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Empagliflozin for the treatment of Type 2 diabetes mellitus (T2DM)

Submitted by Boehringer Ingelheim Ltd

Single technology appraisal (STA)

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List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ACD	Appraisal consultation document
ADA	American Diabetes Association
AE	Adverse event
AIFA	Agenazia Italiana del Farmco
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
BICMQ	BI-customised medical dictionary for drug regulatory activities
BMI	Body mass index
BNF	British national formulary
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centres for Disease Control
CHF	Congestive heart failure
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CRD	Centre for Reviews and Dissemination
CV	Cardiovascular
CVD	Cardiovascular disease
CVZ	College voor Zorgverzekeringen (Health Care Insurance Board)
DAP	Dapagliflozin
DBP	Diastolic blood pressure
DCCT	Diabetes control and complications trial
DPP-4is	Dipeptidyl peptidase-4 inhibitors
DTSQ	Diabetes treatment satisfaction questionnaire
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
ESRD	End-stage renal disease
FAD	Final appraisal determination
FAS	Full analysis set
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
GI	Gastrointestinal

GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
GP	General practitioner
GTI	Genital infection
HAS	Haute Autorité de Santé
HbA_{1C}	Glycated haemoglobin
HCRU	Health care resource utilization
HDL	High density lipoprotein
HEED	Health Economic Evaluation Database
HIC	High-income countries
HOMA-IR	Homeostatic model assessment – insulin resistance
HOMA-IS	Homeostatic model assessment – insulin secretion
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IDF	International Diabetes Federation
IHD	Ischemic heart disease
IU	International units
IXRS	Interactive voice and web response system
IQWIG	The Institute for Quality and Efficiency in Health Care
LADA	Latent autoimmune diabetes antibodies
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LYG	Life Years Gained
MA	Marketing authorisation
MDG	Mean daily glucose
MDI	Multiple daily injections
MDRD	Modification of diet in renal disease
MEPS	Medical expenditure panel survey
MI	Myocardial infarction
MMRM	Mixed model repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta analysis
NPH	Neutral protamine Hagedorn
OAD	Oral antidiabetic drug
OL	Open label
OLS	Open label set
PBAC	Pharmaceutical Benefits Advisory Committee
PPS	Per protocol set
PSA	Probabilistic sensitivity analysis

PSS	Personal social services
PVD	Peripheral vascular disease
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REML	Restricted maximum likelihood
RR	Relative risk
RRT	Renal replacement therapy
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose co-transporter 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
Sita	Sitagliptin
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single technology appraisal
STEMI	ST elevation myocardial infarction
SU	Sulphonylureas
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TLV	Tandvård-s och Läkemedelsförmånsverket (The Dental and Pharmaceutical Benefits Agency)
TS	Treated set
TZD	Thiazolidinedione
UKPDS	UK Prospective Diabetes Study
UTI	Urinary tract infection
WHO	World Health Organization

Executive summary

Burden of Diabetes

Type 2 diabetes mellitus (T2DM) is a chronic, metabolic disease characterised by hyperglycaemia, caused by a combination of insulin resistance and an insufficient insulin secretory response by pancreatic beta cells. It is frequently under diagnosed with approximately 50% of individuals with T2DM being unaware of their condition.(1, 2)

T2DM substantially contributes to global morbidity and mortality.(3) The effects of chronic hyperglycaemia resulting in microvascular and macrovascular complications contribute to the significant clinical and economic burden of T2DM.

In 2013 there were an estimated 2.9 million adults with diabetes in England and Wales, of which 90% are estimated to have T2DM.(4, 5) According to CSD MAT data 2014, there are approximately 1.6 million patients in England and Wales on anti-diabetic medication. Of these, 45% are on some form of combination therapy. The current appraisal of empagliflozin therefore, covers approximately 720,000 patients.(6)

Technology – empagliflozin 10mg, 25mg once daily (Jardiance®)

Empagliflozin is a sodium-glucose cotransporter 2 protein inhibitor (SGLT2i). This transport protein is predominantly found in the kidneys, and is responsible for approximately 90% of glucose reabsorption from the kidneys. Empagliflozin demonstrates significant clinical benefits including:

- Reduction in glucose reabsorption via kidneys leading to urinary excretion and a reduction in blood glucose levels
- An insulin independent mechanism of action resulting in low incidences of hypoglycaemia unless used in combination with sulphonylureas (SU) and insulin therapy

- Caloric loss and osmotic diuresis leading to significant reduction in body weight and blood pressure
- Potential for use across the disease spectrum, due to maintained efficacy irrespective of ß-cell function and insulin resistance.

License and launch particulars

Empagliflozin does not currently have a marketing authorisation within the UK; it is currently being reviewed by the EMA via the centralised procedure and received a positive opinion from the CHMP on the 20th March 2014. Marketing authorisation is expected in May 2014.

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

Monotherapy

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

Add-on combination therapy

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

The price for a 28 day pack of empagliflozin is £36.59. The annual cost is £477.30.

Place in therapy and comparators

In line with the licensed indication and the treatment pathway (NICE CG 87), empagliflozin 10 mg and 25 mg can be positioned in the following pathways:

Dual therapy

Adults with T2DM who are inadequately controlled on monotherapy with metformin.

Triple therapy

Adults with T2DM who are inadequately controlled on dual therapy with either:

- Metformin in combination with a SU
- Metformin in combination with a thiazolidinedione (TZD).

Add-on therapy to insulin

Adults with T2DM who are inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.

Clinical evidence

The empagliflozin clinical trial programme provides a comprehensive evidence-base to support its use in the management of adults with T2DM. The eight multi-centre, randomised, controlled studies presented in this submission demonstrate the efficacy and safety of empagliflozin 10 mg and 25 mg in both short- and long-term trials.

Overview of clinical trial results

The key efficacy results for the empagliflozin clinical trial programme can be seen below:

- Both doses of empagliflozin were associated with a statistically significant reduction in mean HbA_{1C} compared with placebo in treatment-naïve patients and patients on different background therapies, including insulin

    - these reductions in HbA_{1C} were maintained throughout treatment duration and in the long-term safety and efficacy study (1245.31)

- Empagliflozin 25 mg was also non-inferior compared with glimepiride in terms of change in HbA_{1C}, body weight and blood pressure from baseline at 104 weeks (1245.28)

- Treatment with both doses of empagliflozin also resulted in statistically significant reductions in body weight and blood pressure compared with placebo in treatment- naïve and previously treated patients, including insulin
    - both of these are important cardiovascular risk factors in patients with T2DM
- In the dedicated hypertension study (1245.48), statistically significant and clinically meaningful reductions in mean 24-hour systolic blood pressure (SBP) from baseline were observed with stable antihypertensive background medication
- The efficacy of empagliflozin is attenuated by increasing age and decreasing renal function, however empagliflozin has still demonstrated superiority compared with placebo in patients with mild-to-moderate renal impairment (1245.36).

Clinical safety

Both doses of empagliflozin have a favorable safety profile and are well tolerated, with adverse events (AEs) and serious adverse events (SAEs) similar to placebo in the clinical studies

The key safety results for the empagliflozin clinical trial programme can be seen below:

- The incidence of hypoglycaemia was low in empagliflozin-treated patients with T2DM which may be due to its insulin-independent mechanism of action. The incidence of patients experiencing

hypoglycaemia was only increased when used as add-on to sulphonylureas (SU) or insulin therapy

- As is consistent with the treatment class, empagliflozin was associated with a slightly higher incidence in the frequency of genital tract infections (GTIs) compared with placebo. There was no difference in the frequency of urinary tract infections (UTIs) across treatment groups, although empagliflozin was associated with an increased rate of UTIs in females vs. placebo.
    - most patients who reported events consistent with UTI or genital infection experienced only one such episode and this was most often of mild intensity. Furthermore, discontinuation due to either of these events was uncommon
- Rates of volume depletion events were low in all trials, and were highest in patients with moderate renal impairment in the dedicated renal impairment trial (1245.36).

An indirect comparison between empagliflozin, sitagliptin, dapagliflozin and canagliflozin all given against a background therapy of either: metformin, metformin and SU, metformin and TZD and insulin showed empagliflozin was in general comparable with the other therapies with no consistent statistical differences between options.

Cost effectiveness

A cost utility analysis was undertaken comparing empagliflozin to dapagliflozin, canagliflozin and sitagliptin in combination with metformin, metformin and SU, metformin and TZD and insulin.

A de Novo cost effectiveness model was developed based on existing cost effectiveness models submitted to health technology assessment (HTA) organisations for diabetes. Assumptions and parameters were identified from previous NICE appraisals and from the outputs of the UK Prospective Diabetes Study (UKPDS). The model linked surrogate outcomes: HbA1c, SBP and weight change to long term complications using the UKPDS risk

equations. This approach was adopted as it was consistent with previous NICE assessments of anti-diabetic medications and the approach has been accepted by Appraisal Committees.

The base case results are summarised in Table 1.

Table 1: Base case incremental results

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Metformin combinations					
Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	£133	Dominated by sitagliptin 100 mg
Met + Canagliflozin 100 mg	7.415	-0.01	£32,300	£255	Dominated by sitagliptin 100 mg
Met + Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
Met + Empagliflozin 10 mg	7.424	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Metformin and SU combinations					
Met + SU + Canagliflozin 100 mg	6.98	-	£31,217	-	-
Met + SU + Sitagliptin 100 mg	6.959	-0.021	£31,365	£148	Dominated by canagliflozin 100 mg
Met + SU + Empagliflozin 10 mg	6.991	0.011	£31,409	£192	£17,445
Met + SU + Empagliflozin 25 mg	6.978	-0.013	£31,557	£148	Dominated by empagliflozin 10 mg
Met + SU + Canagliflozin 300 mg	6.976	-0.015	£32,087	£679	Dominated by empagliflozin 10 mg
Metformin and TZD combinations					
Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-
Met + TZD + Canagliflozin 100 mg	6.983	0.016	£31,329	£26	£1,644
Met + TZD + Empagliflozin 25 mg	6.999	0.016	£31,486	£157	£9,806
Met + TZD + Canagliflozin 300 mg	6.978	-0.021	£31,866	£380	Dominated by empagliflozin 25 mg
Met + TZD + Empagliflozin 10 mg	6.996	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg
Insulin combinations					
Insulin + Canagliflozin 100 mg	6.944	-	£30,418	-	-
Insulin + Dapagliflozin 10 mg	6.953	0.009	£30,545	£128	£14,178
Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg

Insulin + Canagliflozin 300mg	6.957	0.004	£30,842	£296	£74,075

ICER = incremental cost-effectiveness ratio; Met = metformin; NHS = National Health Service; QALY = quality-adjusted life year; SU = sulphonylurea; TZD = thiazolidinedione

The absolute differences in quality-adjusted life years (QALYs) and costs between the SGLT2is are very small across all background treatments and all combinations. These differences are clinically not significant when it is considered they are over a 40 year time horizon. This is consistent with the conclusions of the network meta-analysis which indicated that there were few statistically significant differences between the SGLT2is. The main drivers for the differences are numerical differences in the mean estimates in the efficacy and AEs. These results were robust to a number of sensitivity analyses exploring key areas of uncertainty including treatment duration, weight development and other structural assumptions. In addition, when 52 week data and the CORE model were utilised there were no differences in the conclusions.

Conclusion

The results of the clinical effectiveness and cost effectiveness reviews suggest that empagliflozin is clinically equivalent to other SGLT2is and offers significant benefits over DPP-4is in terms of weight and blood pressure reduction. In addition, there is little difference between empagliflozin and SGLT2is/ DPP-4is in terms of incremental costs, suggesting again broad equivalence in terms of cost effectiveness. These results are consistent with previous Appraisal Committee deliberations for dapagliflozin and canagliflozin where it concluded that given there were marginal differences between the SGLT2is and DPP-4is and therefore, recommended that they be used in the same point in the treatment pathway. Hence, given the results empagliflozin should be considered as an alternative to DPP-4is and SGLT2is in combination therapy.

Section A – Decision problem

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

1 Description of technology under assessment

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

Brand name: Jardiance®

Approved name: Empagliflozin

Pharmacotherapeutic group: Drugs used in diabetes; other blood glucose lowering agents

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

Empagliflozin inhibits the sodium-glucose cotransporter 2 protein (SGLT2) . This transport protein is predominantly found in the kidneys, and is responsible for approx. 90% of glucose reabsorption from the kidneys. Inhibition of SGLT2 causes a reduction of glucose re-absorption, which leads to urinary glucose excretion and thus a reduction of blood glucose levels in patients with Type 2 diabetes mellitus (T2DM). Because the effects of SGLT2 inhibition are achieved independently of insulin, incidence of hypoglycaemia is low unless empagliflozin is used in combination with sulphonylurea (SU) or insulin. Pharmacological blockade of glucose reabsorption via SGLT2 inhibition also results in caloric loss and osmotic diuresis, with potential benefits on body weight and blood pressure.

As the disease progresses, changes in ß-cell function and insulin resistance lead to further increases in blood glucose levels. However, because SGLT2 inhibition works independently of ß-cell function and insulin resistance it can be used effectively across the disease spectrum.

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

Empagliflozin does not currently have a marketing authorisation within the UK; it is currently being reviewed by the European Medicines Agency (EMA) via the centralised procedure and received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 20th March 2014. Marketing authorisation is expected in May 2014.

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

N/A as the European public assessment report (EPAR) has yet to be published.

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

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

Monotherapy

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

Add-on combination therapy

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

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

An overview of the clinical trial program is provided in Table 2.

Table 2: Summary of empagliflozin phase III clinical trial programme

Study	1245.19	1245.20	1245.23	1245.25	1245.28	1245.31	1245.33	1245.36	1245.48	1245.49	1245.52
Name	**EMPA-REG PIO**	**EMPA-REG MONO**	**a. EMPA-REG MET** **b. EMPA-REG METSU**	**EMPA-REG OUTCOME**	**EMPA-REG H2H-SU**	**EMPA-REG EXTEND**	**EMPA-REG BASAL**	**EMPA-REG RENAL**	**EMPA-REG BP**	**EMPA-REG MDI**	**EMPA-REG COMBO JAPAN**
Description	**Add-on to met/pio**	**Mono-therapy**	**a. Add-on to met** **b. Add-on to met+SU**	**CV outcome trial**	**Head-to-head *vs* SU**	**Long-term safety**	**Add-on to basal insulin**	**Renal impairment**	**ABPM trial**	**Add-on to MDI**	**Japanese patients**
Patient population	Patients with T2DM with insufficient glycaemic control			Patients with T2DM with increased CV risk	Patients with T2DM with insufficient glycaemic control	Patients with T2DM who previously completed trial 1245.19, 1245.20 or 1245.23	Patients receiving treatment with basal insulin and insufficient glycaemic control	Patients with T2DM with insufficient glycaemic control and renal impairment	Hypertensive patients with T2DM	Patients with T2DM with insufficient glycaemic control being treated with MDI insulin regimen	Japanese patients with T2DM with insufficient glycaemic control
Test therapy	Empagliflozin 10 mg, 25 mg				Empagliflozin 25 mg	Empagliflozin 10 mg, 25 mg					
Reference therapy	Placebo	Sitagliptin * 100 mg Placebo	Placebo	Placebo	Glimepiride 1 mg-4 mg	Sitagliptin* 100 mg Placebo	Placebo	Placebo	Placebo	Placebo	Metformin for patients on SU background therapy only
Background therapy	Pioglitazone +/- metformin	Drug-naïve patients	Metformin +/- SU	Usual care	Metformin	As specified in study 1245.19, 1245.20 or 1245.23	Basal insulin (glargine, detemir, or NPH insulin only) +/-	Pre-existing antidiabetic therapy	Current anti-hypertensive and antidiabetic therapy	MDI insulin regimen +/- metformin	OAD (SU, biguanide, TZD, alpha glucosidase inhibitor, DPP-4i or

Study	1245.19	1245.20	1245.23	1245.25	1245.28	1245.31	1245.33	1245.36	1245.48	1245.49	1245.52
							metformin and/or SU				glinide)
Study design	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel
Treatment duration	24 weeks	24 weeks	24 weeks	Event-driven	104 weeks	52 weeks	78 weeks	52 weeks	12 weeks	52 weeks	52 weeks
Objective	**Change from baseline in HbA1c** superior vs placebo	**Change from baseline in HbA1c** superior vs placebo	**Change from baseline in HbA1c** superior vs placebo	**First occurrence of any of the adjudicated components of the primary composite endpoint**** non-inferior vs placebo	**Change from baseline in HbA1c** non-inferior vs glimepiride	Assessment of **long-term safety and tolerability**	**Change from baseline in HbA1c** superior vs placebo	**Change from baseline in HbA1c** superior vs placebo	**Change from baseline in HbA1c** superior vs placebo **Change from baseline in 24-hour mean SBP** superior vs placebo	**Change from baseline in HbA1c** superior vs placebo	Assessment of **long-term safety and tolerability**
Completion date†	April 2012	March 2012	February 2012	Estimated April 2015	July 2013	May 2013	May 2012	July 2012	July 2012	April 2013	April 2013
Results available?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Anticipated publication availability for primary data in 2013	Kovacs *et al.* 2013 (7)	Roden *et al.* 2013 (8)	Haring *et al.* 2013 (9)	Inzucchi *et al.* 2013 EASD 2013 (10) Trial design and rationale	Ridderstrale *et al.* 2013(11) Trial design and rationale	–	Rosenstock *et al.* 2013 ADA 2013 (12)	Barnett *et al.* 2013 ADA 2013 (13)	Tikkanen *et al.* 2013 EASD 2013 (14)	–	Woerle *et al.* 2013 EASD '13 (15)

*Sitagliptin comparison versus placebo was used for internal validation of the trial. No formal comparison was made between empagliflozin and sitagliptin
**Primary composite endpoint components: CV death (including fatal stroke and fatal MI), non-fatal MI and non-fatal stroke
† Completion dates refer to final data collection for the primary outcome measure.
ABPM = ambulatory blood pressure monitoring; ADA = American Diabetes Association; CV = cardiovascular; EASD = European Association for the Study of Diabetes; HbA1c = glycosylated haemoglobin A1; MDI = multiple daily injections; SBP = systolic blood pressure; SU = sulphonylurea; TZD = thiazolidinedione

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

We anticipate that stock will be available within the UK in July 2014

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

As of 23 May 2014, empagliflozin has not been approved in any other country.

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

Yes, submission to the Scottish Medicines Consortium (SMC) expected May 2014.

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

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Film coated tablet
Acquisition cost (excluding VAT)	£36.59 per pack of 28 (10 and 25 mg)
Method of administration	Oral
Doses	10 mg, 25 mg
Dosing frequency	Once daily
Average length of a course of treatment	Given the variability in patients the average length of a course cannot be estimated accurately. In the clinical trial program duration of treatment varied from 82 to 450 days, however this was influenced by the planned duration of the trial and therefore unlikely to be representative of UK clinical practice.
Average cost of a course of treatment	1 year treatment costs £470.30
Dose adjustments	The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other glucose lowering medicinal products including insulin. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg

eGFR = estimated glomerular filtration rate; VAT = value added tax

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

N/A

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

It is expected that there will be no requirement for additional testing with empagliflozin.

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

There will be a requirement for renal assessment prior to treatment initiation and an annual assessment thereafter. However, both of these assessments should be part of clinical practice.

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

While the marketing authorisation does not restrict what treatments can be given in combination with empagliflozin, it is expected that the main treatments would be metformin, SU, TZD and insulin. There is currently no evidence of the effectiveness of empagliflozin in combination with GLP-1 receptor agonists (GLP-1 RA), DPP-4 inhibitor (DPP-4i) or other SGLT2is.

2 Context

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

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

Diabetes mellitus, as defined by the American Diabetes Association (ADA), is 'a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both'.(16)
Diabetes develops when the body no longer responds adequately to insulin or when production or secretion of insulin is too low, resulting in abnormally high blood glucose levels. In diabetic patients, glucose uptake into cells from the bloodstream is limited due to the relative lack of insulin and/or insulin resistance.

T2DM is characteristically a disease that effects middle aged or elderly individuals and usually begins insidiously. It is frequently under diagnosed with approximately 50% of individuals with T2DM being unaware of their condition.(1, 2) Obesity, genetic and environmental factors (sedentary lifestyle and high caloric food intake) are important risk factors for T2DM development.

