Table 1). The table showed that in clinical practice, SGLT-2is are prescribed in triple therapy in combination with 'metformin + DPP-4i' (as a percentage of all patients on a triple therapy regimen), the combination ertugliflozin is seeking recommendation for. This data supports the argument that the triple therapy regimen is an established prescribing behaviour within clinical practices, even though it has not been recommended by NICE.
Using the same data source, MSD would like to present additional data which shows an increase in the prescription of this triple therapy regimen in the UK over time. Specifically, MAT data from January 2017 up to December 2018 are presented in Figure 3. The graph shows the prescription of the regimen in question has increased from below 10% in January 2017 to almost 15% in December 2018, indicating a growth of about 50% between 2017 and 2018.

Table 1: MAT data, 2017 [24]

Triple therapy	MAT 2017	
	Units	%
SU + MET + TZD	23,806	7.8
MET + SU + DPP-4i	138,287	45.1
MET + SU + GLP-1	21,172	6.9
MET + SU + SGLT-2i	45,792	15.0
MET + TZD + DPP-4i	10,059	3.3

MET + DPP-4i + GLP-1	1,724	0.5
MET + DPP-4i + SGLT-2i	34,775	11.4
Other	30,656	10.0
Total	306,271	100

Figure 3: MAT data from January 2017 up to December 2018 [24]



2.e CPRD data

MSD presents below an analysis of data extracted from the CPRD, as per Committee's request. The timeframe used for the CPRD was January 2016 until June 2018 (latest available endpoint for the CPRD). This timeframe was chosen to ensure consistency with the above reported IQVIA data, whereby January 2017 time point corresponds to a cumulative proportion of the previous 12 months (January 2016). Figure 4 shows the same conclusions made from the IQVIA data: since 2016 there was an increased trend in prescribing met+DPP-4i+ SGLT-2is. [redacted]. If the June 2018 time point is considered for both databases, it is possible to note that that IQVIA data reports 12.8% of triple therapy prescription, whereas the CPRD [redacted] in reporting between the two. Although MSD did not identify any direct explanation for this, both datasets show a growing trend in the prescribing of the triple therapy under consideration and provide clear evidence that this is already an established behaviour in England. Based on publicly available pricing at a -20% price differential of ertugliflozin versus other SGLT-2is, for patients who are already receiving triple therapy with met + DPP-4i + SGLT-2i, this combination provides a cheaper alternative.

Figure 4: CPRD data on percentage of triple therapy prescription over the time (Jan 2016 – June 2018) [25]

3. Limited justification for not including mortality and complications of diabetes outcomes in the main submission.

In the original submission, MSD did not specify that mortality and complications of diabetes outcomes (including cardiovascular, renal and eye) were not pre-specified outcomes of the VERTIS SITA2 trial [6]. However, Table 27 in section B.2.10.2 of Document B "Summary of adverse reactions", reports the number of deaths occurred over phase A of the trial and some complications of diabetes, such as Vascular (hypertension), Eyes (diabetic retinopathy) and Cardiac disorder at week 26. In Appendix M (Table M.2, page 426 of Document B) the number of deaths is also reported for week 52.
Concerning renal complications, section B.2.10.1 of Document B and Appendix L (eGFR, page 422 and 423) present results for the eGFR analysis. Please find below further information on renal complications occurred during the VERTIS SITA2 trial.

Table 2: Renal disorders in the VERTIS SITA2 trial

VERTIS SITA2	PBO N = 153	ERTU5 N = 156	ERTU15 N = 153
Overall Safety (ER), n (%)			
Renal and urinary disorders	4 (2.6)	5 (3.2)	7 (4.6)

An adverse event of renal failure was reported for one patient in each ertugliflozin group, an adverse event of blood creatinine increased was reported for one patient in the ertugliflozin

15 mg group; and an adverse event of renal impairment was reported for one patient in the placebo group. None of these events was a serious adverse event and none led to discontinuation of study medication.

4. Ertugliflozin data on cardiovascular outcomes

MSD is not able to share preliminary analyses and/or results for the VERTIS CV trial because they are not available at this point on time; the estimated primary completion date for this RCT is September 2019 [26]. However, for clarity, please find below further details.
To demonstrate cardiovascular (CV) safety in support of the United States Food and Drug Administration (FDA) New Drug Application (NDA) submission (i.e., to rule out an 80% increase in CV risk in the pre-marketing period), the Sponsor conducted a CV meta-analysis (CVMA) across all phase 3 studies and a single phase 2 study with a duration of at least 12 weeks, including P004/1021 (VERTIS-CV). VERTIS-CV is a dedicated cardiovascular outcome study (CVOT) designed in part to satisfy the US FDA requirements for evaluating CV risk in both the pre-marketing and post-marketing periods. The CVMA report contains data from adjudication-confirmed CV events (MACE+: composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina). Unlike the other trials in the CVMA, VERTIS-CV remains blinded and will continue into the post- approval period to satisfy the post-marketing CV safety requirement to rule-out a 30% increase in CV risk. VERTIS-CV is also designed to support a potential labelled indication related to CV benefit.