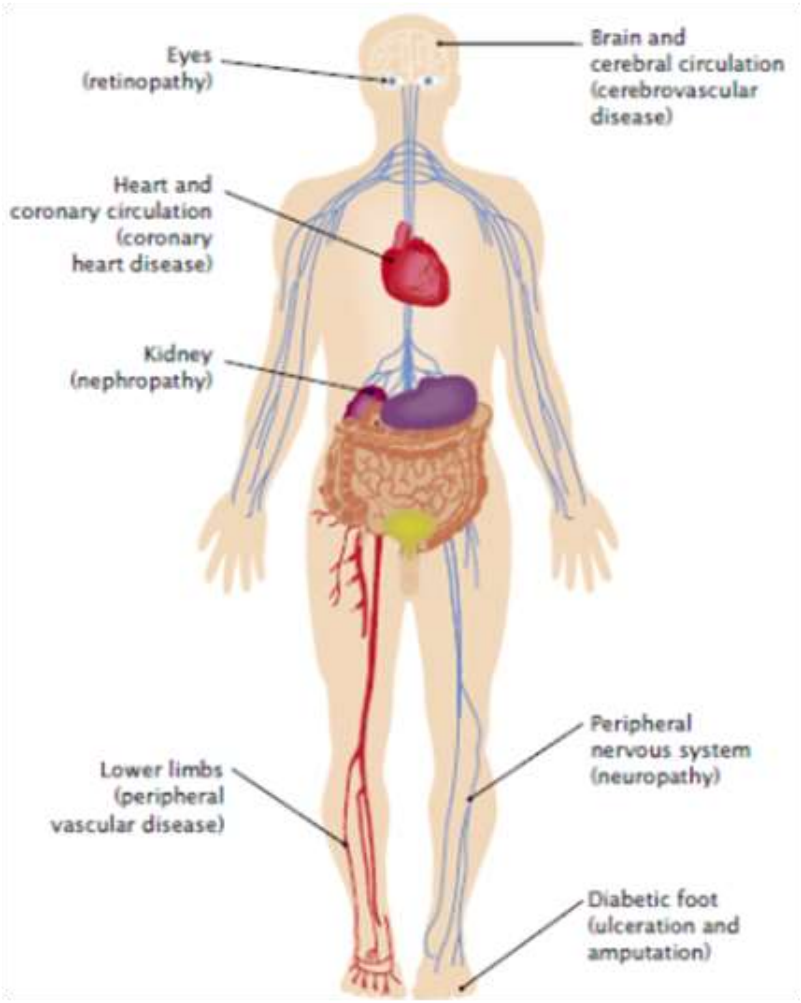
T2DM is characterised by insulin resistance and deficient insulin secretion. Individuals with T2DM are able to produce insulin but not in sufficient quantity and in a manner that is less effective than in patients without diabetes.

T2DM substantially contributes to global morbidity and mortality.(3) It is not the presence of T2DM *per se*, but the effects of chronic hyperglycaemia resulting in microvascular and macrovascular complications, that account for the clinical and economic burden of T2DM.

Diabetic complications can be classified into micro- and macrovascular complications (Figure 1). Microvascular diseases affect the smaller (more distant) blood vessels, including the capillaries, e.g. in the eye, leading to impaired vision (retinopathy), impaired kidney function (nephropathy) and/or

diseases of the peripheral nervous system (neuropathy). Macrovascular complications, such as cardiovascular disease (CVD), affect larger blood vessels, including the coronary arteries, the aorta, and arteries in the brain and in the limbs.

Figure 1: Major diabetic complications



A large body of evidence emerging from two landmark studies, the Diabetes Control and Complications Trial (DCCT) and the UKPDS indicate that chronic hyperglycaemia constitutes a major initiator of microvascular diabetic complications, but the exact mechanisms have not yet been fully elucidated.(17-20) The endothelia of the retina, kidney and peripheral nervous system are particularly susceptible to damage induced by hyperglycaemia associated with diabetes.

T2DM and its complications are major causes of premature mortality in most countries. Patients with diabetes have a 2-fold increased risk of death compared with non-diabetics, independent of age and other known risk factors for CVDs.(21, 22)

According to the International Diabetes Federation (IDF), diabetes accounted for 4.6 million deaths in 2011 (i.e. 8.2% of total world mortality of people between the age of 20–79 years).(23) The estimated number of deaths was similar to the combined deaths from HIV/AIDS and other infections that are major public health priorities.(24) Almost half (48%) of deaths due to diabetes were in people under the age of 60.(23)

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

According to Cegedim Strategic Data Moving Annual Total (CSD MAT) data 2014 there are approximately 1.6 million patients in England and Wales on anti-diabetic medication. Of these 45% are on some form of combination therapy. The current appraisal of empagliflozin therefore, covers approximately 720,000 patients.(6)

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

Patients with diabetes have a shorter life expectancy than individuals without diabetes. (25, 26) Analysis of data from the UKPDS indicated that mean life expectancy for men between the ages of 45 and 50 years at diagnosis of diabetes was 25.54 years (95% CI 21.92 to 29.66; Table 4). This compared with 30.05 years remaining life expectancy for men of this age in the UK general population (1999 to 2001), suggesting a loss of approximately 5 years of life attributable to T2DM.(26)

Table 4: Estimated mean life expectancy and mean quality-adjusted life expectancy by age at diagnosis of diabetes in the UKPDS *(26)

Age at diagnosis	Life expectancy (95% CI [years])		Quality-adjusted life expectancy (95% CI [QALYs])	
	Men	Women	Men	Women
45–49	25.54 (21.92–29.16)	26.80 (22.12–31.48)	18.82 (16.48–21.15)	20.06 (16.92–23.19)
50–54	21.51 (18.65–24.37)	23.58 (19.94–27.22)	15.96 (14.14–17.79)	17.62 (15.30–19.93)
55–59	17.94 (15.78–20.11)	20.16 (17.34–22.98)	13.34 (11.97–14.71)	15.10 (13.23–16.97)
60–64	13.91 (12.55–15.27)	17.65 (16.58–19.73)	10.34 (9.46–11.22)	13.15 (11.88–14.42)

CI = confidence interval; QALY = quality-adjusted life year
*Based on 3,405 patients between 45 and 65 years randomised to regimens of intensive or conventional blood glucose control

Further studies of the UKPDS dataset characterised the impact of T2DM on life expectancy. An outcomes simulation model based on patient characteristics and risk profiles in the UKPDS showed that there is substantial variation in life expectancy among patients with T2DM depending on their levels of commonly measured risk factors such as HbA_{1c} and duration of diabetes across different age groups. For example, men aged 55 years with T2DM were predicted to live for 3.6-11.5 years less than the UK general population at the same age.(27)

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

NICE produced clinical guideline No 66 in 2008 and updated it in 2009 as CG 87 to include newer diabetic agents. There are also 4 relevant technology appraisals:

- No. 53 (2002): Diabetes (types 1 and 2) – long acting insulin analogues (including insulin glargine)
- No. 203 (2010): Liraglutide for the treatment of type 2 diabetes mellitus
- No. 248 (2012): Diabetes (type 2) – exenatide (prolonged release)
- No. 288 (2013): Dapagliflozin in combination therapy for treating type 2 diabetes

Currently in development are the following relevant updates:

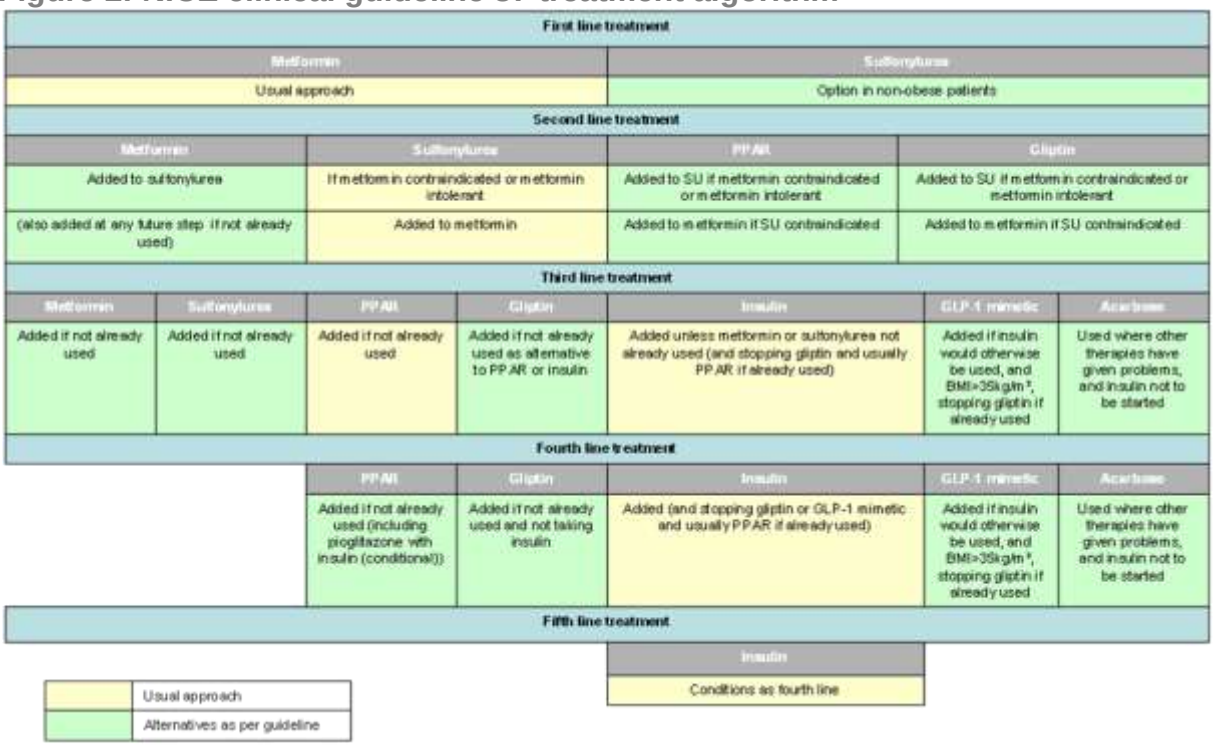
- Type 2 diabetes – diagnosis and treatment
- Canagliflozin for type 2 diabetes

These NICE guidelines and technology appraisals mainly explored subgroups around BMI, baseline HbA_{1C} and chronic kidney disease (CKD) status. However, there have been no specific recommendations around these subgroups

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

Figure 2 outlines the current treatment pathway from CG 87.

Figure 2: NICE clinical guideline 87 treatment algorithm



There are no restrictions within the MA for empagliflozin concerning when it can be used in the treatment pathway or with what treatments it can be combined with. Therefore, potentially it could be used anywhere in the

treatment pathway. However, this appraisal has excluded monotherapy. Therefore, this appraisal will only explore combination therapy such as dual or triple treatment combination or in combination with insulin. It is unlikely that the treatment pathway will change significantly with the addition of a new oral treatment.

NICE clinical guideline 73 (chronic kidney disease) is also relevant for diabetes. Approximately a third of patients with T2DM have moderate or severe renal impairment.(28). In addition, DPP4i's and SGLT2is require dose adjustment as CKD status deteriorates.(29, 30) Table 5 outlines the recommended renal monitoring. The intensity of monitoring will vary depending on whether renal function stabilises or deteriorates.

Table 5: Stages of CKD and frequency of eGFR testing in NICE clinical guideline 73

Stage	eGFR (ml/min/1.73 m^2)	Description	Typical testing frequency
1	≥ 90	Normal or increased glomerular filtration rate (GFR), with other evidence of kidney damage	12 monthly
2	60–89	Slight decrease in GFR, with other evidence of kidney damage	
3A	45–59	Moderate decreased in GFR, with or without other evidence of kidney damage	6 monthly
3B	30–44		
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage	3 monthly
5	< 15	Established renal failure	6 weekly

Test eGFR:

- Annually in all at risk groups.
- During intercurrent illness and perioperatively in all patients with CKD.
- The exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; min = minute

The importance of this guidance in relationship to diabetes is that a number of the oral anti-diabetic treatments require dose adjustment depending on the stage of CKD. For example for all the DPP-4is except linagliptin require dose adjustment in moderate renal impairment. In the case of the SGLT2is

dapagliflozin and canagliflozin cannot be used in patients with an estimated glomerular filtration rate (eGFR) below 60. While for empagliflozin can be used in patients with eGFR up to 45ml/min/1.73m^2. This allows patients to remain on treatment until moderate renal impairment.

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

There have been several publications outlining the current variation in the provision of NHS services for diabetes.

In 2009 and 2010, the National Diabetes Audit found that the proportion of people with diabetes receiving all nine recommended care processes varied from 6% to 69% between primary care trusts. There were also large variations across the NHS in the proportion of patients achieving treatment standards such as recommended levels for glucose control, and developing diabetes-related complications such as end-stage kidney disease. The audit considered that these variations cannot be explained by need or spending alone and are likely to be influenced by the local organisation and management of health services. The active uptake of novel anti-diabetic medications would enable patients to have greater control of their condition. Additionally, if these treatments could support the clinician-patient relationship then it would enable a more active patient participation in regards to their care. There is also a wide variation in the models of care for diabetes and in patients getting access to NICE approved drugs in primary care due to restrictions based on budgets.(31)

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

NICE guidance indicates that the following are potential options at various stages of diabetes management after metformin:

- SU
- DPP-4is
- TZD
- Dapagliflozin
- Canagliflozin (awaiting guidance)

- Liraglutide
- Exenatide
- Prolonged-release exenatide
- Insulin

However, NICE guidance on dapagliflozin and preliminary guidance on canagliflozin suggest that the SGLT2is are considered in the same line of therapy as DPP-4is which is as an option in dual, triple and insulin combinations. The guidance on dapagliflozin and canagliflozin indicate that the SGLT2is are not considered a replacement for SU, but rather should be used by patients for whom SUs are unsuitable. In addition, TZDs were not considered a relevant comparator because their use is falling within the UK and while they are now generic, there are still concerns over their safety including potential links to cancer.

For GLP-1 RAs NICE considered that as they are injectable they are considered at a different point in therapy and therefore were also not a suitable comparator. The same held true for insulin, where patients often consider that insulin is a significant step on the treatment pathway (RCN guidance 2012[a]). Hence the only remaining treatments in the decision space are dapagliflozin, canagliflozin and DPP-4is.

In the DPP-4is market, the leader in terms of market share is currently sitagliptin with over 80% share of the market; linagliptin is the second treatment with about 10% of the market. Therefore, sitagliptin has been selected as the DPP-4i to be used in the dapagliflozin and canagliflozin appraisals. Further details are provided in Section 5.

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

The main AEs associated with the oral anti-diabetics treatments is hypoglycaemia. For SGLT2is there is a low probability of UTIs and GTIs. See Section 6.9 for more details for each adverse event (AE).

[a] Royal College of Nursing Guidance for nurses starting injectable treatment in adults with type 2 diabetes

Urinary Tract Infections

UTI rates were higher for patients receiving empagliflozin compared with placebo, yet they were still relatively uncommon. In addition, infections were generally mild and usually responded to a course of antibiotics such as amoxicillin, trimethoprim or nitrofurantoin.

Genital Infections

GTIs were also higher for patients receiving empagliflozin compared with placebo; again they were still relatively uncommon. In addition, the infections were generally mild and did not lead to considerable rates of discontinuation. Generally, these events were more common in women than men and also in patients who have had a previous GTI event. Therefore, this could be mitigated by careful patient selection. GTIs were treated with antimicrobial agents such as antifungals/oral treatments.

Hypoglycaemia

Insulins and SU have a demonstrated link to an increased risk of hypoglycaemia. In comparison, the risk of hypoglycaemia with empagliflozin is very low. Minor hypoglycaemia can be treated at home by consuming sugary foods or drinks. Severe cases may require the injection of the hormone glucagon and may require the person's admittance to hospital.

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

Empagliflozin will be mainly used in primary care with some limited secondary care initiation. All costs utilised in the submission came from sources previously accepted in NICE technology appraisals. These included estimates from the UKPDS study (please see Section 7.2).

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

It is not anticipated that any additional infrastructure will be required for empagliflozin.

3 Equality

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

3.1 Identification of equality issues

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

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

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

While many of the protected characteristics are associated with aspects of diabetes management, it is considered unlikely that any recommendations or appraisal would result in those groups being unfairly disadvantaged.

3.1.2 How has the analysis addressed these issues?

N/A

4 Innovation

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

Although advances in the management of T2DM have been achieved, current treatment options for patients with the condition still fail to address disease progression. Furthermore, glycaemic control remains suboptimal and many therapies are associated with an increased risk of hypoglycaemia and weight gain. Moreover, there is evidence that patients tend to prefer oral antidiabetic drugs (OADs) to injectable treatments such as insulins and GLP-1 RAs.

Hence, an ideal intervention would be one that:

- Improves glycaemic control without compromising safety
- Could slow and/or reverse beta-cell decline
- Can be used across the disease spectrum (insulin-independent mechanism of action)
- Does not cause hypoglycaemia
- Results in weight loss or avoids additional weight gain
- Addresses cardiovascular (CV) risk factors accompanying diabetes such as hypertension
- Does not increase the rate of cardiac events
- Offers protection against macrovascular disease
- Can be used in patients with hepatic or renal insufficiency or heart failure; and
- Offers a simple therapy regimen that can be taken orally.

All of the currently available classes of antidiabetic agents have limitations; effective alternatives are needed to address the unmet needs of patients with T2DM and offer a more favourable balance between the benefits and disadvantages of treatment.

SGLT2is represent a novel treatment for T2DM by providing HbA_{1C} control and associated weight and SBP reductions. In addition, this class is

associated with low incidence of hypoglycaemia and other AEs. No current treatment option offers this combination with an oral once a day tablet. In the correct patient groups the SGLT2is can provide clinicians with a treatment option that can positively encourage the patient to continue with lifestyle interventions and improve their outcomes.

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

It is expected that all benefits of the treatment would be captured by the QALY.

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

N/A

5 Statement of the decision problem

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

The decision problem can be seen below in Table 6.

Table 6: Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	**Dual therapy** Adults with T2DM that is inadequately controlled on monotherapy with either metformin or a SU **Triple therapy** Adults with T2DM that is inadequately controlled on dual therapy with either: • Metformin in combination with a SU • Metformin or a SU in combination with a TZD, a DPP-4i, or a GLP-1 RA **Add-on therapy to insulin** Adults with T2DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and one or more other oral agents	**Dual therapy** Adults with T2DM that is inadequately controlled on monotherapy with metformin **Triple therapy** Adults with T2DM that is inadequately controlled on dual therapy with either of the following: • Metformin in combination with a SU • Metformin in combination with a TZD **Add-on therapy to insulin** Adults with T2DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents	**Dual therapy** Empagliflozin in combination with a sulphonylurea has been excluded due to the absence of direct trial evidence for this indication **Triple therapy** Empagliflozin has only been studied in combination with metformin and SU and in combination with metformin and TZD

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Intervention	Empagliflozin (in combination with OADs and/or insulin)	Empagliflozin (in combination with OADs and/or insulin)	Empagliflozin in combination with: • Metformin • TZD • Metformin and SU • Metformin and TZD • Insulin The choice of combinations reflects the options utilised in the clinical trial program. There was no clinical evidence for other combinations
Comparator(s)	**Dual therapy** For the combination of empagliflozin and metformin, the comparators are: • SUs (with metformin) • Pioglitazone (with metformin) • DPP-4is (with metformin) • GLP-1RAs (with metformin) • Dapagliflozin (with metformin). For the combination of empagliflozin and SU, the comparators are: • Pioglitazone (with a SU) • DPP-4is (with a SU) • GLP-1RAs (with a SU). **Triple therapy** For the combination of empagliflozin, metformin and a SU, the comparators are: • Pioglitazone (with metformin and a SU) • DPP-4is (with metformin and a SU) • GLP-1RAs (with metformin and a SU) • Insulin (with metformin and a SU) For the combination of empagliflozin,	**Dual therapy** For the combination of empagliflozin and metformin, the comparators are: • SUs (with metformin) • DPP-4is (with metformin) • dapagliflozin (with metformin) **Triple therapy** For the combination of empagliflozin, metformin and a SU, the comparators are: • DPP-4is (with metformin and a SU) • Canagliflozin For the combination of empagliflozin, metformin and pioglitazone, the comparators are: • DPP-4is(with metformin and pioglitazone) • Canagliflozin **Add-on therapy to insulin** One or more oral anti-diabetic agents (in combination with insulin) • DPP-4is • Dapagliflozin	NICE guidance has demonstrated that SGLT2is have been placed in the same treatment position as DPP-4is. Specifically the following treatments were excluded because: • Pioglitazone was considered not relevant since TZDs are currently very rarely and their use is currently falling. • GLP-1RAs were considered irrelevant as an injectable they are considered at a different point in the treatment pathway and they are currently only recommended in specific populations • Insulin was not considered an appropriate comparator since as an injectable it is used at a different point in the treatment pathway. • Canagliflozin was added to the scope as it was considered relevant as the only other licensed SGLT2i currently available

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	metformin and pioglitazone, the comparators are: • DPP-4is (with metformin and pioglitazone) • GLP-1RAs (with metformin and pioglitazone) • Insulin (with metformin and pioglitazone) For the use of empagliflozin in any other triple therapy regimen, the comparator is • Insulin (alone or in combination with one or more oral anti-diabetic agents). **Add-on therapy to insulin** one or more OADs (in combination with insulin)	• Canagliflozin	
Outcomes	The outcome measures to be considered include: • HbA_{1c} /glycaemic control • Frequency and severity of episodes of hypoglycaemia • Change in cardiovascular risk factors (including estimated glomerular filtration rate, albumin creatinine ratio, blood pressure and/or serum lipids) • Weight change • Complications of diabetes e.g. cardiovascular, renal and eye • Mortality • Adverse effects of treatment (including genitourinary tract infection) • Health-related quality of life	The outcome measures to be considered include: • HbA_{1c} /glycaemic control • Frequency and severity of episodes of hypoglycaemia • Change in cardiovascular risk factors (including estimated glomerular filtration rate, albumin creatinine ratio, blood pressure and/or serum lipids) • Weight change • Complications of diabetes e.g. cardiovascular, renal and eye • Mortality • Adverse effects of treatment (including genitourinary tract infection) • Health-related quality of life	All outcomes included within the clinical trial program have been included

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	Cost effectiveness analysis in line with reference case
Subgroups to be considered	If evidence allows, subgroups based on the following criteria will be considered: • BMI • Baseline HbA_{1c}	If evidence allows, subgroups based on the following criteria will be considered: • BMI • Baseline HbA_{1c}	Subgroup data were available is presented in Section 6.3.1
Special considerations, including issues related to equity or equality	None	None	None

BMI = body mass index; DPP-4is = dipeptidyl peptisase-4 inhibitors; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA1c = glycated haemoglobin; OADs = oral antidiabetic drugs; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione

Section B – Clinical and cost effectiveness

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

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

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

6 Clinical evidence

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

6.1 Identification of studies

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

Full details of the search strategy can be seen in Section 9.2, Appendix 2.