Because unblinding of CVMA data or disclosure of CVMA data has the potential to impact the integrity of VERTIS-CV, the US FDA instructed the Sponsor not to submit VERTIS CV data as part of the US NDA submissions except for CV endpoints from VERTIS-CV in the CVMA. These data were available only to a limited number of firewalled Sponsor personnel, with no direct or other involvement in the ertugliflozin program. The unblinding of additional individuals or expansion of access requires notification of and justification to the US FDA and is governed by a confidentiality agreement and data access plan.

In April 2016, the Sponsor requested scientific advice from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), informing them that there will be no safety data from the ongoing CVOT included in the registration dossier. The CHMP agreed that submission of unblinded interim data from the CVOT could give rise to concerns over trial integrity, and therefore, CHMP did not require that the CVMA (which includes the interim data from the ongoing CVOT) be submitted. We note that the ertugliflozin family of products was approved in the EU in March 2018 without submission of the CVMA, or data from VERTIS-CV.

While the CVMA cannot be provided, the Sponsor can provide an alternative analysis of CV safety which is based on CV safety data from 7 Phase 3 studies in nearly 5,000 subjects. Briefly, the Sponsor did an analysis of CV events from the Broad Safety Pool (using the four months safety update report date, which is 4 months later than the cut date used in the original ertugliflozin registration dossier to FDA and EMA), that were potentially submitted for CV adjudication and reported 'death' terms (including cardiac death, death, sudden cardiac death, and sudden death") [MSD internal data].

The results from this analysis (which are not based on the results of adjudication) (Appendix 2) showed that the incidence of CV AEs was similar across groups (ertugliflozin 5 mg: 4.2%; ertugliflozin15 mg: 2.8%; non-ertugliflozin: 4.4%), suggesting that there is no excess CV risk with ertugliflozin. The incidence of specific events in ertugliflozin-treated subjects was low (≤0.5%), and no discernible patterns were observed. In conclusion, based on the totality of the data, the Sponsor believes there is no imbalance suggesting a safety concern for CV events.

Currently, three SGLT-2i cardiovascular outcomes trials, EMPA-REG1, CANVAS2 and DECLARE3 have generated positive CV outcome data. As such, one might expect a positive CV class effect among SGLT-2 inhibitors; although MSD cannot predict the trial outcomes, the similarities between patient populations in EMPA-REG and VERTIS-CV are noteworthy and presented in Table 3.

Table 3: Summary of Baseline Characteristics of Patients in SGLT-2 Cardiovascular Outcome Trials

	VERTIS-CV	EMPA-REG Outcome	CANVAS	DECLARE
N	8,238	7,034	10,142	17,160
Age (years)	64.4 ± 8.1	63.1 ± 8.6	63.3 ± 8.3	63.8 ± 6.8
Male, n (%)	5,764 (70)	5,026 (72)	6,509 (64)	10,738 (63)
Established CVD (%)	99.9	>99	65.6	40.6
Myocardial infarction, n (%)	3,942 (47.9)	3,275 (47)	2,956 (29.2)	3,580 (20.9)
Stroke, n (%)	1,731 (21.0)	1,631 (23)	1,291 (12.8)	1,107 (6.5)[b]
Peripheral arterial disease, n (%)	1,548 (18.8)	1,449 (21)	2,113 (20.8)	1,025 (6.0)
History of heart failure, n (%)	1,900 (23.1)	706 (10.1)[a]	1,461 (14.4)	1,698 (9.9)
eGFR	76.0 ± 20.9	74 ± 21	76.5 ± 20.5	86.1 ± 21.8
Moderate renal impairment, n (%)	1,776 (21.6)	1,796 (26)	2,010 (19.8)	1,565 (9.1)[c]

a. Percentage based on 7,020 subjects; b. Ischemic stroke; c. eGFR<60mL/min/1.73m^2.

CONCLUSIONS

MSD believes that the triple regimen under consideration is an emerging SoC. Evidence to support its use in England was provided by MSD and includes: global guidelines, local formularies, clinicians' statements, increased annual usage as shown by IQVIA and CPRD datasets.

Finally, to re-iterate the rationale for using a cost-comparison approach, as evidenced by the guidelines and previous NICE TAs [2,3,8,9,12], the interventions SUs and pio were considered inappropriate comparators due to their associated risks of hypoglycaemic and cardiac events in the cohort of patients being considered in MSD's submission. As the baseline therapy for this regimen was met + DPP-4i, the only other alternative to add-on was a SGLT-2i. The NMA has shown similar efficacy and safety of ertugliflozin in comparison to the other SGTL-2is. Given this and, the cheaper list price for ertugliflozin, MSD concluded that a cost-comparison analysis was the most appropriate choice economic evaluation.

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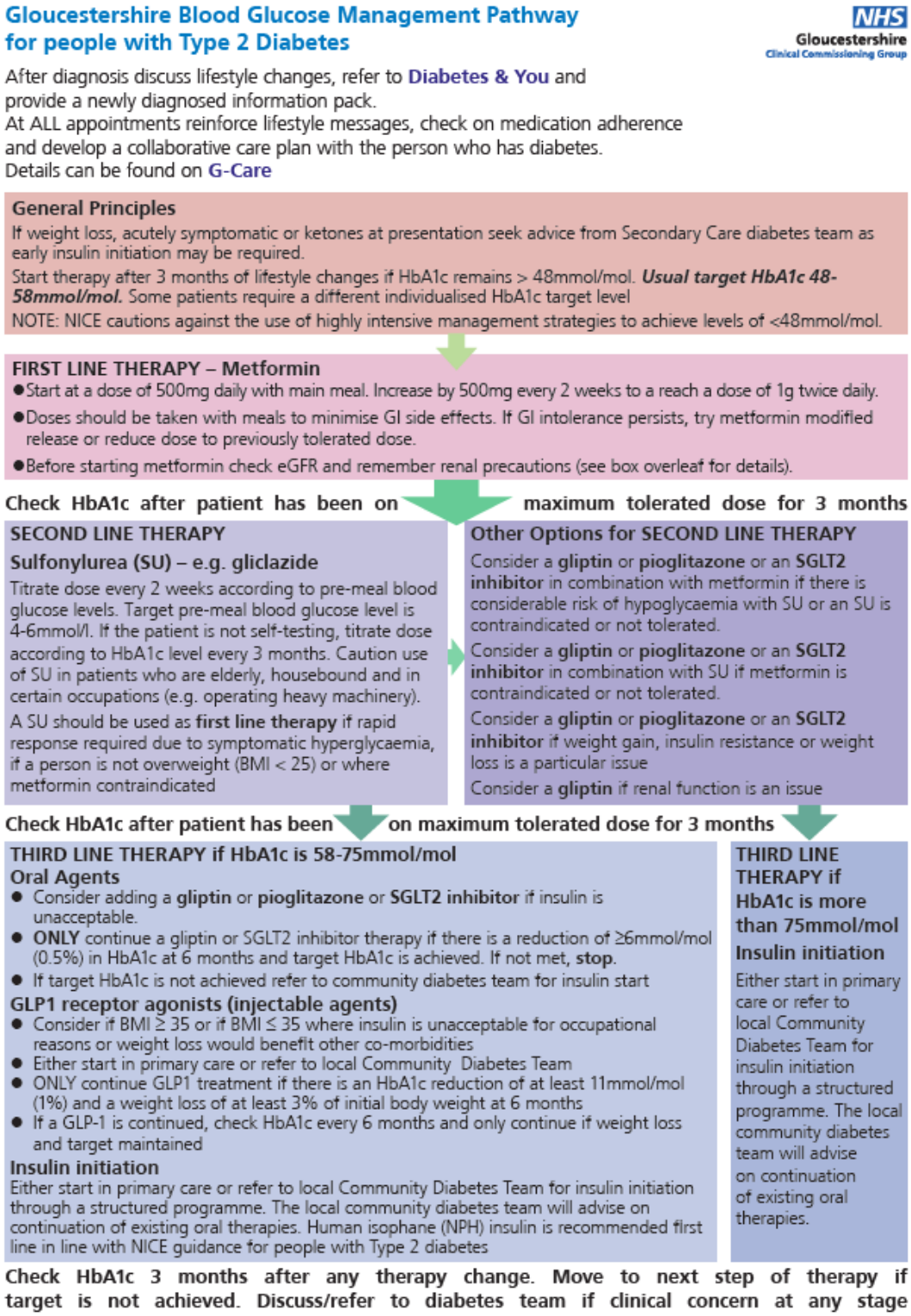
Appendix 1 - Screenshots of the local treatment pathways for T2DM

GLOUCESTERSHIRE



Gloucestershire Blood Glucose Management Pathway for people with Type 2 Diabetes

NHS Gloucestershire Clinical Commissioning Group

After diagnosis discuss lifestyle changes, refer to **Diabetes & You** and provide a newly diagnosed information pack.
At ALL appointments reinforce lifestyle messages, check on medication adherence and develop a collaborative care plan with the person who has diabetes.
Details can be found on **G-Care**

General Principles

If weight loss, acutely symptomatic or ketones at presentation seek advice from Secondary Care diabetes team as early insulin initiation may be required.