6.2 Study selection

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

A systematic review of the medical literature was conducted to identify all randomised controlled trials (RCTs) that assessed empagliflozin, DPP-4is, TZDs, or insulins in adult patients with T2DM experiencing inadequate glycaemic control despite a diet and exercise program and a stable regimen of metformin plus sulphonylurea. In consultation with an academic medical librarian, a systematic search of the medical literature using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register (from inception to December 7, 2013) was conducted. The search strategy was sensitive and broad (see Table 111). Hand searches of the bibliographies of published systematic reviews and HTAs were also performed. In addition, unpublished trials in the empagliflozin clinical trial programme were identified by reviewing a list of all ongoing and completed Boehringer Ingelheim/Lilly RCTs. The eligibility of each of the studies was evaluated based on the full clinical study reports.

Finally, the websites of other pharmaceutical companies manufacturing selected treatments and clinicaltrials.gov were searched to identify any additional unpublished clinical trials that may be eligible for inclusion. All searches were performed independently, in duplicate. The populations, interventions, comparisons, outcomes, and study designs (PICOS) considered for this review are shown below Table 7.

Table 7: PICOS criteria for study inclusion

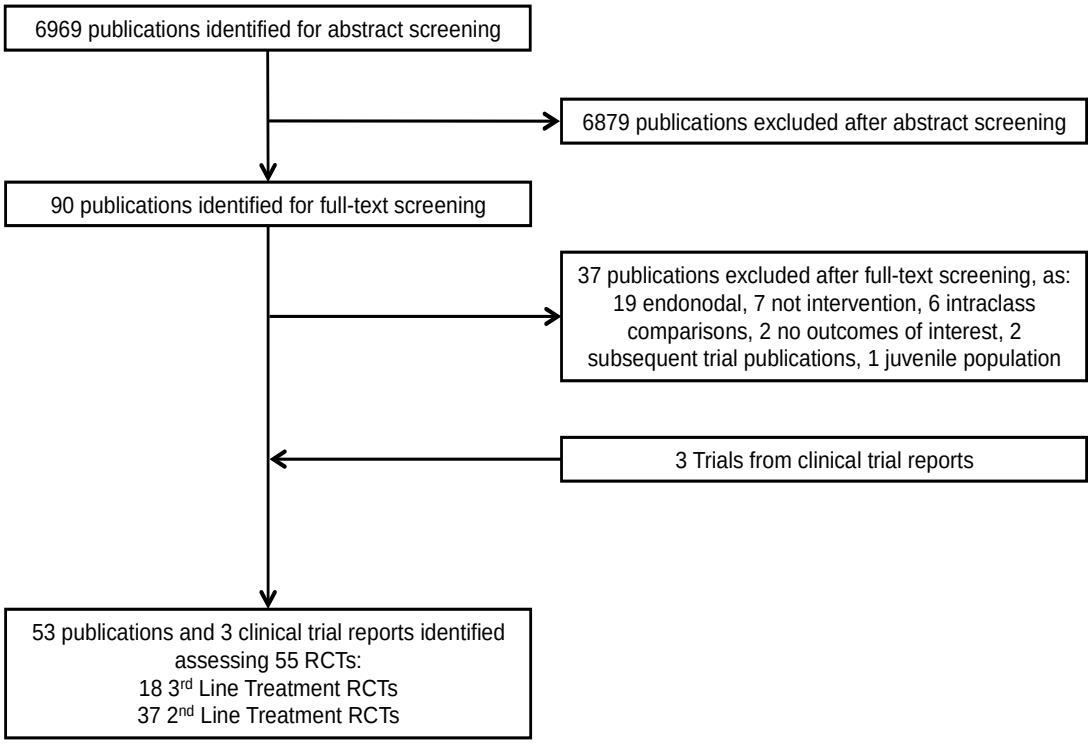
Criteria	Eligibility
Population	• Adult patients with T2DM experiencing inadequate (HbA_{1C} control) despite a diet and exercise program and a stable regimen of metformin plus sulphonylurea.
Interventions	• SGLT2is: • Empagliflozin 10 mg and 25 mg • DPP-4is: • Sitagliptin 100 mg • Saxagliptin 5 mg • Linagliptin 5 mg • Alogliptin 25 mg • Vildagliptin 100 mg • TZD: • Pioglitazone 30 mg • Rosiglitazone 6 mg • Bolus insulin: • Insulin aspart 40 U • Insulin lispro 40 U • Insulin glulisine 40 U • Human insulin 40 U • Basal insulin: • Insulin NPH 40 U • Insulin detemir 40 U • Insulin glargine 40 U • Biphasic insulin: • Premixed regular NPH 40 U • Biphasic insulin aspart 40 U • Biphasic insulin lispro 40 U • If multiple arms of same treatment were available, World Health Organization Defined Dose was used.1
Comparison	• Usual care, placebo, or any of the interventions listed above
Outcomes	• Primary outcomes: • HbA1c change from baseline • SBP change from baseline • Body weight change from baseline • Secondary outcomes: • Hypoglycaemias (severe and non severe, separate and as a composite)

Criteria	Eligibility
	• UTIs (any) • Genital infections (any)
Study design	• RCTs

DPP-4i = dipeptidyl peptisase-4 inhibitors; HbA1c = glycated haemoglobin; RCT = randomised controlled trial; SBP = systolic blood pressure; SGLT2i = sodium-glucose co-transporter 2 inhibitor; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; U = units; UTI = urinary tract infection

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

Figure 3: PRISMA flow chart of studies included in the systematic literature review



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

Studies published in a peer-reviewed journal were used as the primary source of data where available, as was the case for studies 1245.19 and 1245.23. For studies where only the rationale and trial design were published (study

1245.28) or studies which had only been presented in abstract or poster format at an conference (1245.33, 1245.36, 1245.36), clinical study reports (CSRs) were used as an additional data source. CSRs were used as the primary source of information for any studies which had yet to be published or presented at the time of this submission (1245.28 and 1245.49).

It should also be noted that study 1245.31 was a long-term extension study involving patients previously completing study 1245.19, 1245.20 or 1245.23.

Complete list of relevant RCTs

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

A summary of the relevant RCTs trials in the empagliflozin clinical study programme can be seen in Table 8.

Table 8: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population†	Primary study ref.
1245.19 (EMPA-REG PIO; NCT01210001)	Empagliflozin 10 mg or 25 mg once daily add-on to pioglitazone or pioglitazone plus metformin	Placebo	• N=499 • T2DM • ≥18 years (≤65 years in India only) • HbA_{1C} ≥7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Diet and exercise programme • Pioglitazone ≥30mg/day; metformin ≥1,500mg/day • Glucose level ≤13.3 mmol/L • eGFR ≥30 mL/min/1.73 m^2	Kovacs *et al.* 2013(7); Data on file (clinical study report 1245.19) (32)
1245.23 (EMPA-REG MET, EMPA-REG METSU; NCT01159600)	Empagliflozin 10mg or 25mg once daily add-on to metformin or metformin plus SU	Placebo	**All studies:** • T2DM • ≥18 years (and ≤65 years in India) • BMI ≤45kg/m^2 • Diet and exercise programme • Glucose level ≤13.3 mmol/L • eGFR ≥30 mL/min/1.73 m^2 **Metformin only sub-study:** • N=638 • HbA1C ≥7.0% to ≤10% **Open-label metformin only sub-study:** • N=69 • HbA1C >10.0% **Metformin plus SU sub-study:** • N=669 • HbA1C ≥7.0% to ≤10% **Open-label met + SU sub-study**: • N=103 • HbA1C > 10.0%	Haring *et al.* 2013 (9) Data on file (clinical study report 1245.23) (33)

Trial no. (acronym)	Intervention	Comparator	Population†	Primary study ref.
1245.28 (EMPA-REG H2H SU; NCT01167881)	Empagliflozin 25 mg once daily versus glimepiride 1-4 mg once daily as add-on to metformin	Glimepiride 1-4mg	• N=1,549 • ≥18 years • HbA1C ≥7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Metformin ≥1,500mg/day • Glucose level ≤13.3 mmol/L • eGFR ≥60 mL/min/1.73 m^2	Ridderstrale *et al.* 2013 (11); Data on file (clinical trial report 1245.28) (34)
1245.31 (EMPA-REG EXTEND; NCT01289990)	Empagliflozin long-term safety study	Sitagliptin; Placebo	• N=2,700 • Patients originally enrolled in pivotal studies 1245.19, 1245.20 and 1245.23	Data on file (clinical trial report 1245.31) (35)
1245.33 (EMPA-REG BASAL; NCT01011868)	Empagliflozin 10 mg or 25 mg once daily add-on to basal insulin (glargine or detemir insulin [≥20 IU/day] or NPH insulin [≥14 IU/day] with or without concomitant metformin and/or SU	Placebo	• N=494 • T2DM • ≥18years • HbA1C >7.0% to ≤10.0% • BMI ≤45 kg/m2 • Stable insulin dose ≥12 weeks prior to randomisation	Data on file (clinical trial report 1245.33) (36); Rosenstock *et al.* 2013 (37)
1245.36 (EMPA-REG RENAL; NCT01164501)	Empagliflozin 10 mg or 25 mg once daily	Placebo	• N=741 • T2DM • ≥18 years • HbA1C >7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Previously treated with any antidiabetic therapy excluding SGLT2is • Mild RI: • eGFR ≥60 and <90mL/min/1.73m^2 (n=292) • Moderate RI: • eGFR ≥30 and <60mL/min/1.73m^2 (n=375) • Severe RI: • eGFR ≥15 and • <30ml/min/1.73m^2 (n=74)	Data on file (clinical trial report 1245.36 (38); Barnett *et al.* 2013 (13)

Trial no. (acronym)	Intervention	Comparator	Population[†]	Primary study ref.
1245.48 (EMPA-REG BP; NCT01370005)	Empagliflozin 10 mg or 25 mg once daily	Placebo	• N=825 • T2DM • ≥18 years • HbA1C >7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Patients with hypertension (mean SBP 130-159 mmHg and DBP 80-99 mmHg)	Data on file (clinical trial report 1245.48) (39); Tikkanen *et al.* 2013 *(14);*
1245.49 (EMPA-REG MDI; NCT01370005)	Empagliflozin 10 mg or 25 mg once daily add-on to multiple daily injections of insulin (total insulin >60IU/day) either alone or with metformin	Placebo	• N=566 • T2DM • ≥18 years • HbA1C >7.5% to ≤10.0% • BMI 30-45kg/m^2 • Stable insulin dose ≥12 weeks prior to randomisation	Data on file (clinical trial report 1245.49) (40)

[†] Randomised patients

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1C} = glycated haemoglobin; IU = international units; MDI = multiple daily injections; RI = renal impairment; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus

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

All studies summarised in Table 8 compared empagliflozin with either placebo or appropriate active comparator as described in the decision problem. Study 1245.28 compared empagliflozin 10 mg and 25 mg with glimepiride 1-4 mg (a SU), whilst the 1245.31 extension study included a comparison of empagliflozin against sitagliptin (study 1245.20 – not included in this submission).

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

None of the studies summarised in Table 8 were excluded from further discussion in this submission.

List of relevant non-RCTs

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

No non-RCT data have been presented in this submission.

6.3 Summary of methodology of relevant RCTs

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

Methods

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

A brief overview of the trial design, methodology and patient populations in each of the studies can be seen below. Additional details are presented in Table 9.

Empagliflozin as add-on to pioglitazone or pioglitazone plus metformin (1245.19 – EMPA-REG PIO)

A phase III, 24 week, randomised, double-blind, parallel-group, placebo-controlled trial comparing the efficacy, safety and tolerability of empagliflozin 10 mg and 25 mg once daily with placebo as add-on therapy to pioglitazone alone or pioglitazone plus metformin in patients with T2DM. Patients with HbA_{1C} of ≥7.0% to ≤10.0% and BMI ≤45kg/m^2 and who were aged ≥18 years (≤65 years in India) and had been taking a stable dose of pioglitazone monotherapy or pioglitazone plus metformin were randomised to placebo, empagliflozin 10 mg or empagliflozin 25 mg, following a 2 week open-label placebo run-in period.

Empagliflozin as add-on to metformin plus sulphonylurea (1245.23 – EMPA-REG MET, EMPA-REG METSU)

A phase III, 24 week, randomised, double-blind, parallel-group, placebo-controlled trial comparing the efficacy, safety and tolerability of empagliflozin 10 mg and 25 mg once daily with placebo as add-on therapy to metformin and SU in patients with T2DM. Patients with HbA_{1C} of ≥7.0% to ≤10.0% and BMI ≤45kg/m^2 and who were aged ≥18 years (≤65 years in India) at screening were randomised to placebo, empagliflozin 10 mg, or empagliflozin 25 mg as add-on to metformin monotherapy (≥ 1,500 mg/day) or metformin plus a SU (≥ half the maximum recommended dose). Patients with very poor glycaemic control (HbA_{1C} >10%) were included in an additional open-label treatment group and were assigned to empagliflozin 25 mg for 24 weeks without a placebo run-in.

Empagliflozin versus glimepiride as add-on to metformin (1245.28 – EMPA-REG H2H-SU)

A phase III, 2 year, randomised, double-blind, active-controlled, parallel-group trial to evaluate the long-term efficacy, safety and tolerability of empagliflozin 25 mg once daily compared with glimepiride 1–4 mg once daily as add-on therapy to metformin in patients with T2DM. Patients completing the initial 2 year randomisation period will be eligible to participate in a 2 year double-blind extension.

Long-term efficacy and safety of empagliflozin (1245.31 – EMPA-REG EXTEND)

A phase III, double-blind, placebo-controlled, parallel-group, extension study to assess the long-term safety and efficacy of empagliflozin 10 mg and 25 mg once daily in patients with T2DM who had previously completed study 1245.19, 1245.20 (not included in this submission) or 1245.23. Treatment

duration was 52 weeks in addition to 24 weeks from any of the preceding studies (76 weeks total). No randomisation was carried out; patients continue with the treatment they were randomised to in the previous study. Empagliflozin 10 mg and 25 mg were assessed as both a monotherapy compared with sitagliptin 100 mg and as an add-on treatment to the background therapies specified in studies 1245.19 and 1245.23.

Empagliflozin as add-on combination to basal insulin with or without metformin and/or sulphonylureas (1245.33 – EMPA-REG BASAL)

A phase IIb, randomised, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of empagliflozin 10 mg and 25 mg once daily at both 18 and 78 weeks in patients with T2DM and who are taking basal insulin (glargine or detemir insulin ≥20 IU/day; NPH insulin ≥14 IU/day). Patients with HbA_{1C} of ≥7.0% to ≤10.0% and BMI ≤45kg/m^2 and who were aged ≥18 years were randomised to empagliflozin 10 mg, empagliflozin 25 mg or placebo. The basal insulin dose was not changed during the first 18 weeks; during the next 60 weeks, insulin dose was adjusted at the discretion of the investigator for any confirmed fasting plasma glucose (FPG) level >110 mg/dL.

Empagliflozin in patients with renal impairment (1245.36 – EMPA-REG RENAL)

A phase III, randomised, double-blind, placebo-controlled, study to investigate the efficacy , safety and tolerability of empagliflozin 10 mg and 25 mg once daily for 52 weeks, compared with placebo, as add-on to existing antidiabetic therapy in patients with T2DM and renal impairment. Patients with HbA_{1C} of ≥7.0% to ≤10.0% and BMI ≤45 kg/m^2 and who were aged ≥18 years with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2) were randomised to empagliflozin 10 mg, empagliflozin 25 mg or placebo; patients with moderate or severe renal impairment (moderate, eGFR ≥30 and <60 mL/min/1.73 m^2;

severe, eGFR ≥15 and <30 ml/min/1.73m^2) were randomised to empagliflozin 25mg or placebo.

Empagliflozin in patients with hypertension (1245.48 – EMPA-REG BP)

A phase III, randomised, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of empagliflozin 10 mg and 25 mg once daily in patients with T2DM and hypertension. Patients with hypertension (mean SBP 130-159 mmHg and diastolic blood pressure [DBP] 80-99 mmHg) who were aged ≥18 years, with HbA_{1C} of ≥7.0% to ≤10.0% and BMI ≤45 kg/m^2, were randomised to empagliflozin 10 mg, 25 mg or placebo for 12 weeks.

Empagliflozin add-on to multiple daily injections of insulin (1245.49 EMPA-REG MDI)

A phase III, randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety and tolerability of empagliflozin 10 mg and 25 mg once daily compared with placebo, at 52 weeks, in patients with T2DM and insufficient glycaemic control despite treatment with multiple daily injections of insulin, alone or in combination with metformin.

Table 9: Comparative summary of methodology of the RCTs

Trial no. (acronym)	Location	Design	Duration of study	Method of randomisation	Method of blinding (care provider, patient and outcome assessor)	Intervention(s) (n =)† and comparator(s) (n =)†	Primary outcomes (including scoring methods and timings of assessments)	Secondary outcomes (including scoring methods and timings of assessments)	Duration of follow-up
1245.19 (EMPA-REG PIO)	Multicentre: 69 trial sites in 8 countries across Asia Europe and North America	Phase III, randomised, double-blind, parallel-group, placebo-controlled	24 week treatment period (2 week open-label placebo run-in period)	Interactive voice and web response system (IXRS)	Patient, investigator and outcome assessor	Empagliflozin 10 mg (n=165), empagliflozin 25 mg (n=168), placebo (n=166)	Change from baseline in HbA_{1C} at 24 weeks	Change from baseline in FPG and body weight at 24 weeks	7 days or enrolment in extension trial 1245.31
1245.23 (EMPA-REG MET, EMPA-REG METSU)	Multicentre: 148 trial sites in 12 countries across Asia Europe and North America	Phase III, randomised, double-blind, parallel-group, placebo-controlled	24 week treatment period (2 week open-label placebo run-in period)	IXRS	Patient, investigator and outcome assessor	**Metformin only sub-study:** Empagliflozin 10 mg (n=217), empagliflozin 25 mg (n=214), placebo (n=207) **Metformin only open-label group:** Empagliflozin 25 mg (n=69) **Metformin plus SU sub-study:** Empagliflozin 10 mg (n=226), empagliflozin 25 mg (n=218), placebo (n=225) **Metformin plus**	Change from baseline in HbA_{1C} at 24 weeks	Change from baseline in body weight and MDG at 24 weeks	7 days or enrolment in extension trial 1245.31

Trial no. (acronym)	Location	Design	Duration of study	Method of randomisation	Method of blinding (care provider, patient and outcome assessor)	Intervention(s) (n =)† and comparator(s) (n =)†	Primary outcomes (including scoring methods and timings of assessments)	Secondary outcomes (including scoring methods and timings of assessments)	Duration of follow-up
						SU open-label group: Empagliflozin (n=103)			
1245.28 (EMPA- REG H2H-SU)	Multicentre: 181 trial sites in 23 countries across Africa, Asia, Europe and North America	Phase III, randomised, double-blind, parallel group, active-controlled	2 year treatment period (2-week open-label placebo run-in period	IXRS	Patient, investigator and outcome assessor	Empagliflozin 25 mg (n=769), glimepiride (n=780)	Change from baseline in HbA_{1C} at 104 weeks	Change from baseline 104 weeks in: • Body weight • Confirmed hypoglycaemic events • SBP and DBP	4 weeks
1245.31 (EMPA-REG EXTEND)	Multicentre: 300 trial sites across 20 countries	Phase III, double-blind, placebo-controlled, parallel group, extension	52 weeks in addition to time in previous trials (i.e. 76 week minimum treatment period)	Previously randomised in trials 1245.19, 1245.20 or 1245.23	Patient, investigator and outcome assessor	Patients continue on the treatment they were randomised to in the preceding trials	Long-term safety and tolerability	Long-term efficacy of empagliflozin compared with: • Sitagliptin or placebo as monotherapy (1245.20) • Placebo on a background of pioglitazone (1245.19) • Placebo on a background of metformin (1245.23)	4 weeks

Trial no. (acronym)	Location	Design	Duration of study	Method of randomisation	Method of blinding (care provider, patient and outcome assessor)	Intervention(s) (n =)† and comparator(s) (n =)†	Primary outcomes (including scoring methods and timings of assessments)	Secondary outcomes (including scoring methods and timings of assessments)	Duration of follow-up
								• Placebo on a background of metformin plus SU (1245.23)	
1245.33 (EMPA-REG BASAL)	Multicentre: 97 trial sites in 7 countries across Asia, Europe and North America	Phase IIb, randomised, double-blind, parallel-group, placebo-controlled	78 weeks (2 week open-label placebo run-in period)	IXRS	Patient, investigator and outcome assessor	Empagliflozin 10 mg (n=169), empagliflozin 25 mg (n=155), placebo (n=170)	Change from baseline in HbA_{1C} at 18 weeks	Change from baseline in HbA_{1C} and basal insulin dose at 78 weeks	4 weeks
1245.36 (EMPA-REG RENAL)	Multicentre: 127 trial sites in 15 countries across Africa, Asia, Europe and North America	Phase III randomised, double-blind, parallel-group, placebo-controlled	52 weeks (2 week open-label placebo run-in period)	IXRS	Patient, investigator and outcome assessor	**Patients with mild renal impairment:** Empagliflozin 10 mg (n=98), empagliflozin 25 mg (n=97), placebo (n=97) **Patients with moderate renal impairment:** Empagliflozin 25 mg (n=188), placebo (n=187) **Patients with severe renal impairment:** Empagliflozin 25 mg (n=37), placebo (n=37)	Change from baseline in HbA_{1C} at 24 weeks	-	3 weeks

Trial no. (acronym)	Location	Design	Duration of study	Method of randomisation	Method of blinding (care provider, patient and outcome assessor)	Intervention(s) (n =)† and comparator(s) (n =)†	Primary outcomes (including scoring methods and timings of assessments)	Secondary outcomes (including scoring methods and timings of assessments)	Duration of follow-up
1245.48 (EMPA-REG BP)	Multicentre: 121 trial sites in 12 countries across Asia, Europe and North America	Phase III randomised, double-blind, parallel-group, placebo-controlled	12 weeks (2 week open-label placebo run-in period)	IXRS	Patient, investigator and outcome assessor	Empagliflozin 10 mg (n=276), empagliflozin 25 mg (n=277), placebo (n=272)	Change from baseline in HbA_{1C} and mean 24hr BP at 12 weeks	Change from baseline in mean 24hr DBP at 12 weeks	2 weeks
1245.49 (EMPA-REG MDI)	Multicentre: 104 trial sites in 14 countries across Europe, Latin America and North America	Phase III randomised, double-blind, treat-to-target, parallel-group, placebo-controlled	52 weeks (2 week open-label placebo run-in period)	IXRS	Patient, investigator and outcome assessor	Empagliflozin 10 mg (n=187), empagliflozin 25 mg (n=190), placebo (n=189)	Change from baseline in HbA_{1C} at 18 weeks	Change from baseline at 52 weeks in • Total insulin daily dose • Body weight • HbA_{1C}	4 weeks

† Randomised patients
BP = blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; IXRS = Interactive voice and web response system; MDG = mean daily glucose; SBP = systolic blood pressure

Participants

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

Table 10 provides a detailed outline of the eligibility criteria of each of the studies in the empagliflozin clinical development programme.