Start therapy after 3 months of lifestyle changes if HbA1c remains > 48mmol/mol. ***Usual target HbA1c 48-58mmol/mol.*** Some patients require a different individualised HbA1c target level

NOTE: NICE cautions against the use of highly intensive management strategies to achieve levels of <48mmol/mol.

FIRST LINE THERAPY – Metformin

- Start at a dose of 500mg daily with main meal. Increase by 500mg every 2 weeks to a reach a dose of 1g twice daily.
- Doses should be taken with meals to minimise GI side effects. If GI intolerance persists, try metformin modified release or reduce dose to previously tolerated dose.
- Before starting metformin check eGFR and remember renal precautions (see box overleaf for details).

Check HbA1c after patient has been on maximum tolerated dose for 3 months

SECOND LINE THERAPY

Sulfonylurea (SU) – e.g. gliclazide

Titrate dose every 2 weeks according to pre-meal blood glucose levels. Target pre-meal blood glucose level is 4-6mmol/l. If the patient is not self-testing, titrate dose according to HbA1c level every 3 months. Caution use of SU in patients who are elderly, housebound and in certain occupations (e.g. operating heavy machinery).

A SU should be used as **first line therapy** if rapid response required due to symptomatic hyperglycaemia, if a person is not overweight (BMI < 25) or where metformin contraindicated

Other Options for SECOND LINE THERAPY

Consider a **gliptin** or **pioglitazone** or an **SGLT2 inhibitor** in combination with metformin if there is considerable risk of hypoglycaemia with SU or an SU is contraindicated or not tolerated.

Consider a **gliptin** or **pioglitazone** or an **SGLT2 inhibitor** in combination with SU if metformin is contraindicated or not tolerated.

Consider a **gliptin** or **pioglitazone** or an **SGLT2 inhibitor** if weight gain, insulin resistance or weight loss is a particular issue

Consider a **gliptin** if renal function is an issue

Check HbA1c after patient has been on maximum tolerated dose for 3 months

THIRD LINE THERAPY if HbA1c is 58-75mmol/mol

Oral Agents

- Consider adding a **gliptin** or **pioglitazone** or **SGLT2 inhibitor** if insulin is unacceptable.
- **ONLY** continue a gliptin or SGLT2 inhibitor therapy if there is a reduction of ≥6mmol/mol (0.5%) in HbA1c at 6 months and target HbA1c is achieved. If not met, **stop**.
- If target HbA1c is not achieved refer to community diabetes team for insulin start

GLP1 receptor agonists (injectable agents)

- Consider if BMI ≥ 35 or if BMI ≤ 35 where insulin is unacceptable for occupational reasons or weight loss would benefit other co-morbidities
- Either start in primary care or refer to local Community Diabetes Team
- ONLY continue GLP1 treatment if there is an HbA1c reduction of at least 11mmol/mol (1%) and a weight loss of at least 3% of initial body weight at 6 months
- If a GLP-1 is continued, check HbA1c every 6 months and only continue if weight loss and target maintained

Insulin initiation

Either start in primary care or refer to local Community Diabetes Team for insulin initiation through a structured programme. The local community diabetes team will advise on continuation of existing oral therapies. Human isophane (NPH) insulin is recommended first line in line with NICE guidance for people with Type 2 diabetes