Table 10: Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
All studies	• T2DM • Males and females • ≥18 years (and ≤65 years in India) • HbA_{1C} ≥7.0% to ≤10.0% • BMI≤45kg/m^2 • Diet and exercise regimen • Previous treatment with metformin (unchanged regimen for 12 weeks prior to randomisation). Minimum dose for metformin: ≥1500 mg/day or maximum tolerated dose (the investigator had to document the reason why up-titration to ≥1500 mg/day was not possible) or the maximum dose according to local label	• Uncontrolled hyperglycaemia >13.3 mmol/l after an overnight fast during a 2 week open-label placebo run-in (confirmed by a second measurement) • Any other antidiabetic medication taken within 12 weeks prior to randomisation, except those defined as the permitted background medication • Acute coronary syndrome (non-STEMI, STEMI, and unstable angina pectoris), stroke or transient ischaemic attack ≤3 months prior to consent • Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatise >3 x upper limit of normal as determined during screening or during the placebo run-in period (i.e. at a visit prior to randomisation visit) • Renal dysfunction, defined as eGFR <30ml/min/1.73m^2 (severe renal impairment, (modification of diet in renal disease (MDRD) formula) as determined during screening or during the placebo run-in period (i.e. at a visit prior to randomisation visit) • Bariatric surgery within the past 2 years or other gastrointestinal surgeries that induce chronic mal-absorption • History of cancer (except for basal cell carcinoma) or treatment for cancer within the last 5years • Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells (e.g. malaria, babesiosis, haemolytic anaemia) • Contraindication to metformin according to the local label • Treatment with anti-obesity drugs ≤3 months prior to

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		consent or any other treatment at the time of screening (i.e. surgery, aggressive diet regiment etc.) leading to unstable body weight • Treatment with systemic steroids at time of consent • Change in dosage of thyroid hormones ≤6 weeks of consent • Any uncontrolled endocrine disorder except T2DM • Premenopausal women (last menstruation ≤1year prior to consent) who were nursing or pregnant or were of child-bearing potential and were not practicing an acceptable method of birth control or did not plan to continue using this method throughout the trial and did not agree to submit to periodic pregnancy testing during the trial. Acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine device/systems, oral, implantable or injectable contraceptives, sexual abstinence (if acceptable to local authorities), double barrier method, and vasectomised partner • Alcohol or drug abuse ≤3months prior to consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to trial procedures or trial medication intake • Intake of an investigational drug in another trial ≤30 days prior to intake of trial medication • Any other clinical condition that would jeopardise patient safety while participating in this trial
1245.19 (EMPA-REG PIO)	• Previous treatment with pioglitazone alone or pioglitazone in combination with metformin (unchanged regimen for 12 weeks prior to randomisation). Minimum dose for pioglitazone ≥30 mg/day or the maximum tolerated dose or	• Contraindication to pioglitazone according to the local label

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	maximum dose according to the local label.	
1245.23 (EMPA-REG, EMPA-REG METSU)	• Patients with HbA1C >10% were eligible to participate in an open-label treatment arm • Previously treated with metformin alone or metformin in combination with a SU (unchanged treatment regimen for ≥12 weeks prior to randomisation). SU dosage was to be at least half of the maximum recommended dose up to the maximum tolerated dose or, if applicable, the maximum tolerated dose according to local label.	• Contraindication to SU according to the local label • Additional criteria in China: eGFR<60 ml/min (moderate to severe renal impairment and end stage renal disease; MDRD formula); alpha-1 microglobulin/creatinine ratio >28 mg/g at screening
1245.28 (EMPA-REG H2H-SU)	• T2DM • Males and females • ≥18 years (and ≤65 years in India) • HbA1C ≥7.0% to ≤10.0% • BMI≤45kg/m^2 • Diet and exercise program	• Contraindication to SU according to the local label • Renal dysfunction, defined as eGFR <60ml/min/1.73m^2 (moderate to severe renal impairment, MDRD formula) as determined during screening or during the placebo run-in period (i.e. at a visit prior to randomisation visit)
1245.31 (EMPA-REG EXTEND)	• Patients completing the entire treatment period of the preceding double-blind trial 1245.19, 1245.20 or 1245.23 with or without rescue therapy	• Patients who meet one or more of the withdrawal criteria for the treatment period of the previous trials 1245.19, 1245. 20 or 1245.23.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
1245.33 (EMPA-REG BASAL)	• Treated with basal glargine or detemir insulin (≥20 IU/day) or NPH insulin (≥14 IU/day) with or without concomitant met and/or SU. The total insulin dose was not to change by more than 10% of the baseline value within 12 weeks prior to randomisation.	• Frequent (investigator's discretion) episodes of hypoglycaemic events on basal insulin therapy • Contraindication to SU according to the local label • Contraindication to background basal insulin (glargine, detemir or NPH) according to the local label • History of having received chronic short acting insulin, a GLP-1 analogue or an Amylin agonist ≤3 months of consent • Intake of an investigational drug in another trial ≤2 months prior to intake of trial medication
1245.36 (EMPA-REG RENAL)	• Renal dysfunction, defined as eGFR <90 ml/mn/1.73m^2 during screening and the run-in phase • Previously treated with any antidiabetic therapy excluding SGLT2is. Background medication had to be dosed at the maximum tolerated level and was to be unchanged for 12 weeks prior to randomisation. For the following antidiabetic medications doses had to be: • ≥1,500 mg/day or maximum tolerated dose or maximum dose according to local label for metformin • Unchanged by +10% within 12 weeks prior to randomisation from the baseline value at randomisation prescribed for insulin • ≥30 mg/day or maximum dose according to local label for pioglitazone • At least half the recommended maximum dose according to local label for SU	• Renal dysfunction, defined as eGFR <15ml/min/1.73m^2 (MDRD formula) as determined during screening or during the placebo run-in period (i.e. at a visit prior to randomisation visit) • Renal impairment requiring any form of chronic dialysis • Renal impairment requiring acute dialysis ≤3months prior to informed consent • Renal transplant recipient

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
1245.48 (EMPA-REG BP)	• Drug naive (defined as absence of any oral antidiabetic therapy, GLP-1 analogue or insulin for 12 weeks or 16 weeks for pioglitazone prior to randomisation) or pre-treated with any oral antidiabetic therapy, GLP-1 analogue or insulin for 12 weeks prior to randomisation. Pre-existing antidiabetic therapy doses were to have remained unchanged for 12 weeks (16 weeks for pioglitazone) prior to randomisation and the prescribed insulin dose was not to be changed within 12 weeks prior to randomisation by more than 10% from the baseline dose at randomisation • Mean seated SBP 130 to 159 mmHg and DBP 80 to 99 mmHg • Treatment with stable doses of antihypertensive medication ≥4 weeks at screening and throughout the screening/run-in phase • ≤2 antihypertensive medications at screening and throughout screening/run-in phase	• Renal dysfunction, defined as eGFR <60ml/min/1.73m^2 (moderate renal impairment, MDRD formula) as determined during screening and/or during the placebo run-in period (i.e. at a visit prior to randomisation visit) • Mean seated SBP ≥160 mmHg and/or mean seated DBP ≥100 mgHg during placebo run-in visit and confirmed by a second measurement (not on the same day) preferably within one day • Upper arm circumference that exceeded the upper circumference level of the cuff size of either ABPM and/or BP measurement device used in the study and/or unsuccessful completion of ABPM testing prior to randomisation • Night shift workers who routinely sleep during the daytime and whose work hours included midnight to 04.00h • Current treatment and/or treatment within the last 16 weeks with rosiglitazone • Known or suspected secondary hypertension (e.g. renal artery stenosis, phaeochromocytoma) • History or evidence of hypertensive retinopathy (Keith Wagener grade III or IV) and/or hypertensive encephalopathy • Clinically significant valvular heart disease or severe aortic stenosis

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
1245.49 (EMPA-REG MDI)	• Treatment with multiple daily injections of insulin alone or in combination with immediate or extended release met. Insulin therapy was to include both basal and prandial insulin. Any type of basal and any type of prandial insulin were allowed; pre-mixed insulin preparations were not allowed • Total prescribed insulin dose was to be >60 IU/day at visit 1 (week-3; screening visit) and not to be changed within 12 weeks prior to randomisation by more than 10% from the baseline value at randomisation (visit 3; week-0)	• Renal dysfunction, defined as eGFR <60ml/min/1.73m^2 (moderate renal impairment, MDRD formula) as determined during screening and/or during the placebo run-in period (i.e. at a visit prior to randomisation visit)

ABPM = ambulatory blood pressure monitoring; ALT = alanine aminotransferase; AST = asparate aminotransferase; BP = blood pressure; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GCP = good clinical practice; GLP-1 = glucagon-like peptide-1; HbA_{1C} = glycated haemoglobin; IU = international units; MDRD = modification of diet in renal disease; NPH insulin = neutral protamine Hagedorn insulin; STEMI = ST segment elevation myocardial infarction; T2DM = type 2 diabetes mellitus

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

Baseline characteristics and efficacy variables for subjects across the empagliflozin development programme can be seen below in Table 11.

Table 11: Characteristics of participants in the RCTs across randomised groups (FAS)

Baseline characteristic	Treatment group			
1245.19 (EMPA-REG PIO) (N=498)	**Placebo (n =165)**	**Empagliflozin 10mg (n=165)**	**Empagliflozin 25mg (n=168)**	
Demographic data				
Age, mean (SD) [years]	54.6 (10.5)	54.7 (9.9)	54.2 (8.9)	
Gender, N (%)				
Male	73 (44.2)	83 (50.3)	85 (50.6)	
Female	92 (55.8)	82 (49.7)	83 (49.4)	
Race, N (%)				
American Indian/Alaska native	1 (0.6)	1 (0.6)	0	
Asian	103 (62.4)	91 (55.2)	94 (56.0)	
Black/African American	1 (0.6)	4 (2.4)	6 (3.6)	
White	60 (36.4)	69 (41.8)	68 (40.5)	
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	85.49 (20.07)	84.26 (20.91)	87.43 (24.36)	
Baseline efficacy variables				
HbA_{1C} [%], mean (SD)	8.16 (0.92)	8.07 (0.89)	8.06 (0.82)	
Time since diagnosis of T2DM, N (%)				
≤1 year	19 (11.5)	29 (17.6)	17 (10.1)	
>1 to 5 years	78 (47.3)	60 (36.4)	76 (45.2)	
>5 to 10 years	42 (25.5)	45 (27.3)	28 (28.6)	
>10 years	26 (15.8)	31 (18.8)	27 (16.1)	
Weight, mean (SD) [kg]	78.1 (20.1)	78.0 (19.1)	78.9 (19.9)	
BMI, mean (SD), [kg/m^2]	29.32 (5.39)	29.15 (5.59)	29.08 (5.54)	
SBP, mean (SD) [mmHg]	125.7 (12.1)	126.5 (13.7)	125.9 (13.9)	
FPG, mean (SD) [mg/dL]	151.9 (40.4)	152.0 (38.2)	151.9 (37.0)	
1245.23 (EMPA-REG MET, EMPA-REG METSU) metformin only (N=706)	**Placebo (n=207)**	**Empagliflozin 10mg (n=217)**	**Empagliflozin 25mg (n=213)**	**Open-label empagliflozin 25mg (n=69)**
Demographic data				
Age, mean (SD) [years]	56.0 (9.7)	55.5 (9.9)	55.6 (10.2)	49.8 (11.5)
Gender, N (%)				
Male	116 (56.0)	125 (57.6)	120 (56.3)	41 (59.4)

Baseline characteristic	Treatment group			
Female	91 (44.0)	92 (42.4)	93 (43.7)	28 (40.6)
Race, N (%)				
American Indian/Alaska native	0	2 (0.9)	2 (0.9)	2 (2.9)
Asian	92 (44.4)	99 (45.6)	98 (46.0)	14 (20.3)
Black/African American	2 (1.0)	4 (1.8)	0	4 (5.8)
White	113 (54.6)	112 (51.6)	113 (53.1)	49 (71.0)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	89.7 (21.4)	89.5 (19.6)	87.7 (19.3)	95.5 (20.7)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	7.90 (0.88)	7.94 (0.79)	7.86 (0.87)	110.7 (1.29)
Time since diagnosis of T2DM, N (%)				
≤1year	19 (9.2)	20 (9.2)	19 (8.9)	5 (7.2)
>1 to 5years	83 (40.1)	78 (35.9)	69 (32.4)	28 (40.6)
>5 to 10 years	65 (31.4)	68 (31.3)	74 (34.7)	19 (27.5)
>10 years	40 (19.3)	51 (23.5)	51 (23.9)	17 (24.6)
Weight, mean (SD) [kg]	79.73 (18.57)	81.59 (18.51)	82.21 (19.29)	85.07 (21.96)
BMI, mean (SD), [kg/m^2]	28.70 (5.22)	29.12 (5.48)	29.72 (5.72)	30.37(5.51)
SBP, mean (SD) [mmHg]	128.6 (14.7)	129.6 (14.1)	130.0 (15.1)	126.2 (11.4)
MDG, mean (SD) [mg/dL]	169.53 (37.77)	168.03 (32.14)	167.87 (34.14)	226.32 (54.14)
1245.23 (EMPA-REG MET, EMPA-REG METSU) metformin plus SU (N=767)	**Placebo (n=225)**	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Demographic data				
Age, mean (SD) [years]	56.9 (9.2)	57.0 (9.2)	57.4 (9.3)	53.4 (10.5)
Gender, N (%)				
Male	112 (49.8)	113 (50.2)	114 (52.8)	54 (53.5)
Female	113 (50.2)	112 (49.8)	102 (47.2)	47 (46.5)
Race, N (%)				
American Indian/Alaska native	3 (1.3)	4 (1.8)	3 (1.4)	2 (2.0)
Asian	127 (56.4)	129 (57.3)	125 (57.9)	48 (47.5)
Black/African American	7 (3.1)	3 (1.3)	3 (1.4)	1 (1.0)
White	88 (39.1)	89 (39.6)	85 (39.4)	50 (49.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.9 (20.1)	86.5 (21.8)	88.3 (22.6)	93.1 (23.7)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	8.15 (0.83)	8.07 (0.81)	8.10 (0.83)	11.18 (1.25)
Time since diagnosis of T2DM, N (%)				
≤1 year	2 (0.9)	3 (1.3)	7 (3.2)	4 (4.0)
>1 to 5 years	36 (16.0)	59 (26.2)	43 (19.9)	26 (25.7)
>5 to 10 years	94 (41.8)	74 (32.9)	79 (36.6)	33 (32.7)
>10 years	93 (41.3)	89 (39.6)	87 (40.3)	38 (37.6)
Weight, mean (SD) [kg]	76.23 (16.88)	77.08 (18.34)	77.50 (18.81)	76.93 (18.00)

Baseline characteristic	Treatment group			
BMI, mean (SD), [kg/m^2]	27.90 (4.93)	28.32 (5.43)	28.32 (5.45)	28.70 (5.49)
SBP, mean (SD) [mmHg]	128.8 (14.3)	128.7 (13.9)	129.3 (14.2)	126.4 (12.4)
MDG, mean (SD) [mg/dL]	170.45 (30.38)	170.28 (29.06)	172.72 (37.79)	233.07 (63.34)
1245.28 (EMPA-REG H2H-SU) (N=1,545)		**Empagliflozin 25mg (n=765)**		**Glimepiride 1-4mg (n=780)**
Demographic data				
Age, mean (SD) [years]		56.2 (10.3)		55.7 (10.4)
Gender, N (%)				
Male		432 (56.5)		421 (54.0)
Female		333 (43.5)		359 (46.0)
Race, N (%)				
American Indian/Alaska native		0		0
Asian		254 (33.2)		253 (32.4)
Black/African American		12 (1.6)		8 (1.0)
Hawaiian/pacific Islander		1 (0.1)		0
White		498 (65.1)		519 (66.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]		87.94 (16.82)		88.11 (17.85)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]		7.92 (0.81)		7.92 (0.86)
Time since diagnosis of T2DM, N (%)				
≤1 year		79 (10.3)		93 (11.9)
>1 to 5 years		341 (44.6)		336 (43.1)
>5 to 10 years		214 (28.0)		211 (27.1)
>10 years		131 (17.1)		140 (17.9)
Weight, mean (SD) [kg]		82.52 (19.16)		83.03 (19.22)
BMI, mean (SD), [kg/m^2]		29.95 (5.28)		30.27 (5.3)
SBP, mean (SD) [mmHg]		133.4 (15.9)		133.5 (16.0)
DBP, mean (SD) [mmHg]		79.5 (9.6)		79.4 (9.2)
1245.31 (EMPA-REG EXTEND) monotherapy (1245.20 roll-over)	**Placebo (n=228)**	**Empagliflozin 10mg (n=224)**	**Empagliflozin 25mg (n=224)**	**Sitagliptin 100mg (n=223)**
Demographic data				
Age, mean (SD) [years]	54.9 (10.9)	56.2 (11.6)	53.8 (11.6)	55.1 (9.9)
Gender, N (%)				
Male	123 (53.9)	142 (63.4)	145 (64.7)	141 (63.2)
Female	105 (46.1)	82 (36.6)	79 (35.3)	82 (36.8)
Race, N (%)				
American Indian/Alaska native	0	0	0	1 (0.4)
Asian	146 (64.0)	143 (63.8)	144 (64.3)	143 (64.1)
Black/African American	6 (2.6)	3 (1.3)	7 (3.1)	3 (1.3)
Hawaiian/pacific Islander	0	1 (0.4)	0	0
White	76 (33.3)	77 (34.4)	73 (32.6)	76 (34.1)

Baseline characteristic	Treatment group			
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.76 (17.94)	87.70 (19.16)	87.61 (18.28)	87.57 (17.30)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	7.91 (0.78)	7.87 (0.88)	7.86 (0.85)	7.85 (0.79)
Time since diagnosis of T2DM, N (%)				
≤1 year	72 (31.6)	87 (38.8)	91 (40.6)	93 (41.7)
>1 to 5 years	104 (45.6)	92 (41.1)	83 (37.1)	86 (38.6)
>5 to 10 years	33 (14.5)	29 (12.9)	37 (16.5)	32 (14.3)
>10 years	19 (8.3)	16 (7.1)	13 (5.8)	12 (5.4)
Weight, mean (SD) [kg]	78.23 (19.86)	78.35 (18.67)	77.80 (17.96)	79.31 (20.40)
BMI, mean (SD), [kg/m^2]	28.73 (6.15)	28.31 (5.46)	28.17 (5.52)	28.23 (5.21)
SBP, mean (SD) [mmHg]	130.4 (16.3)	133.0 (16.6)	129.9 (17.5)	132.5 (15.8)
1245.31 (EMPA-REG EXTEND) background of pioglitazone (1245.19 roll-over)	**Placebo (n=165)**	**Empagliflozin 10mg (n=165)**		**Empagliflozin 25mg (n=165)**
Demographic data				
Age, mean (SD) [years]	54.6 (10.5)	54.7 (9.9)		54.2 (8.9)
Gender, N (%)				
Male	73 (44.2)	83 (50.3)		85 (50.6)
Female	92 (55.8)	82 (49.7)		83 (49.4)
Race, N (%)				
American Indian/Alaska native	1 (0.6)	1 (0.6)		0
Asian	103 (62.4)	91 (55.2)		94 (56.0)
Black/African American	1 (0.6)	4 (2.4)		6 (3.6)
White	60 (36.4)	69 (41.8)		68 (40.5)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	85.49 (20.07)	84.26 (20.91)		87.43 (24.36)
Baseline efficacy variables				
HbA_{1C}, mean (SD) [%]	8.16 (0.92)	8.07 (0.89)		8.06 (0.82)
Time since diagnosis of T2DM, N (%)				
≤1 year	19 (11.5)	29 (17.6)		17 (10.1)
>1 to 5 years	78 (47.3)	60 (36.4)		76 (45.2)
>5 to 10 years	42 (25.5)	45 (27.3)		48 (28.6)
>10 years	26 (15.8)	31 (18.8)		27 (16.1)
Weight, mean (SD) [kg]	78.10 (20.11)	77.97 (19.15)		78.93 (19.93)
BMI, mean (SD), [kg/m^2]	29.32 (5.39)	29.15 (5.59)		29.08 (5.54)
SBP, mean (SD) [mmHg]	125.7 (12.1)	126.5 (13.7)		125.9 (13.9)
1245.31 (EMPA-REG EXTEND) metformin background (1245.23 roll-over)	**Placebo (n=207)**	**Empagliflozin 10mg (n=217)**		**Empagliflozin 25mg (n=213)**
Demographic data				
Age, mean (SD) [years]	56.0 (9.7)	55.5 (9.9)		55.6 (10.2)
Gender, N (%)				
Male	116 (56.0)	125 (57.6)		120 (56.3)