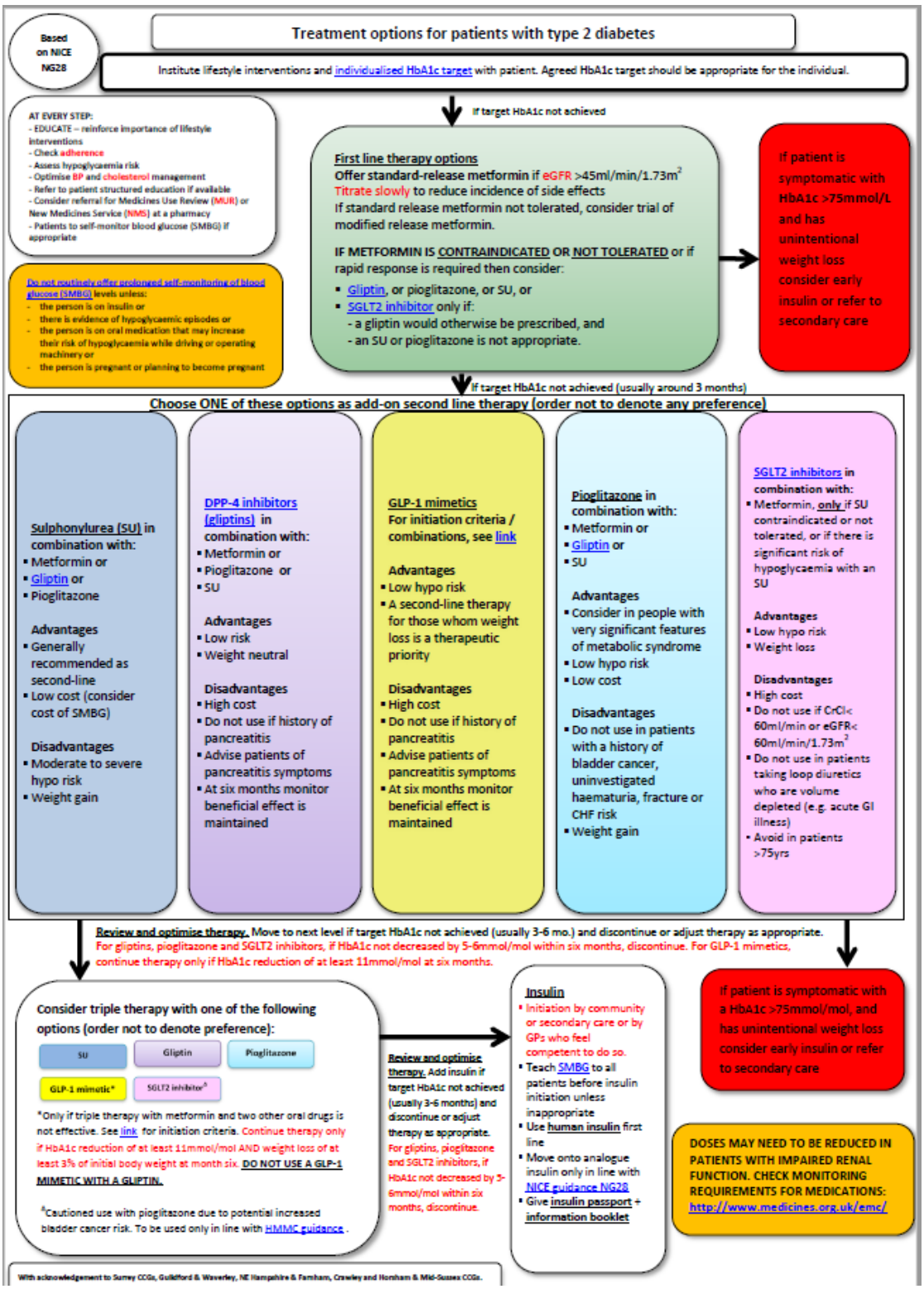
THIRD LINE THERAPY if HbA1c is more than 75mmol/mol

Insulin initiation

Either start in primary care or refer to local Community Diabetes Team for insulin initiation through a structured programme. The local community diabetes team will advise on continuation of existing oral therapies.

Check HbA1c 3 months after any therapy change. Move to next step of therapy if target is not achieved. Discuss/refer to diabetes team if clinical concern at any stage

HERTS VALLEY



HULL AND EAST RIDING

HERPC
Hull and East Riding Prescribing Committee

NHS
Hull and East Riding Diabetes Network

Algorithm for the Management of Type 2 Diabetes Mellitus

STEP-1
Lifestyle advice + Living with Diabetes + Metformin

If HbA1c>6.5% (48 mmol/mol) or individually agreed target after lifestyle advice

STEP-2			
If hypo risk a major issue consider the following, based on individual assessment of patient:			For non-obese younger patients consider
SGLT-2 inhibitors	DPP-4 inhibitors Suitable for elderly	Pioglitazone	Sulphonylureas
SGLT-2 inhibitors - do not initiate if eGFR <60			*Blood glucose monitoring required in view of hypoglycaemia risk* *If BMI <25kg/m^2 and osmotic symptoms – consider straight to insulin*

If HbA1c>7.5% (58 mmol/mol) or individually agreed target

	STEP-3		
Triple OHA Therapy	OHA + GLP-1RA*	OHA + insulin	OHA + GLP-1RA* + insulin
Metformin, SGLT-2i DPP-4i, sulphonylureas and pioglitazone in any triple combination (rarely 4 agent combinations can be used)	Metformin, SGLT-2i, sulphonylureas and pioglitazone in any combination with GLP-1RA	Metformin, SGLT-2i, DDP-4i and sulphonylurea in any combination with insulin	GLP-1RA + OHA (excluding DPP4-i and pioglitazone) + insulin

**If BMI ≥35kg/m^2 or ≥32kg/m^2 and If occupational issues or co-morbidities likely to benefit from weight loss*

OHA – oral hypoglycemic agents
SGLT-2i – SGLT-2 inhibitor
DPP4i – DPP-4 inhibitors

NORTH CENTRAL LONDON

Advantages and disadvantages of treatment combinations in adults with type 2 diabetes eligible for METFORMIN

Metformin (with active dose titration) – refer to Algorithm 1 on page 6.

Consider trial of modified release metformin ONLY if GI tolerability prevents continuing metformin despite gradual titration.

If metformin is contraindicated or patient intolerant refer to Algorithm 2 on page 7.

Impact on HbA1c: High
Other advantages: ↓CV events
Hypo risk: Low
Weight: -0.5Kg
Disadvantage: GI, lactic acidosis (rare), vitamin B12 deficiency
Cost (£): Low

FIRST INTENSIFICATION if uncontrolled on monotherapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

Metformin + gliclazide	Metformin + sitagliptin	Metformin + SGLT2-i 'flozin'	Metformin + pioglitazone	Metformin + insulin
Impact on HbA1c: High Other advantages: ↓microvascular risk, no cardiovascular risk Hypo risk: Moderate Weight: +1.5 to +2Kg Disadvantage: hypos, low durability Cost (£): Low	Impact on HbA1c: Moderate Other advantages: Nil Hypo risk: Low Weight: Nil Disadvantage: ?↑HF hospitalisation Cost (£): High	Impact on HbA1c: Moderate Other advantages: ↓BP, ↓CVD events Hypo risk: Low Weight: -3 to -4Kg Disadvantage: GU infections, polyuria, volume depletion, ↑risk of AKI, DKA, bone fractures, ? lower limb amputation Cost (£): High	Impact on HbA1c: High Other advantages: ?↓CVD events, durability, ↑HDL-C, ↓TG Hypo risk: Low Weight: +3 to +4Kg Disadvantage: Oedema, HF hospitalisation, bladder Ca, bone fractures Cost (£): Low	Impact on HbA1c: Highest Other advantages: ↓microvascular risk, near universal response, no cardiovascular risk Hypo risk: High Weight: +4 to +5Kg Disadvantages: Injection, need for titration Cost (£): Variable

SECOND INTENSIFICATION if uncontrolled on dual therapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

Metformin + gliclazide	Metformin + sitaglitpin	Metformin + SGLT2-i	Metformin + pioglitazone	Metformin + insulin
+ sitagliptin *or* + SGLT2-i *or* + insulin *or* + pioglitazone *or* + GLP-1RA (in line with SCG only)	+ gliclazide *or* + SGLT2-i* *or* + insulin *or* + pioglitazone	+ gliclazide *or* + sitagliptin* *or* + pioglitazone (not with dapagliflozin) + insulin	+ gliclazide *or* + sitagliptin *or* + SGLT2-i (not with dapagliflozin) *or* + insulin *or* + GLP-1RA (in line with SCG only)	+ gliclazide *or* + sitagliptin *or* + SGLT2-i *or* + pioglitazone *or* + GLP-1RA (in line with SCG only)

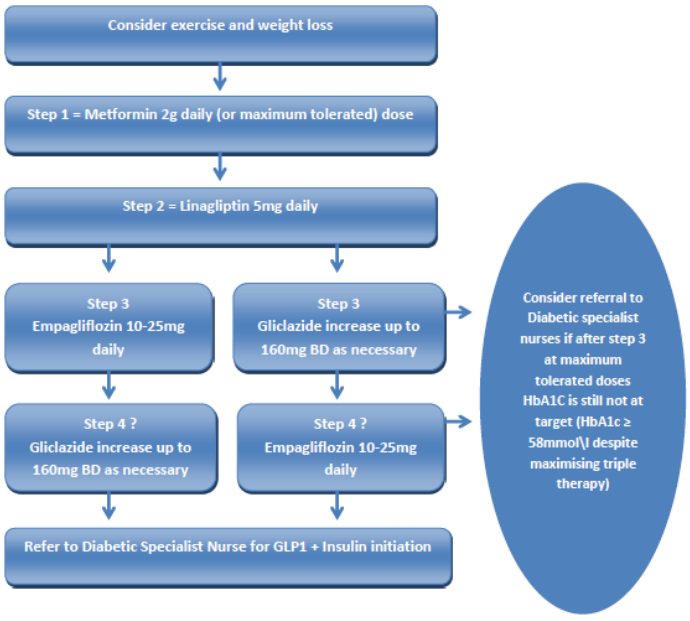
*Combination not included in NICE NG28. RCT evidence to support this combination is very limited therefore only consider if other combinations are cautioned or contraindicated.