Baseline characteristic	Treatment group		
Female	91 (44.0)	92 (42.4)	93 (43.7)
Race, N (%)			
American Indian/Alaska native	0	2 (0.9)	2 (0.9)
Asian	92 (44.4)	99 (45.6)	98 (46.0)
Black/African American	2 (1.0)	4 (1.8)	0
White	113 (54.6)	112 (51.6)	113 (53.1)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	89.70 (21.40)	89.48 (19.63)	87.71 (19.26)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	7.90 (0.88)	7.94 (0.79)	7.86 (0.87)
HbA_{1C} category, N (%)			
<8.0%	121 (58.5)	122 (56.2)	124 (58.2)
8.0% to < 9.0%	60 (29.0)	67 (30.9)	66 (31.0)
≥9.0%	26 (12.6)	28 (12.9)	23 (10.8)
FPG, mean (SD) [mg/dL]	156.0 (32.5)	154.6 (35.4)	149.4 (30.7)
Time since diagnosis of T2DM, N (%)			
≤1 year	19 (9.2)	20 (9.2)	19 (8.9)
>1 to 5 years	83 (40.1)	78 (35.9)	69 (32.4)
>5 to 10 years	65 (31.4)	68 (31.3)	74 (34.7)
>10 years	40 (19.3)	51 (23.5)	51 (23.9)
Weight, mean (SD) [kg]	79.79 (18.57)	81.59 (18.51)	82.21 (19.29)
BMI, mean (SD), [kg/m^2]	28.70 (5.22)	29.12 (5.48)	29.72 (5.72)
Waist circumference, mean (SD) [cm]	99.3 (12.8)	99.1 (13.8)	100.0 (14.5)
SBP, mean (SD) [mmHg]	128.6 (14.7)	129.6 (14.1)	130.0 (15.1)
DBP, mean (SD) [mmHg]	78.1 (7.9)	79.6 (8.0)	78.4 (8.4)
Blood pressure controlled (SBP <130 and DBP <80mmHg), N (%)	71 (34.3)	75 (34.6)	75 (35.2)
History of hypertension, N (%)	107 (51.7)	124 (57.1)	124 (58.2)

1245.31 (EMPA-REG EXTEND) metformin plus SU background (1245.23 roll-over)	**Placebo (n=225)**	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**
Demographic data			
Age, mean (SD) [years]	56.9 (9.2)	57.0 (9.2)	57.4 (9.3)
Gender, N (%)			
Male	112 (49.8)	113 (50.2)	114 (52.8)
Female	113 (50.2)	112 (49.8)	102 (47.2)
Race, N (%)			
American Indian/Alaska native	3 (1.3)	4 (1.8)	3 (1.4)
Asian	127 (56.4)	129 (57.3)	125 (57.9)
Black/African American	7 (3.1)	3 (1.3)	3 (1.4)
White	88 (39.1)	89 (39.6)	85 (39.4)

Baseline characteristic	Treatment group		
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	86.91 (20.11)	86.49 (21.79)	88.33 (22.63)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.15 (0.83)	8.07 (0.81)	8.10 (0.83)
Time since diagnosis of T2DM, N (%)			
≤1 year	2 (0.9)	3 (1.3)	7 (3.2)
>1 to 5 years	36 (16.0)	59 (26.2)	43 (19.9)
>5 to 10 years	94 (41.8)	74 (32.9)	79 (36.6)
>10 years	93 (41.3)	89 (39.6)	87(40.3)
Weight, mean (SD) [kg]	76.23 (16.88)	77.08 (18.34)	77.50 (18.81)
BMI, mean (SD), [kg/m^2]	27.90 (4.93)	28.32 (5.43)	28.32 (5.45)
SBP, mean (SD) [mmHg]	128.8 (14.3)	128.7 (13.9)	129.3 (14.2)
1245.33 (EMPA-REG BASAL) (N=494)	**Placebo (n =170)**	**Empagliflozin 10mg (n=169)**	**Empagliflozin 25mg (n=155)**
Demographic data			
Age, mean (SD) [years]	58.1 (9.4)	58.6 (9.8)	59.9 (10.5)
Gender, N (%)			
Male	90 (52.9)	93 (55.0)	93 (60.0)
Female	80 (47.1)	76 (45.0)	62 (40.0)
Race, N (%)			
Asian	33 (19.4)	37 (21.9)	28 (18.1)
Black/African American	21 (12.4)	12 (7.1)	15 (9.7)
Other	3 (1.8)	1 (0.6)	1 (0.6)
White	113 (66.5)	119 (70.4)	111 (71.6)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	83.89 (22.73)	85.01 (23.63)	82.88 (25.46)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.18 (0.79)	8.27 (0.83)	8.27 (0.84)
Time since diagnosis of diabetes, N (%)			
≤1 year	4 (2.4)	0	1 (0.6)
>1 to 5 years	20 (11.8)	15 (8.9)	12 (7.7)
>5 years	146 (85.9)	154 (91.1)	142 (91.6)
Weight, mean (SD) [kg]	90.46 (22.47)	91.59 (20.05)	94.71 (20.70)
BMI, mean (SD), [kg/m^2]	31.75 (5.98)	32.13 (5.77)	32.65 (5.90)
SBP, mean (SD) [mmHg]	133.9 (16.3)	132.4 (15.5)	132.8 (15.1)
1245.36 (EMPA-REG RENAL) (All renal impairment categories N=738)	**Placebo (n=319)**	**Empagliflozin 10mg (n=98)**	**Empagliflozin 25mg (n=321)**
Demographic data			
Age, mean (SD) [years]	64.1 (8.7)	63.2 (8.5)	63.9 (9.0)
Gender, N (%)			
Male	181 (56.7)	60 (61.2)	189 (58.9)
Female	138 (43.3)	38 (38.8)	132 (41.1)
Race, N (%)			

Baseline characteristic	Treatment group		
American Indian/Alaska native	1 (0.3)	0	0
Asian	119 (37.3)	25 (25.5)	122 (38.0)
Black/African American	6 (1.9)	3 (3.1)	13 (4.0)
White	191 (59.9)	69 (70.4)	185 (57.6)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	49.90 (18.62)	70.77 (10.34)	51.12 (18.39)
Efficacy variables			
HbA_{1C}, mean (SD) [%]	8.07 (0.82)	8.02 (0.84)	8.01 (0.81)
Time since diagnosis of diabetes, N (%)			
≤1 year	2 (0.6)	0	4 (1.2)
>1 to 5 years	50 (15.7)	18 (18.4)	39 (12.1)
>5 to 10 years	75 (23.5)	22 (22.4)	74 (23.1)
>10 years	192 (60.2)	58 (59.2)	204 (63.6)
Weight, mean (SD) [kg]	83.7 (19.0)	92.1 (21.4)	84.1 (20.1)
BMI, mean (SD), [kg/m^2]	30.60 (5.47)	32.41 (5.43)	30.38 (5.45)
SBP, mean (SD) [mmHg]	137.0 (18.7)	137.4 (15.0)	136.7 (18.5)
1245.48 (EMPA-REG BP) (N=823)	**Placebo (n=271)**	**Empagliflozin 10mg (n=276)**	**Empagliflozin 25mg (n=276)**
Demographic data			
Age, mean (SD) [years]	60.3 (8.8)	60.6 (8.5)	59.9 (9.7)
Gender, N (%)			
Male	168 (62.0)	171 (62.0)	156 (56.5)
Female	103 (38.0)	105 (38.0)	120 (43.5)
Race, N (%)			
American Indian/Alaska native	0	1 (0.4)	1 (0.4)
Asian	1 (0.4)	3 (1.1)	4 (1.4)
Black/African American	13 (4.8)	14 (5.1)	14 (5.1)
Hawaiian/ Pacific islander	1 (0.4)	0	0
White	256 (94.5)	258 (93.5)	257 (93.1)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	84.96 (16.97)	83.41 (16.71)	83.50 (17.80)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	7.90 (0.72)	7.87 (0.77)	7.92 (0.72)
Time since diagnosis of T2DM, N (%)			
≤1 year	7 (2.6)	9 (3.3)	12 (4.3)
>1 to 5 years	70 (25.8)	62 (22.5)	73 (26.4)
>5 to 10 years	83 (30.6)	92 (33.3)	90 (32.6)
>10 years	111 (41.0)	113 (40.9)	101 (36.6)
SBP, 24h mean [mmHg] (ABPM)	131.7 (11.8)	131.3 (13.0)	131.2 (12.1)
DBP, 24h mean [mmHg] (ABPM)	75.2 (7.5)	75.1 (8.3)	74.6 (7.5)
SBP, mean (SD) [mmHg] (office measurement)	142.0 (12.4)	142.3 (12.1)	141.9 (12.5)
DBP, mean (SD) [mmHg] (office measurement)	83.7 (7.1)	84.1 (7.3)	83.8 (6.8)
SBP, daytime mean [mmHg] (ABPM)	136.1 (12.0)	135.3 (13.0)	135.1 (12.2)

Baseline characteristic	Treatment group		
DBP, daytime mean [mmHg] (ABPM)	78.7 (7.7)	78.4 (8.4)	77.9 (7.9)
SBP, night-time mean (SD) [mmHg] (ABPM)	123.1 (13.7)	123.5 (14.7)	123.3 (13.8)
DBP, night-time mean (SD) [mmHg] (ABPM)	68.2 (8.8)	68.7 (9.6)	68.0 (8.3)
Orthostatic BP test positive, N (%)	47 (17.3)	43 (15.6)	55 (19.9)
BP controlled (SBP <130 and DBP <80 mmHg) (office measurement), N (%)	30 (11.1)	25 (9.1)	29 (10.5)
Weight, mean (SD) [kg]	95.22 (17.47)	94.71 (19.77)	95.59 (17.37)
BMI, mean (SD), [kg/m^2]	32.43 (4.93)	32.36 (5.32)	33.00 (4.97)
1245.49 (EMPA-REG MDI) (N=563)	**Placebo (n=188)**	**Empagliflozin 10mg (n=186)**	**Empagliflozin 25mg (n=189)**
Demographic data			
Age, mean (SD) [years]	55.3 (10.1)	56.7 (8.7)	58.0 (9.4)
Gender, N (%)			
Male	75 (39.9)	97 (52.2)	84 (44.2)
Female	113 (60.1)	89 (47.8)	105 (55.6)
Race, N (%)			
American Indian/Alaska native	4 (2.1)	3 (1.6)	2 (1.1)
Asian	2 (1.1)	0	2 (1.1)
Black/African American	8 (4.3)	7 (3.8)	4 (2.1)
Hawaiian/ Pacific islander	0	1 (0.5)	0
White	174 (92.6)	175 (94.1)	182 (96.3)
eGFR (MDRD), mean (SD) [ml/min/1.73m^2]	83.41 (15.40)	84.14 (17.76)	84.35 (16.59)
Baseline efficacy variables			
HbA_{1C}, mean (SD) [%]	8.33 (0.72)	8.39 (0.74)	8.29 (0.72)
Time since diagnosis of T2DM, N (%)			
≤1 year	1 (0.5)	0	0
>1 to 5years	17 (9.0)	22 (11.8)	11 (5.8)
>5 to 10 years	40 (21.3)	44 (23.7)	38 (20.1)
>10 years	130 (69.1)	120 (64.5)	140 (74.1)
Body weight, mean (SD) [kg]	95.5 (17.5)	96.7 (17.9)	95.9 (17.3)
BMI, mean (SD) [kg]	34.65 (4.30)	34.72 (3.83)	34.99 (4.04)
SBP, mean (SD) [mmHg]	132.6 (15.8)	134.2 (16.4)	132.9 (14.2)

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; IU = international units; MDG = mean daily glucose; MDI = multiple daily injections; Met = metformin = PIO = pioglitazone; SBP = systolic blood pressure; SD = standard deviation; T2DM = type 2 diabetes mellitus

Outcomes

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

The primary and secondary outcomes summarised in Table 12 are all widely accepted measures currently used in clinical practice to evaluate treatments in patients with T2DM. The primary outcome of HbA_{1C} is a well established diagnostic measure of overall long-term glycaemic control and is recommended for use in current NICE guidance.(41) The secondary endpoints in the clinical studies included FPG, MDG, change in body weight, change in blood pressure, total insulin dose, safety and tolerability, all of which have significant clinical relevance to both clinicians and patients.

Table 12: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
1245.19 (EMPA-REG PIO)	Change from baseline in HbA_{1C} at 24 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline in FPG and body weight at 24 weeks	Clinically relevant outcome for both clinicians and patients
1245.23 (EMPA-REG MET, EMPA-REG METSU)	Change from baseline in HbA_{1C} at 24 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline in MDG and body weight at 24 weeks	Clinically relevant outcome for both clinicians and patients
1245.28 (EMPA-REG H2H-SU)	Change from baseline in HbA_{1C} at 104 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline at 52 and 104 weeks in: ▪ body weight ▪ confirmed hypoglycaemic events ▪ SBP and DBP	Clinically relevant outcomes for both clinicians and patients
1245.31 (EMPA-REG EXTEND			Long-term safety and efficacy of empagliflozin compared with: ▪ sitagliptin or placebo as monotherapy (1245.20) ▪ placebo on a background of pioglitazone (1245.19) ▪ placebo on a background of metformin (1245.23) placebo on a background of metformin plus SU (1245.23)	Clinically relevant outcome for both clinicians and patients
1245.33 (EMPA-REG BASAL)	Change from baseline in HbA_{1C} at 18 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline in HbA_{1C} and basal insulin dose at 78 weeks	Clinically relevant outcome for both clinicians and patients
1245.36 (EMPA-REG RENAL)	Change from baseline in HbA_{1C} at 24 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	-	-

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
1245.48 (EMPA-REG BP)	Change from baseline in HbA_{1C} and mean 24hr SBP at 12 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline in mean 24hr DBP at 12 weeks	Clinically relevant outcome for both clinicians and patients
1245.49 (EMPA-REG MDI)	Change from baseline in HbA_{1C} at 18 weeks	Well-established diagnostic measurement of long-term glycaemic control in patients with T2DM	Change from baseline at 52 weeks in: ▪ Total insulin daily dose ▪ Body weight ▪ HbA_{1C}	Clinically relevant outcome for both clinicians and patients

DBP = diastolic blood pressure; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; MDG = mean daily glucose; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus

Statistical analysis and definition of study groups

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

The primary hypothesis, statistical analysis and sample size calculation for each clinical study can be seen in Table 13.

Table 13: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
1245.19 (EMPA-REG PIO)	The objective of this study was to investigate the efficacy, safety and tolerability of empagliflozin 10 and 25mg given for 24 weeks, as add-on to pioglitazone alone or pioglitazone in combination with metformin to patients with T2DM and insufficient glycaemic control.	Primary analyses were carried out using an analysis of covariance (ANCOVA) model including background therapy, treatment and baseline eGFR as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the full analysis set (FAS). Key secondary and continuous exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate. Primary analyses were repeated as sensitivity analyses using different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach. Safety parameters were analysed using the treated set (TS) (all patients treated with ≥1 dose of randomised trial medication).	To show a difference of 0.5% in HbA_{1C} between empagliflozin and placebo groups with a 2-sided significance level of 2.5%, and assuming the HbA_{1C} values follow a normal distribution, a sample size of 148 patients per treatment group was required to provide a power of ≥95% for the pair-wise comparison and an overall power of 90%. Allowing for a 5% drop-out rate and assuming a SD of 1.1%, the sample size needed to be 156 for each treatment group; 468 patients in total.	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A last observation carried forward (LOCF) approach was used to impute missing data.
1245.23 (EMPA-REG MET, EMPA-REG METSU)	The objective of this study was to investigate the efficacy, safety, and tolerability of empagliflozin 10 and 25mg compared with placebo given for 24weeks as add-on therapy to metformin alone	Primary analyses were carried out using an ANCOVA model including randomised treatment, geographical region, and renal function as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the FAS. Key secondary and continuous	To show a difference of 0.5% in HbA_{1C} between empagliflozin and placebo groups with a 2-sded significance level of 2.5% and assuming the HbA_{1C} values follow a normal distribution, a sample size of 174 patients per treatment group was required to provide a power of	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	or a SU in combination with metformin in patients with T2DM with insufficient glycaemic control.	exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate. Primary analyses were repeated as sensitivity analyses using the different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a REML based MMRM approach. Safety parameters were analysed using the TS.	≥95% for the pair-wise comparison and an overall power of 90%. Allowing for a 15% drop-out rate and assuming a SD of 1.2%, the sample size needed to be 205 for each treatment group; 1,230 patients in total (615 patients per sub-study) In addition 160 patients were to be entered into the open-label arm of the study, with 80 patients in each sub-study	
1245.28 (EMPA-REG H2H-SU)	The objective of this study was to investigate the efficacy, safety and tolerability of empalgliflozin25mg compared with glimepiride (1-4mg) given for 2years in patients with T2DM with insufficient glycaemic control	Primary analyses were carried out using an ANCOVA model including randomised treatment, geographical region, and renal function as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the FAS. Key secondary and continuous exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate Primary analyses were repeated as sensitivity analyses using the different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity	It was estimated that the standard deviation of change in HbA_{1C} from baseline after 52 weeks and 104 weeks of treatment would be 1.2% in the FAS. The non-inferiority margin for comparison after 52 weeks and after 104 weeks of treatment was δ=0.3%. Adjusting for multiplicity related to the interim analysis, the power for each comparison was chosen as 95% and the significance level as α=0.0125 (=1.25%) 1-sided. Assuming a difference between empagliflozin and glimepiride of 0.0, a sample size of 485 patients per treatment group was need to provide a power of at least 95% to show non-inferiority (698 patients	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		analyses for the primary endpoint used a REML based MMRM approach. Safety parameters were analysed using the TS.	were required per treatment group for a difference of 0.05 and 1,089 patients per treatment group were needed for a difference of 0.10). It was therefore planned to randomise 700 patients to each treatment group to have at least 95% power per comparison to show non-inferiority if the treatment effect was 0.05%. The planned treatment group sizes based on primary efficacy were also considered sufficient for the evaluation of safety, tolerability, secondary efficacy, pharmacokinetics and pharmacodynamics.	
1245.31 (EMPA-REG EXTEND	The objective of this study was to investigate the long-term safety and efficacy of empagliflozin 10 and 25mg	No confirmatory statistical analysis was performed, as this was considered an extension of the preceding trials 1245.19, 1245.20 and 1245.23. For the final analysis presented here, the data of the respective preceding trial were combined with those obtained din the extension trial, and the final analysis was performed after 52 weeks in the extension trial. All patients participating in the preceding trial were included in this analysis and no separate analysis of the extension trial was performed. Secondary efficacy endpoints were analysed in a similar manner as in the preceding trial i.e. using ANCOVA model and REML based MMRM.		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
1245.33 (EMPA-REG BASAL)	The objective of this study was to investigate the safety, efficacy, tolerability and pharmacokinetics of empagliflozin 10 and 25mg compared with placebo given for 78weeks in combination with background basal insulin therapy (glargine, detemir, or NPH insulin only) at a fixed dose for 18 weeks (except for rescue therapy), and at an adjustable dose for 60 weeks with or without concomitant SU and/or metformin therapy, in patients with T2DM with insufficient glycaemic control.	Primary analyses were carried out using an ANCOVA model including randomised treatment, geographical region as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the FAS Key secondary and continuous exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate. Primary analyses were repeated as sensitivity analyses using the different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a REML based MMRM approach Safety parameters were analysed using the TS	To show a difference of 0.4% in HbA_{1C} between empagliflozin and placebo groups with a 2-sided significance level of 2.5% and assuming a SD of 1.0%, the sample size needed to be 150 patients per treatment group. With a slightly higher SD of 1.1% power is reduced to 81%. The observed SD ranged from 0.78% to 1.07% for baseline and 18-week HbA_{1C} levels. Average treatment differences were greater than 0.4% giving a greater power to the study	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
1245.36 (EMPA-REG RENAL)	The objective of this study was to investigate the efficacy, safety and tolerability of empagliflozin 10 and 25mg compared with placebo as add-on to pre-existing anti-diabetic therapy in patients with T2DM with insufficient glycaemic control and different degrees of renal impairment (RI) based on eGFR.	Primary analyses were carried out using an ANCOVA model including treatment and background therapy as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the FAS RI was included in the ANCOVA model as a fixed effect for analysis of patient subgroups, with balanced numbers of patients in the treatment arms for mild, moderate and severe impairment Primary analyses were repeated as sensitivity analyses using the different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a REML based MMRM approach Safety parameters were analysed using the TS	It was estimated that the reduction in HbA_{1C} from the baseline after 24weeks of treatment would be 0.5% for empagliflozin treatment (10 or 25mg) of patients with mild RI, 0.3% for empagliflozin treatment (25mg) for patients with moderate RI and 0% for placebo treatment. The SD of the difference was expected to be 1.1%; A sample size of 85 patients with RI in each treatment group was needed to provide a power of 83%. A further 167 patients with moderate RI were to be assigned to each empagliflozin 25mg and placebo, providing a power of 70%. Additionally, 30 patients with severe RI were to be assigned to the empagliflozin 25mg and placebo treatment groups in order to provide safety data. Therefore, a total of 649 patients were required. Allowing for a 5% drop-out rate, the sample size for the study was 682 patients.	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.
1245.48 (EMPA-REG BP)	The objective of this study was to investigate the efficacy and safety of empagliflozin 10 and 25mg compared with placebo in patients with T2DM with insufficient glycaemic control and hypertension.	Primary analyses were carried out using an ANCOVA model including treatment, renal function at baseline, geographical region and number of antihypertensive medications at baseline as fixed effects; baseline HbA_{1C} was a linear covariate. In addition to baseline HbA_{1C}, baseline mean 24-hr SBP was included as a linear covariate for this study. The analysis was carried out using the FAS. Primary analyses were repeated as sensitivity analyses using the different	It was estimated that the difference sin the change from baseline in mean 24-hr SBP between empagliflozin and placebo treatment groups would be 4mmHg, assuming a SD of 14mmHg. In order to show a difference, a sample size of 259 patients per treatment group was required to provide a power of ≥90%. Allowing for a drop-out rate of 5%, the sample size needed to be 272 for	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a REML based MMRM approach. Key secondary and continuous exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate. Safety parameters were analysed using the TS.	each treatment group; 816 patients in total. With this sample size, the power to detect a 0.5% difference in HbA_{1C} would be >95% assuming a SD of 1.1%. The power to detect a difference in DBP of 2mmHg assuming a SD of 7mmHg would be 90%.	