ROTHERHAM

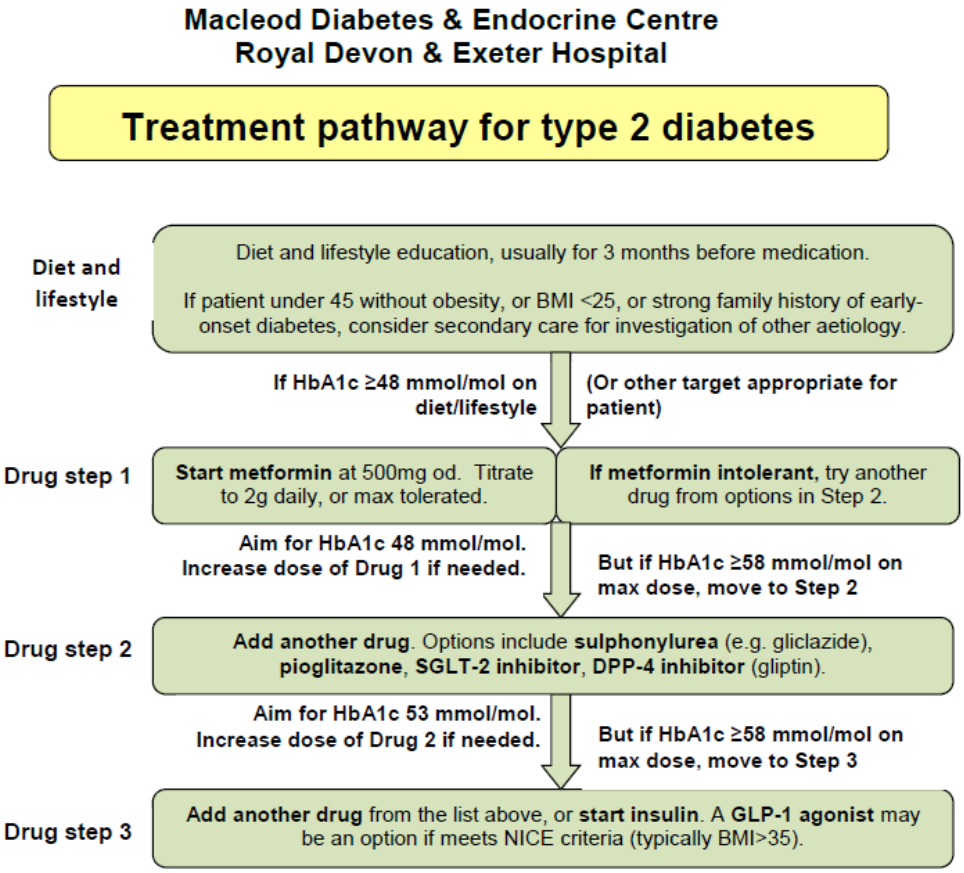
NHS
Rotherham
Clinical Commissioning Group

HbA1C management pathway

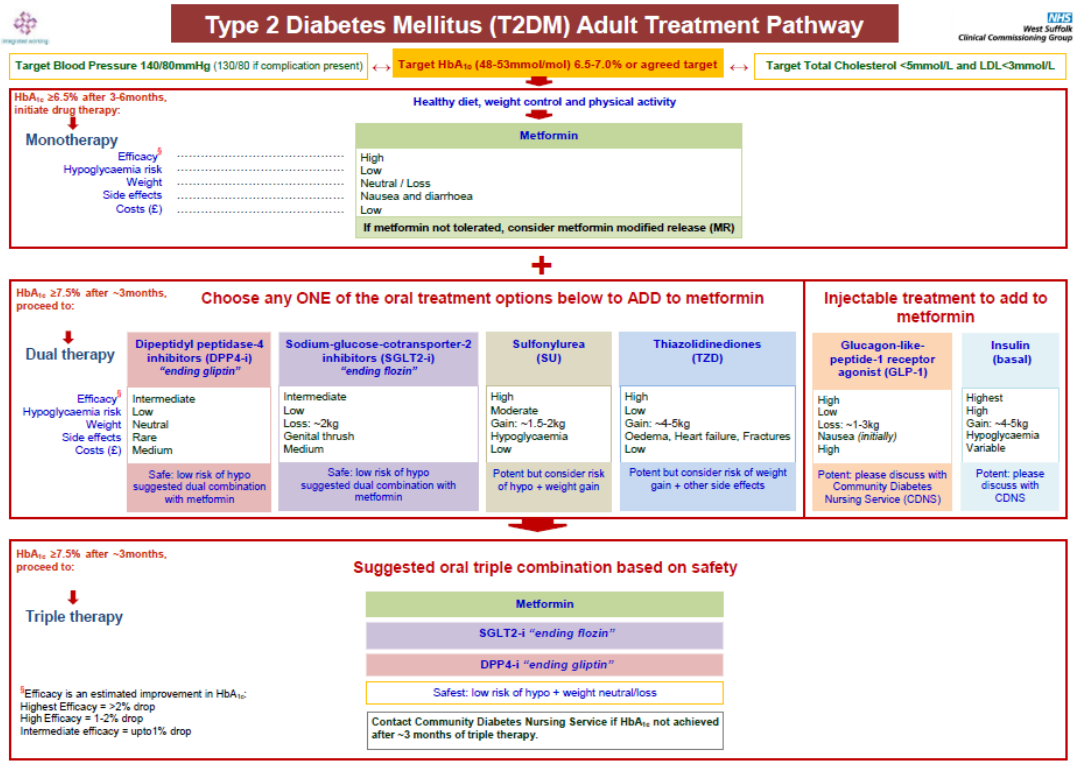
Recommended First Line Choices



ROYAL DEVON AND EXETER



WEST SUFFOLK



Appendix 2 - Subjects With Cardiovascular Adverse Events by SOC and PT (Incidence > 0% in One or More Treatment Groups); All Subjects as Treated Broad Pool: All Post-Randomization Follow-up

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]		[redacted]		[redacted]		[redacted]	
with one or more cardiovascular adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no cardiovascular adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure chronic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Coronary artery stenosis	■	■	■	■	■	■	■	■
Diastolic dysfunction	■	■	■	■	■	■	■	■
Dilatation ventricular	■	■	■	■	■	■	■	■
Left ventricular dysfunction	■	■	■	■	■	■	■	■
Left ventricular failure	■	■	■	■	■	■	■	■
Microvascular coronary artery disease	■	■	■	■	■	■	■	■
Myocardial infarction	■	■	■	■	■	■	■	■
Myocardial ischaemia	■	■	■	■	■	■	■	■
Right ventricular dysfunction	■	■	■	■	■	■	■	■
Silent myocardial infarction	■	■	■	■	■	■	■	■
General disorders and administration site conditions	■	■	■	■	■	■	■	■
Cardiac death	■	■	■	■	■	■	■	■
Death	■	■	■	■	■	■	■	■
Oedema	■	■	■	■	■	■	■	■

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)

General disorders and administration site conditions								
Oedema peripheral								
Peripheral swelling								
Sudden cardiac death								
Sudden death								
Investigations								
Ejection fraction decreased								
Electrocardiogram ST segment depression								
Exercise test abnormal								
Troponin increased								
Nervous system disorders								
Carotid arteriosclerosis								
Carotid artery stenosis								
Cerebral arterioscleros is								
Cerebral haemorrhage								
Cerebral infarction								
Cerebral ischaemia								

Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemiplegia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Internal carotid artery kinking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moyamoya disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruptured cerebral aneurysm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertebral artery stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertebrobasilar insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory, thoracic and mediastinal disorders	■	■	■	■	■	■	■	■
Pulmonary congestion	■	■	■	■	■	■	■	■
Pulmonary embolism	■	■	■	■	■	■	■	■
Pulmonary oedema	■	■	■	■	■	■	■	■
Vascular disorders	■	■	■	■	■	■	■	■
Deep vein thrombosis	■	■	■	■	■	■	■	■
Post thrombotic syndrome	■	■	■	■	■	■	■	■
Thrombophlebitis superficial	■	■	■	■	■	■	■	■
Venous thrombosis	■	■	■	■	■	■	■	■
Venous thrombosis limb	■	■	■	■	■	■	■	■

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Cardiovascular events were defined by a sponsor-generated Custom MedDRA Query.

MedDRA Version 19.0

Source: Merck internal data