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
1245.49 (EMPA-REG MDI)	The objective of this study was to investigate the safety and efficacy of empagliflozin 10 and 25mg compared with placebo, added to an insulin regimen of multiple daily injections (MDI) alone or in combination with met in patients with T2DM with insufficient glycaemic control.	Primary analyses were carried out using an ANCOVA model including treatment, background therapy, geographical region and baseline renal function as fixed effects; baseline HbA_{1C} was a linear covariate. The analysis was carried out using the FAS. Key secondary and continuous exploratory endpoints were analysed for the FAS using the ANCOVA model previously describe with the respective efficacy variable at baseline as another linear covariate. Primary analyses were repeated as sensitivity analyses using the different analysis sets, which included patients potentially excluded from the FAS based on protocol violations. Sensitivity analyses for the primary endpoint used a REML based MMRM approach. Safety parameters were analysed using the TS.	To show a difference of 0.5% between empagliflozin and placebo groups with a 2-sded significance level of 2.5% and assuming the HbA_{1C} values follow a normal distribution, a sample size of 157 patients per treatment group was required to provide an overall power of at least 90%. Allowing for a 15% drop-out rate and assuming a SD of 1.25%, the sample size needed to be 185 patients for each treatment group; 555 patients in total.	Primary analyses were performed on the FAS which included all patients who were randomised, treated with ≥1 dose of trial medication, and who had a baseline HbA_{1C} assessment. A LOCF approach was used to impute missing data.

ANCOVA = analysis of covariance; EMPA = Empagliflozin; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; MDI = multiple daily injections; MMRM = mixed model repeated measures; PLACEBO = placebo; PIO = pioglitazone; REML = restricted maximum likelihood; RI = renal impairment; SBP = systolic blood pressure; SD = standard deviation; SU = sulphonylurea; T2DM = type 2 diabetes mellitus; TS = treated set

6.3.1 *Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc***.**

Table 14 illustrates the pre-planned subgroup categories which were investigated during the empagliflozin clinical programme. Each of the subgroups was chosen as they as they are known risk factors or treatment modifying risk factors for T2DM.

Table 14: Subgroups analysed in the empagliflozin clinical trial programme

Study	1245.19	1245.23	1245.28	1245.31	1245.33	1245.36	1245.48	1245.49
Subgroups analysed								
Age	●	●	●	●	●	●	●	●
Baseline HbA_{1C}	●	●	●	●	●	●	●	●
BMI	●	●	●	●	●	●	●	●
Weight	●	●	●	●	●	●	●	●
Geographical region	●	●	●	●	●	●	●	●
Race	●	●	●	●	●	●	●	●
Sex	●	●	●	●	●	●	●	●
Ethnicity	●	●	●	●	●	●	●	●
Time since diagnosis of T2DM	●	●	●	●	●	●	●	●
Renal function	●	●	●	●	●	●	●	●
Background medication	●	●		●	●	●		
Blood pressure	●		●	●				
Hypertension	●	●	●	●				●
Homeostatic model assessment – insulin resistance (HOMA-IR)		●	●					●
Homeostatic model assessment – insulin		●	●					●

secretion (HOMA-IS)												
Proinsulin to insulin ratio			●		●							●
Latent autoimmune diabetes antibodies (LADA)					●							
Treated in extension trial							●					
Metformin posology at baseline							●					
Number of antihypertensive medications at baseline										●		

BMI = body mass index; HbA_{1C} = glycated hameoglobin; T2DM = type 2 diabetes mellitus

Participant flow

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

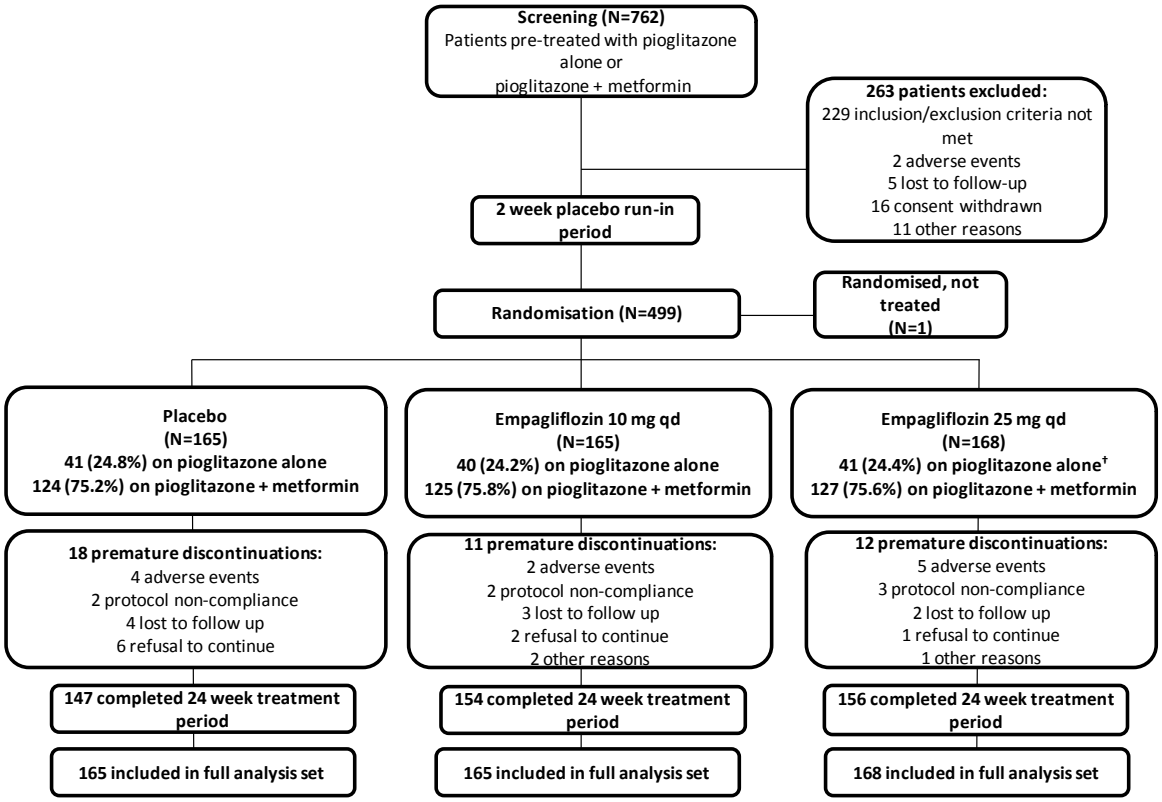
Details of the numbers of patients who were eligible to enter the relevant RCTs, randomised and allocated to each treatment can be seen below. CONSORT flow charts illustrating these numbers can be seen in Figures 1 to 8.

Empagliflozin as add-on to pioglitazone or pioglitazone plus metformin (1245.19 – EMPA-REG PIO)

A total of 762 patients were screened across 69 centres in 8 countries. Of the 762 patients screened, 499 were randomised to double-blind treatment with placebo (166 patients), empagliflozin 10 mg (165 patients) or empagliflozin 25 mg (168 patients). The main reason for not randomising screened patients was HbA_{1C} values which were not in the range defined by the study inclusion/exclusion criteria. One randomised patient in the placebo group did not receive any study medication as they withdrew consent to participate in the trial. Of the treated patients, 457 (91.8%) completed the 24 week treatment period. The proportion of patients who prematurely discontinued treatment was higher in the placebo group (10.9%) compared with the empagliflozin 10 mg group (6.7%) and empagliflozin 25mg group (7.1%). The most frequent reason for discontinuation of study medication was AEs (2.2%).

A CONSORT flow chart summarising patient disposition in study 1245.19 can be seen Figure 4.

Figure 4: EMPA-REG PIO (1245.19) design and patient randomisation



Empagliflozin as add-on to metformin plus sulphonylurea (1245.23 – EMPA-REG MET, EMPA-REG METSU)

Metformin only substudy

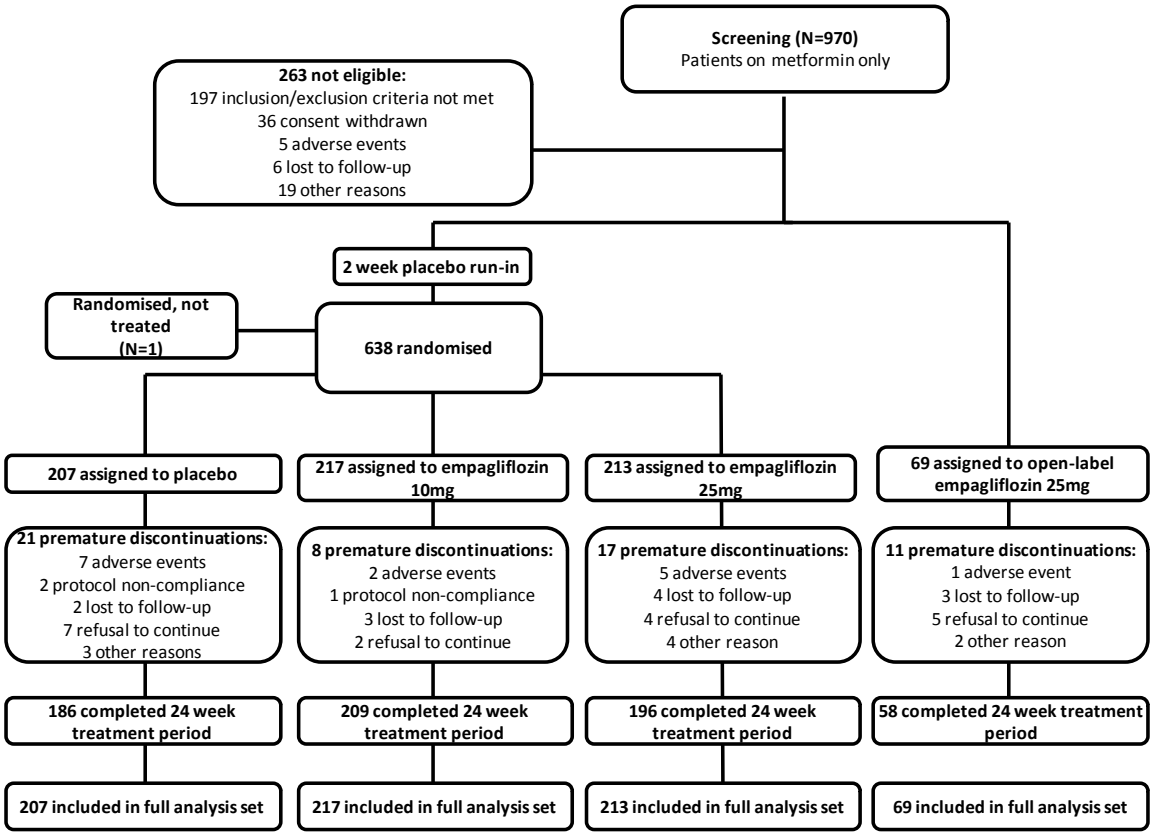
A total of 970 patients with metformin only background medication were recruited in 136 centres across 12 countries. Of the patients screened, a total of 638 were randomised to double-blind treatment with placebo (207 patients), empagliflozin 10mg (217 patients) or empagliflozin 25 mg (214 patients). The main reason for not randomising screened patients was HbA_{1C} values which were not in the range defined by the study inclusion/exclusion criteria. One patient was randomised to the empagliflozin 25 mg group but was not treated. Of the 637 patients who received study treatment, 591 (92.8%) completed the 24 week treatment period. The proportion of patients who prematurely discontinued treatment was slightly higher in the placebo treatment group (10.1%) compared with the empagliflozin

10 mg and empagliflozin 25 mg group (3.7% and 8.0%, respectively). The most frequent reason for premature discontinuation of study medication was AEs (2.2%) and refusal to continue medication (2.0%).

Of all the patients assigned to this substudy, 69 were entered into the open-label empagliflozin 25 mg group. Of these, 2 patients had erroneously started the placebo run-in period but were then assigned to the open-label treatment. 58 patients (84.1%) completed the 24-week treatment period. The most frequent reasons for premature discontinuation were refusal to continue (7.2%) and loss to follow-up (4.3%).

A summary of patient disposition in study 1245.23 (metformin only substudy) can be seen in Figure 5.

Figure 5: EMPA-REG MET (metformin only) (1245.23) design and patient randomisation



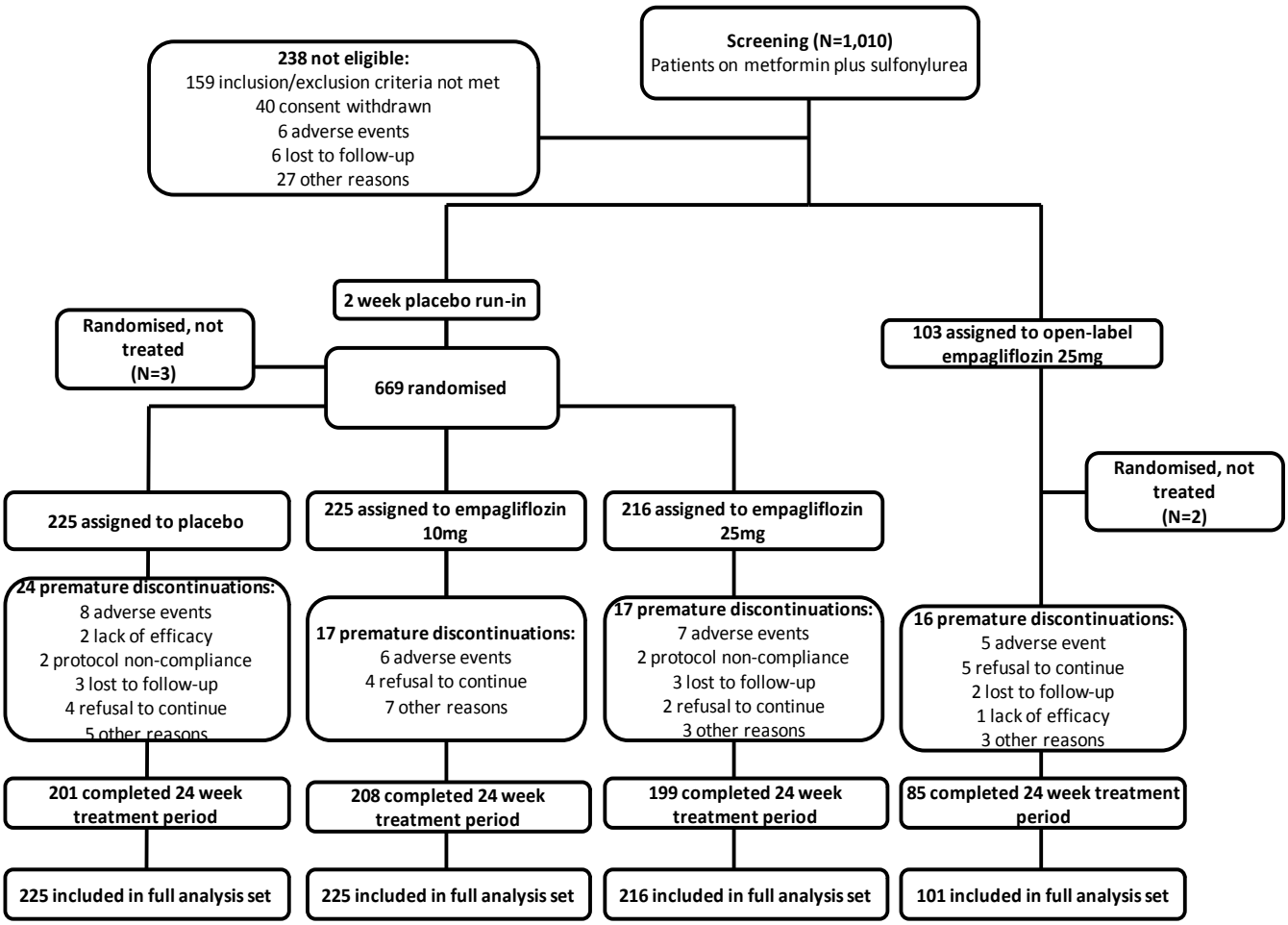
Metformin plus SU substudy

A total of 1,010 patients with metformin plus SU medication background were screened in 129 centres across 12 countries. A total of 669 were randomised to double-blind treatment with placebo (225 patients), empagliflzon 10 mg (226 patients) or empagliflozin 25 mg (218 patients). The main reason for not randomising screened patients was HbA_{1C} values which were not in the range defined by the study inclusion/exclusion criteria. Of the 669 randomised patients, 666 were treated with double-blind study medication; 3 patients were randomised but not treated: 1 patient in the empagliflozin 10 mg group and 2 patients in the empagliflozin 2 5mg group. Of the 666 patients who received study medication, a total of 608 (91.3%) completed the 24 week treatment period. The proportion of patients who did not complete the treatment period was slightly higher in the placebo treatment group compared with the empagliflozin 10 mg group and empagliflozin 25 mg group (10.7%, 7.6% and 7.9%, respectively). The most frequent reason for premature discontinuation was the occurrence of AEs (placebo: 3.6%; empagliflozin 10 mg: 2.7%; empagliflozin 25 mg: 3.2%). Two patients in the placebo group (0.9%) discontinued the trial medication prematurely due to lack of efficacy.

103 patients were entered into the empagliflozin 25 mg group open-label treatment group. Of these, 1 patient had erroneously started the placebo run-in period but was then assigned to open-label treatment. A total of 85 patients (84.2%) completed the 24-week treatment period. The most frequent reasons for premature trial discontinuation in the open-label group were refusal to continue trial medication and AEs (5.0% for each).

A CONSORT flow chart summarising patient disposition in study 1245.23 (metformin plus SU) can be seen in Figure 6.

Figure 6: EMPA-REG METSU (metformin plus SU) (1245.23) design and patient randomisation



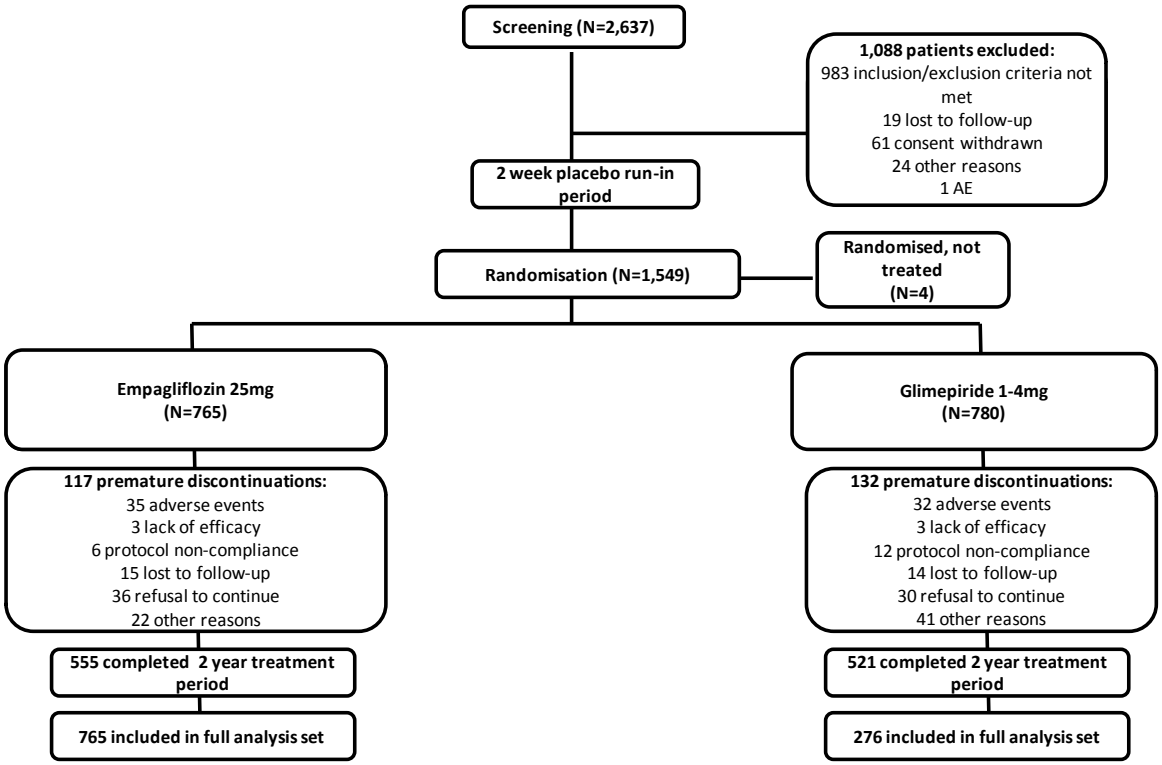
Empagliflozin versus glimepiride as add-on to metformin (1245.28 – EMPA-REG H2H-SU)

A total of 2,637 patients in 181 centres across 23 countries were screened in study 1245.28. Of the patients screened, 1,549 were randomised to double-blind treatment with empagliflozin (769 patients) or glimepiride (780 patients). Commonly reported reasons for non-randomisation were out of range HbA_{1C} values and renal impairment. Of the 1,549 randomised patients, 69.6% were still receiving study medication after 2 years (72.5% empagliflozin vs 66.8% glimepiride). A total of 14.2% of patients (12.2% empagliflozin vs 16.3% glimepiride) did not continue into the study extension period and 16.1% prematurely discontinued study medication. The proportion of patients who

discontinued treatment was similar between the empagliflozin (15.3%) and glimepiride (16.9%) groups. The most frequent reason for premature discontinuation of study medication was AEs (4.3%) and refusal to continue medication (2.0%).

A summary of patient disposition in study 1245.28 can be seen in **Figure 7**

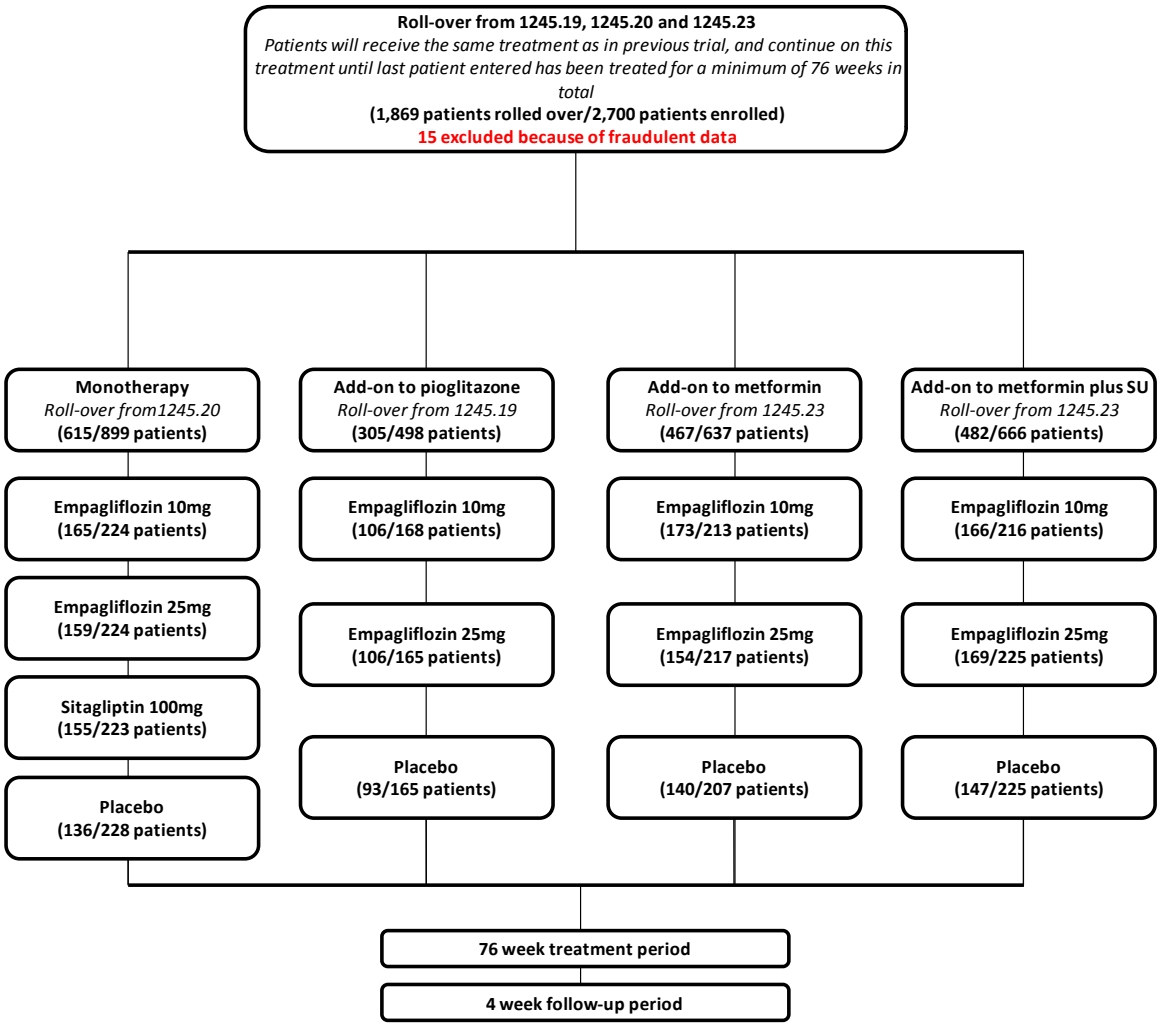
Figure 7: EMPA-REG H2H-SU (1245.28) design and patient randomisation



Long-term efficacy and safety of empagliflozin (1245.31 – EMPA-REG EXTEND)

Out of the 2,700 patients who completed studies 1245.19, 20 and 23, a total of 1,869 rolled over to study 1245.31 (Figure 8).

Figure 8: EMPA-REG EXTEND (1245.31) design and patient randomisation



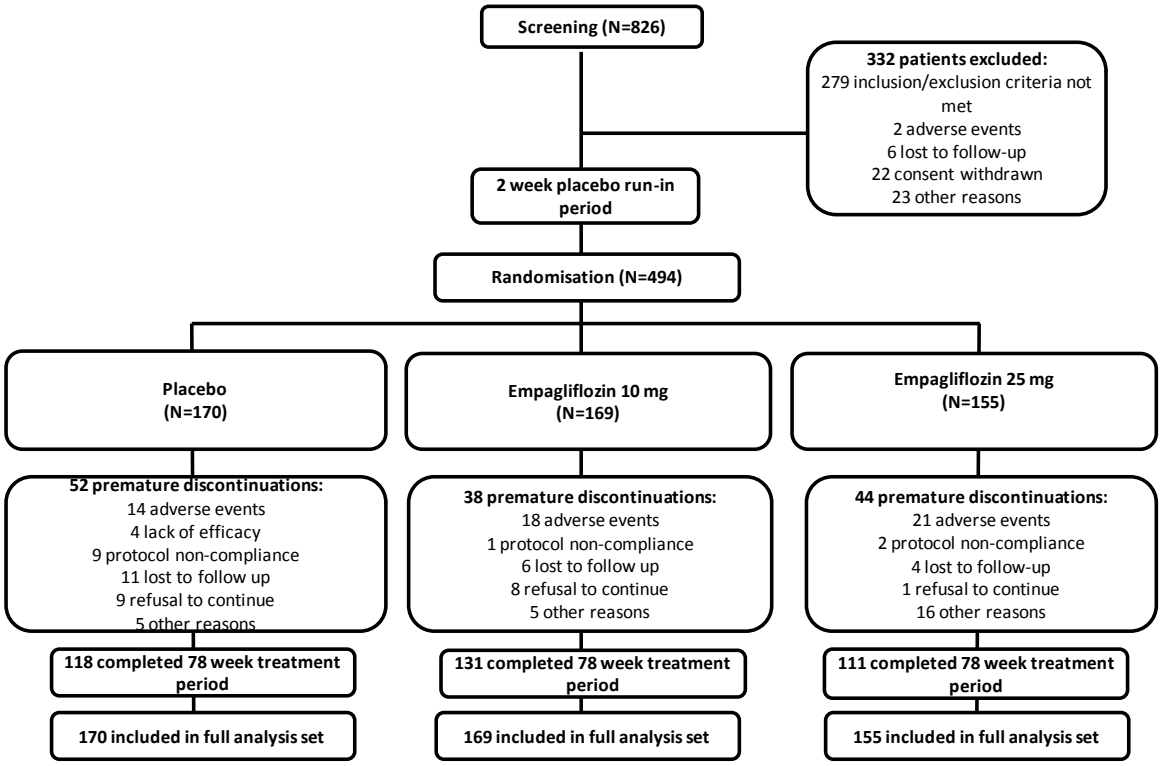
Empagliflozin as add-on combination to basal insulin with or without metformin and/or sulphonylureas (1245.33 – EMPA-REG BASAL)

A total of 826 patients were screened by 97 centers in 7 countries. Of the 826 patients screened, a total of 494 were randomised to receive double-blind treatment with placebo (170 patients), empagliflozin 10 mg (169 patients) or empagliflozin 25 mg (155 patients). The main reason for not randomising screened patients was HbA_{1C} values which were not in the range defined by the study inclusion/exclusion criteria. At week 76, 360 patients (72.9%) had

completed the treatment period. A higher proportion of patients in the placebo group prematurely discontinued treatment (30.6%) compared with both empagliflozin treatment groups (22.5% in the empagliflozin 10 mg group and 28.4% in the empagliflozin 25 mg group). The most frequent reasons for premature discontinuation included AEs (10.7% overall), other reasons (5.3% overall), lost to follow-up (4.3% overall), and patient refusal to continue (not due to AEs; 3.6% overall). The incidence of withdrawals due to AEs or other reasons was higher in the empagliflozin 25 mg group compared with the empagliflozin 10 mg group or the placebo group whereas the incidence of lost to follow-up or patient refusal to continue was lower in the empagliflozin 25 mg group compared with the empagliflozin 10 mg group or the placebo group.

A CONSORT flow chart summarising patient disposition in study 1245.33 can be seen in Figure 9.

Figure 9: EMPA-REG BASAL (1245.33) design and patient randomisation



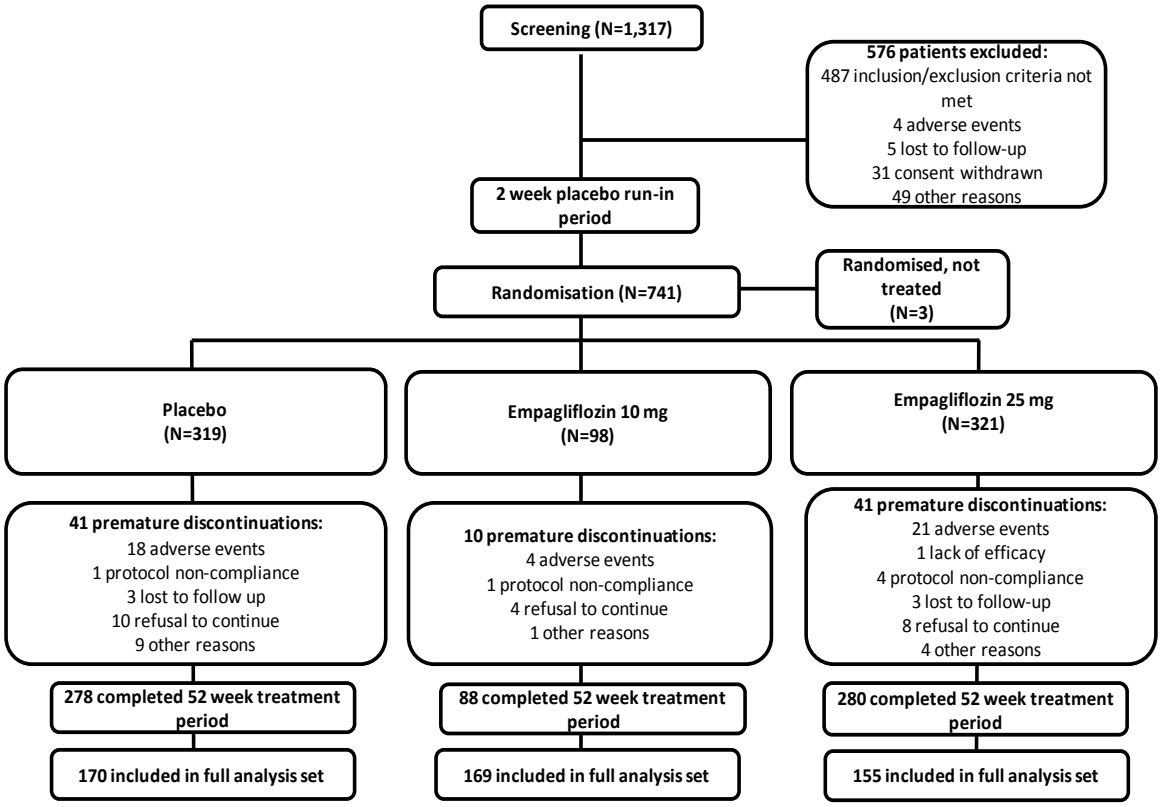
Empagliflozin in patients with renal impairment (1245.36 – EMPA-REG RENAL)

In study 1245.36, a total of 1,317 patients were screened in 127 centres across 15 countries. Of these, 741 patients were randomised to double-blind treatment with placebo (321 patients), empagliflozin 10 mg (98 patients) or empagliflozin 25 mg (322 patients). The main reasons for not randomising screened patients were failure to meet with inclusion or exclusion criteria; in most cases, an out-of-range HbA1c value (17.4%) or no T2DM or eGFR ≥90mL/min/1.73m^2 (10.7%). Of the 741 patients randomised 738 received double-blind trial medication; 2 patients in the placebo group and 1 in the empagliflozin group were randomised but not treated.

Of the 738 patients who received study medication, a total of 646 (87.5%) completed the 52 week treatment period. The most frequent reason for premature discontinuation of trial medication was AEs (5.8%).

The overall disposition of patients in trial 1245.36 can be seen in Figure 10.

Figure 10: EMPA-REG RENAL (1245.36) design and patient randomisation



Disposition by renal impairment

In study 1245.36 patients were randomised to different treatment arms based on their renal impairment category.

In total, 292 patients with mild renal impairment were randomised to placebo (97 patients), empagliflozin 10 mg (98 patients) or empagliflozin 25 mg (97 patients). 2 patients in the placebo group were not treated with any study medication. At the end of the 52 week treatment period, 91.0% of patients with mild renal impairment had completed treatment. The most frequent reason for premature discontinuation was AEs (4.5%).

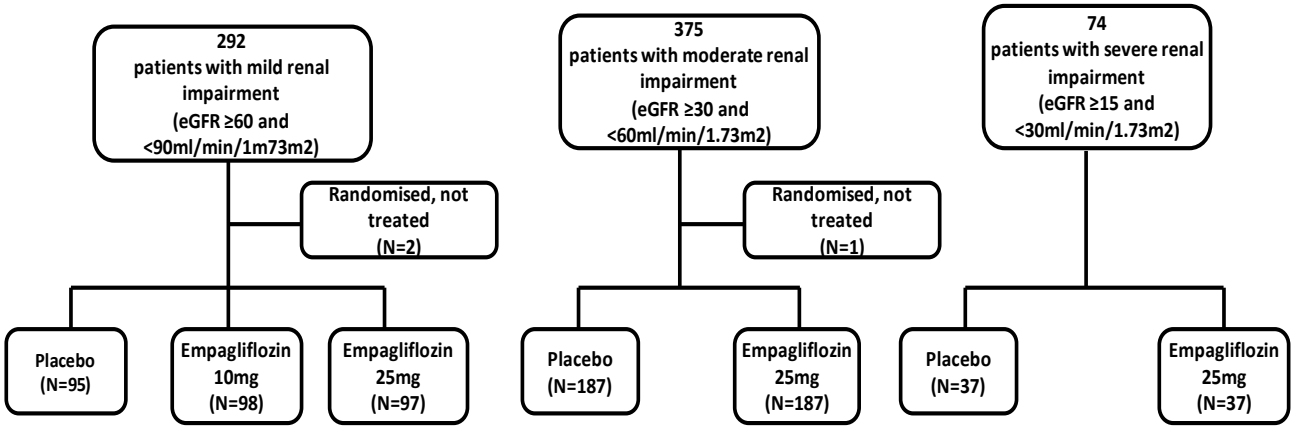
In the moderate renal impairment category, 375 patients were randomised to either placebo (187 patients) or empagliflozin 25 mg (188 patients). All patients were treated with study medication with the exception of 1 patient in the empagliflozin 25 mg group. This resulted in 187 patients in each treatment group. Overall, 88.5% of patients with moderate renal impairment completed the 52 week treatment period. The most frequent reason for premature discontinuation

of trial medication was AEs (4.3%); the proportion of patients discontinuing due to this reason was slightly higher in the empagliflozin 25 mg group (5.3%) compared with the placebo group (3.2%).

Overall, 74 patients with severe renal impairment were randomised to either placebo (37 patients) or empagliflozin 25 mg (37 patients) and all received at least one dose of study medication. 68.9% of patients with severe renal impairment completed the 52 week treatment period. The proportion of patients who prematurely discontinued trial medication was 32.4% in the placebo group and 29.7% in the empagliflozin 25 mg group. The most frequently reported reason for premature treatment discontinuation was AEs, reported for 18.9% of patients (7 patients) in both treatment groups.

The disposition of patients in study 1245.36 according to their renal impairment category can be seen in Figure 11.

Figure 11: EMPA-REG RENAL (1245.36) design, patient randomisation and demographics

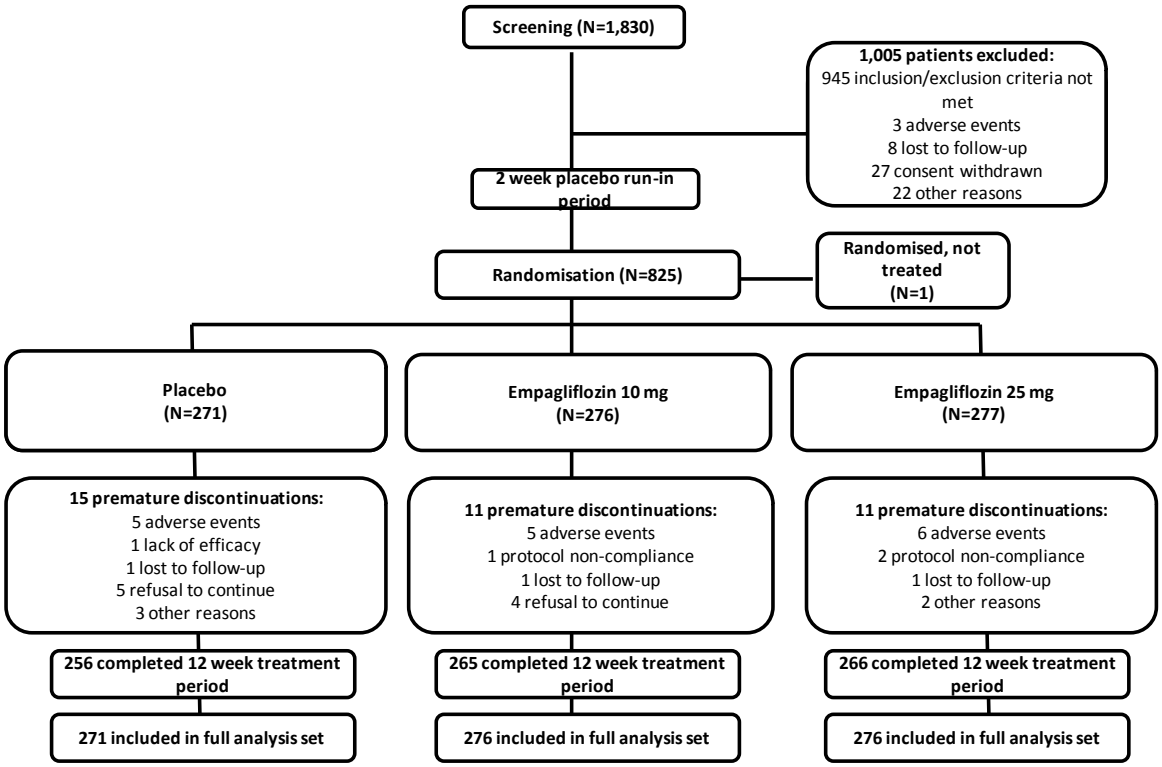


Empagliflozin in patients with hypertension (1245.48 – EMPA-REG BP)

A total of 1,830 patients were screened by 121 centres across 12 countries. 825 patients were randomised following screening. The main reason for not randomising screened patients was HbA_{1C} values which were not in the range defined by the study inclusion/exclusion criteria. One patient in the placebo treatment group was randomised but not treated. 787 patients (95.5%) completed the 12 week treatment period with a slightly number of patients in the placebo treatment group discontinuing treatment prematurely compared with the empagliflozin treatment groups (5.5% for placebo vs 4.0% for both empagliflozin groups). The most frequent reasons for premature discontinuation of study medication were the occurrence of AEs (placebo: 1.8%, empagliflozin 10mg: 1.8%, empagliflozin 25mg: 2.2%) followed by refusal to continue trial medication (placebo: 1.8%, empagliflozin 10 mg: 1.4%, empagliflozin 25 mg: 0%). Discontinuation due to lack of efficacy was reported for 1 patient in the placebo group.

A summary of the disposition of patients in study 1245.48 can be seen in Figure 12.

Figure 12: EMPA-REG BP (1245.48) design and patient randomisation

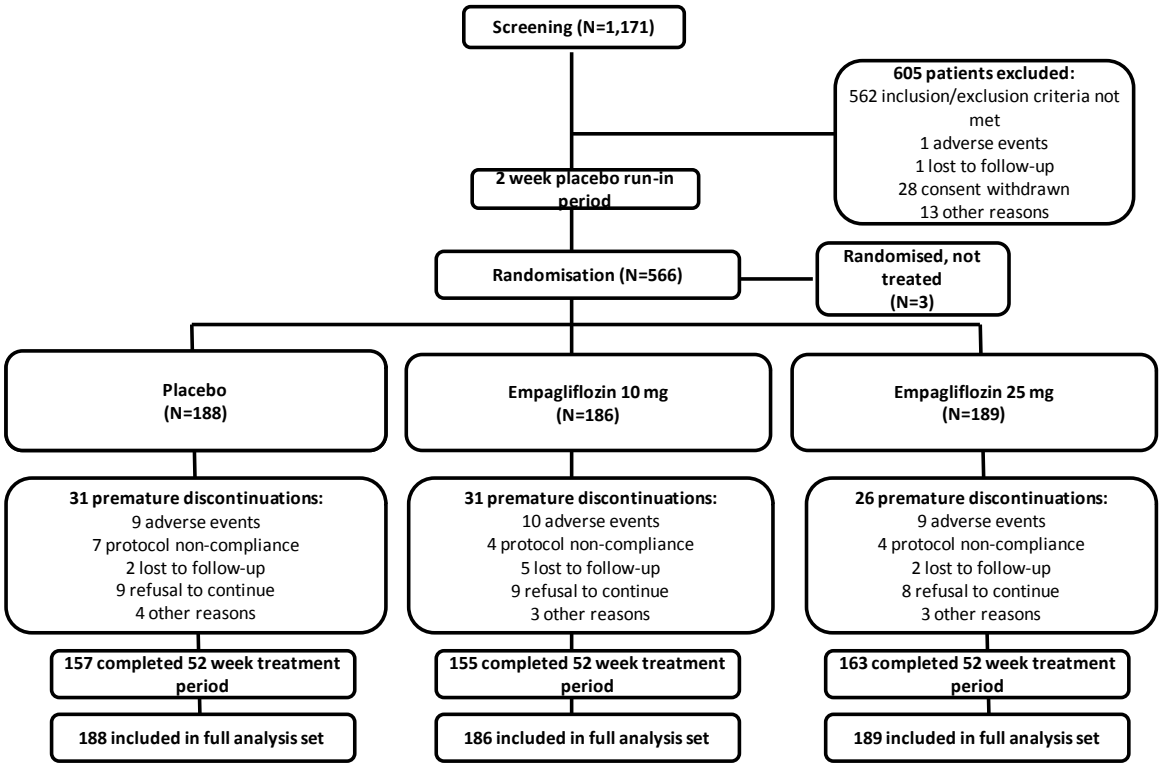


Empagliflozin add-on to multiple daily injections of insulin (1245.49 EMPA-REG MDI)

In study 1245.49 a total of 1,171 patients were screened by 14 centres in 104 countries. Of these 1,171 screened patients, 566 were randomised to double-blind treatment with placebo (189 patients), empagliflozin 10mg (187 patients) or empagliflozin 25mg (190 patients). The main reason for not randomising screened patients was failure to meet the inclusion/exclusion criteria for the study. A total of three randomised patients were not treated (one patients in each treatment group). Of the treated patients, 84.4% did not prematurely discontinue trial medication. The main reasons for premature discontinuation of study medication were AEs (5.0%) and refusal to continue trial medication (4.6%).

A summary of the disposition of patients in study 1245.48 can be seen in Figure 13.

Figure 13: EMPA-REG MDI (1245.49) design and patient randomisation



6.4 Critical appraisal of relevant RCTs

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

- *Was the method used to generate random allocations adequate?*
- *Was the allocation adequately concealed?*
- *Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?*
- *Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?*
- *Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?*

- *Is there any evidence to suggest that the authors measured more outcomes than they reported?*
- *Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*

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

A complete quality assessment of each of the studies can be seen in Section 9.3, Appendix 3.

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

A critical appraisal summary of each of the studies in the empagliflozin clinical programme can be seen in Table 15. Full details of each of the studies can be seen in Section 9.3, Appendix 3.

Table 15: Quality assessment results for RCTs

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
1245.19 (EMPA-REG PIO)	Yes	Yes	Yes	Yes	Yes (premature discontinuations: placebo:10.9%; empagliflozin 10mg: 6.7%; empagliflozin 25mg: 7.1%	No	Yes
1245.23 (EMPA-REG MET, EMPA-REG METSU)	Yes	Yes	Yes	Yes	Yes (premature discontinuations: placebo: 10.7%; empagliflozin 10mg: 7.6%; empagliflozin 25mg: 7.9%)	No	Yes
1245.28 (EMPA-REG H2H-SU)	Yes	Yes	Yes	Yes	No	No	Yes

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
1245.31 (EMPA-REG EXTEND)	Patients continued with the treatment they had been randomised to in the preceding trial			Yes	No	No	Yes
1245.33 (EMPA-REG BASAL)	Yes	Yes	Yes	Yes	Yes (premature discontinuations: placebo: 30.6%; empagliflozin 10mg: 22.5%; empagliflozin 25mg: 28.4%)	No	Yes
1245.36 (EMPA-REG RENAL)	Yes	Yes	Yes	Yes	No	No	Yes
1245.48 (EMPA-REG BP)	Yes	Yes	Yes	Yes	No	No	Yes
1245.49 (EMPA-REG MDI)	Yes	Yes	Yes	Yes	Yes (premature discontinuations: placebo: 16.5%; empagliflozin10mg: 16.7%; empagliflozin 25mg: 13.8%)	No	Yes

6.5 Results of the relevant RCTs

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

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

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

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

The results on the empagliflozin clinical development programme are outlined below.

Adjusted mean results for primary and key secondary endpoints represent analyses carried out using the ANCOVA model previously described in Table 13, unless stated otherwise. The numbers displayed for each of the study endpoints represent the number of analysed patients and subsequently may be different to the number of patients randomised in each treatment group of the study.

Empagliflozin as add-on to pioglitazone or pioglitazone plus metformin (1245.19 – EMPA-REG PIO)

The primary endpoint of study 1245.19 was the change from baseline in HbA_{1C} after 24 weeks of treatment. Key secondary endpoints included change from baseline in FPG and body weight

At week 24, adjusted mean ± standard error (SE) treatment differences from baseline in HbA_{1C} were -0.59 ± 0.07% in the empagliflozin 10mg group and -0.72 ± 0.07% in the empagliflozin 25mg group, compared with -0.11 ± 0.07% in the placebo treatment group (P<0.001 for both groups). The adjusted mean ± SE differences compared to placebo were -0.48 ± 0.09% (95% CI: -0.66, -0.29) in the empagliflozin 10mg group and -0.61 ± 0.09% (95% CI: -0.79 to -0.42) in the empagliflozin 25mg group (P<0.0001 for both doses). Reductions in adjusted mean difference in HbA_{1C} from baseline to week 24 were similar in patients receiving background therapy with pioglitazone alone and with pioglitazone plus metformin.

At week 24, adjusted mean ± SE treatment differences from baseline in FPG were -17.00 ± 2.63 mg/dL in the empagliflozin 10mg group and -21.99 ± 2.59mg/dL in the empagliflozin 25 mg group, compared with 6.47 ± 2.61mg/dL in the placebo group. The adjusted mean ± SE difference compared to placebo was -23.48 ± 3.71 mg/dL (97.5% CI: -31.81, to -15.15) and -28.46 ± 3.68 mg/dL (97.5%: -36.73 to -20.19) in the empagliflozin 10 mg and 25 mg groups, respectively.

Adjusted mean ± SE treatment differences from baseline in body weight at 24 weeks were -1.62 ± 0.21kg and -1.47 ± 0.21kg in the empagliflozin 10 mg and 25 mg groups, respectively, compared with 0.34 ± 0.21kg in the placebo treatment group. The adjusted mean ± SE treatment differences compared with placebo for body weight were -1.95 ± 0.30 kg (97.5% CI: -2.64 to -1.27) in the empagliflozin 10 mg group and -1.81 ± 0.30 kg (97.5% CI: -2.49, -1.13) in the empagliflozin 25 mg group.

A summary of the primary and secondary endpoints for study 1245.19 can be seen in Table 16. A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 14.

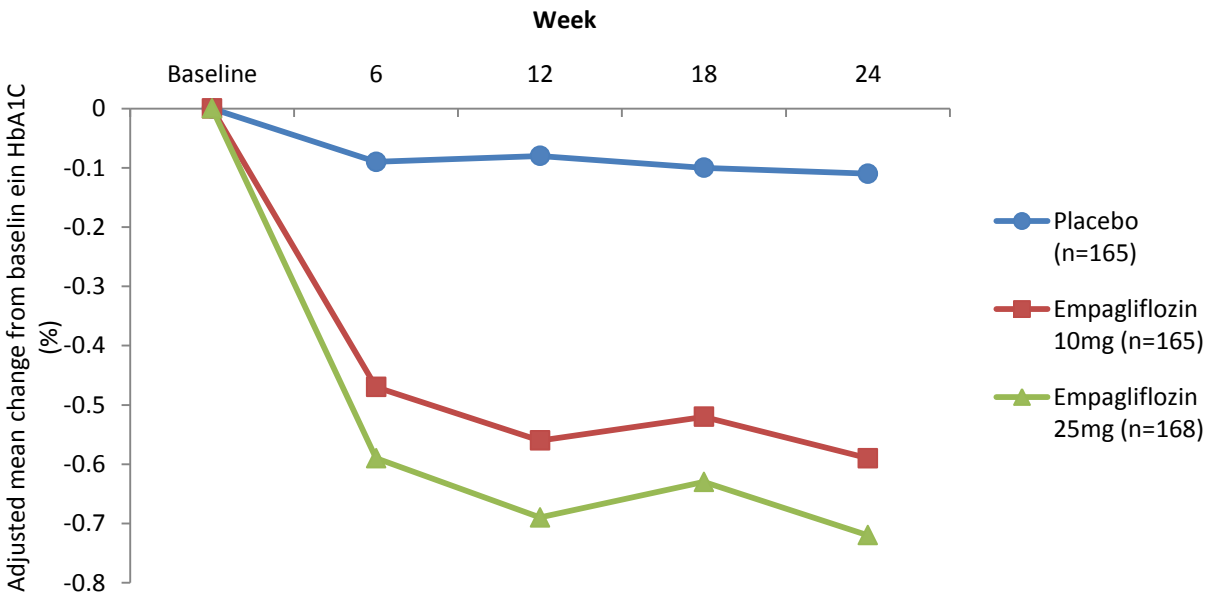
Table 16: Summary of primary and secondary endpoints in study 1245.19

Efficacy Results			
	Placebo (n=165)	**Empagliflozin 10 mg (n=165)**	**Empagliflozin 25 mg (n=168)**
Mean baseline HbA_{1C} (%) ± SE	8.16 ± 0.07	8.07 ± 0.07	8.06 ± 0.06
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF)	8.02 ± 0.09	7.50 ± 0.07	7.36 ± 0.07
Adjusted mean change from baseline (%) ± SE	−0.11 ± 0.07	−0.59 ± 0.07	−0.72 ± 0.07
Adjusted mean difference vs placebo (%) ± SE		−0.48 ± 0.09	−0.61 ± 0.09
[97.5% CI]		[−0.66, −0.29]	[−0.79, −0.42]
P value		<0.0001	<0.0001
	Placebo (n=165)	**Empagliflozin 10mg (n=163)**	**Empagliflozin 25mg (n=168)**
Mean baseline FPG (mg/dL) ± SE	151.93 ± 3.14	152.01 2.99	151.86 ± 2.86
Mean FPG at week 24 (mg/dL) ± SE – FAS (LOCF)	158.56 ± 3.59	134.85 ± 3.36	129.86 ± 2.15
Adjusted mean change from baseline (mg/dL) ± SE	6.47 ± 2.61	-17.00 ± 2.63	-21.99 ± 2.59
Adjusted mean difference vs placebo (mg/dL) ± SE		-23.48 ± 3.71	-28.46 ± 3.68
[97.5% CI]		[-31.81, -15.15]	[-36.73, -20.19]
P value		<0.001	<0.001
	Placebo (n=165)	**Empagliflozin 10 mg (n=165)**	**Empagliflozin 25 mg (n=168)**
Mean baseline body weight (kg) ± SE	78.10 ± 1.57	77.97 ± 1.49	78.93 ± 1.54
Mean body weight at week 24 (kg) ± SE – FAS (LOCF)	78.45 ± 1.54	76.37 ± 1.46	77.44 ± 1.51
Adjusted mean change from baseline (kg) ± SE	0.34 ± 0.21	−1.62 ± 0.21	−1.47 ± 0.21
Adjusted mean difference vs placebo (kg) ± SE		−1.95 ± 0.30	−1.81 ± 0.30
[97.5% CI]		[−2.64, −1.27]	[−2.49, −1.13]
P value		<0.0001	<0.0001

	Placebo (n=165)	Empagliflozin 10 mg (n=165)	Empagliflozin 25 mg (n=168)
Mean baseline SBP (mmHg) ± SE	125.71 ± 0.94	126.51 ± 1.06	125.95 ± 1.07
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF)	126.58 ± 1.15	123.28 ± 1.03	121.89 ± 1.01
Adjusted mean change from baseline (mmHg) ± SE	0.72 ± 0.85	−3.14 ± 0.85	−4.00 ± 0.84
Adjusted mean difference vs placebo (mmHg) ± SE		−3.86 ± 1.20	−4.73 ± 1.20
[95% CI]		[−6.23, −1.50]	[−7.08, −2.37]
P value		0.0014	<0.0001

CI = confidence interval; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; SBP = systolic blood pressure; SE = standard error

Figure 14: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.19) - FAS (LOCF)



Empagliflozin as add-on to metformin plus sulphonylurea (1245.23 – EMPA-REG MET, EMPA-REG METSU)

The primary endpoint of study 1245.23 was the change from baseline in HbA_{1C} after 24 weeks of treatment. Key secondary endpoints included change from baseline in body weight and MDG after 24 weeks.

Metformin only substudy

At week 24, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.70 ± 0.05% in the empagliflozin 10mg group and -0.77 ± 0.05% in the empagliflozin 25 mg, compared with -0.13 ± 0.05% in the placebo group. The adjusted mean ± SE treatment differences compared with placebo were -0.57 ± 0.07% (97.5% CI: -0.72 to -0.42) and -0.64 ± 0.07% (97.5% CI: -0.79 to -0.48) in the empagliflozin 10mg and 25mg groups, respectively (P<0.0001 for both doses).

At week 24, mean ± SE treatment differences from baseline in body weight were -2.08 ± 0.17kg in the empagliflozin 10mg group and -2.46 ± 0.17 kg in the empagliflozin 25mg group, compared with -0.45 ± 0.17 kg in the placebo treatment group. The adjusted mean ± SE treatment differences compared with placebo in body weight were -1.63 ± 0.24 kg (97.5% CI: -2.17 to -1.08) in the empagliflozin 10mg group and -2.01 ± 0.24 kg (97.5% CI: -2.56 to -1.46) in the empagliflozin 25mg group (P<0.0001 for both doses).

Adjusted mean ± SE treatment differences from baseline in MDG at week 24 were -1.99 ± 1.99 mg/dL and -9.64 ± 1.89 mg/dL for empagliflozin 10mg and 25mg, respectively. The adjusted mean ± SE treatment differences compared with placebo -7.65 ± 2.75 mg/dL (97.5% CI: -13.81 to -1.48; P=0.0055) in the empagliflozin 10 mg group and -12.37 ± 2.75 mg/dL (97.5% CI: -18.55 to -2.75; P<0.0001) in the empagliflozin 25 mg group.

A summary of the primary and secondary endpoints for study 1245.23 (metformin only substudy) can be seen in Table 17. A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 15.

Metformin plus SU substudy

At week 24, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were 0.82 ± 0.05% in the empagliflozin 10mg group and -0.77 ± 0.05% in the empagliflozin 25mg group, compared with -0.17 ± 0.05% in the placebo group. The adjusted mean ± SE treatment differences compared with placebo were -0.64 ± 0.07% (97.5% CI: -0.79 to -0.49) in the empagliflozin 10mg group and -0.59 ± 0.07 (97.5% CI: -0.74 to -0.44) in the empagliflozin 25mg group (P<0.0001 for both doses).

At week 24, adjusted mean ± SE treatment differences from baseline in body weight were -2.16 ± 0.15kg in the empagliflozin 10mg group and -2.39 ± 0.16kg in the empagliflozin 25mg group, compared with -0.39 ± 0.15kg in the placebo group. The adjusted mean ± SE treatment differences compared with placebo were -1.76 ± 0.22kg (97.5% CI: -2.25 to -1.28) and -1.99 ± 0.22kg (97.5% CI: -2.48 to -1.50) in the empagliflozin 10mg and 25mg groups, respectively (P<0.0001 for both doses).

At week 24, adjusted mean ± SE treatment differences from baseline in MDG were -10.01 ± 1.80mg/dL in the empagliflozin 10mg group and -13.06 ± 2.03mg/dL in the empagliflozin 25mg group, compared with 0.00 ± 1.78mg/dL in the placebo group. The adjusted mean ± SE treatment differences compared with placebo in MDG were -10.02 ± 2.53mg/dL (97.5% CI: -15.72 to -4.32) in the empagliflozin 10mg group and -13.06 ± 2.70mg/dL (97.5% CI: -19.15 to -6.98) in the empagliflozin 25mg group (P<0.0001 for both doses).

A summary of the primary and secondary endpoints for study 1245.23 (metformin plus SU substudy) can be seen in Table 18. A graphical representation of changes in HbA_{1C} over time can be seen in Figure 16.

Table 17: Summary of primary and secondary endpoints in study 1245.23 (metformin only)

Efficacy Results				
	Placebo (n=207)	**Empagliflozin 10 mg (n=217)**	**Empagliflozin 25 mg (n=213)**	**Open-label empagliflozin 25mg (n=69)**
Mean baseline HbA_{1C} (%) ± SE	7.90 ± 0.06	7.94 ± 0.05	7.86 ± 0.06	11.07 ± 0.16
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF), OLS (LOCF)	7.77 ± 0.07	7.22 ± 0.05	7.11 ± 0.06	8.29 ± 0.15
Adjusted mean change from baseline (%) ± SE	-0.13 ± 0.05	-0.70 ± 0.05	-0.77 ± 0.05	-2.78 ± 0.21[†]
Adjusted mean difference vs placebo (%) ± SE		-0.57 ± 0.07	-0.64 ± 0.07	
[97.5% CI]		[-0.72, -0.42]	[-0.79, -0.48]	
P value		<0.0001	<0.0001	
	Placebo (n=207)	**Empagliflozin 10 mg (n=217)**	**Empagliflozin 25 mg (n=213)**	**Open-label empagliflozin 25mg (n=69)**
Mean baseline body weight (kg) ± SE	79.73 ± 1.29	81.59 ± 1.26	82.21 ± 1.32	85.07 ± 2.64
Mean body weight at week 24 (kg) ± SE – FAS (LOCF), OLS (LOCF)	79.33 ± 1.28	79.51 ± 1.22	79.71 ± 1.27	83.74 ± 2.61
Adjusted mean change from baseline (kg) ± SE	-0.45 ± 0.17	-2.08 ± 0.17	-2.46 ± 0.17	-1.33 ± 0.43[†]
Adjusted mean difference vs placebo (kg) ± SE		-1.63 ± 0.24	-2.01 ± 0.24	
[97.5% CI]		[-2.17, -1.08]	[-2.56, -1.46]	
P value		<0.0001	<0.0001	
	Placebo (n=133)	**Empagliflozin 10 mg (n=148)**	**Empagliflozin 25 mg (n=147)**	**Open-label empagliflozin 25mg (n=43)**
Mean baseline MDG (mg/dL) ± SE	169.53 ± 3.27	168.03 ± 2.64	167.87 ± 2.82	226.32 ± 8.26
Mean MDG at week 24 (mg/dL) ± SE – FAS (LOCF), OLS (LOCF)	167.25 ± 2.67	158.41 ± 2.71	153.75 ± 2.60	190.85 ± 8.15
Adjusted mean change from baseline (mg/dL) ± SE	-1.99 ± 1.99	-9.64 ± 1.89	-14.36 ± 1.89	-35.47 ± 7.34[†]
Adjusted mean difference vs placebo (mg/dL) ± SE		-7.65 ± 2.74	-12.37 ± 2.75	
[97.5% CI]		[-13.81, -1.48]	[-18.55, -6.19]	
P value		0.0055	<0.0001	
	Placebo (n=207)	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Open-label empagliflozin 25mg**

		(n=217)	(n=213)	(n=69)
Mean baseline SBP (mmHg) ± SE	128.6 ± 1.0	129.6 ± 1.0	130.0 ± 1.0	126.2 ± 1.4
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF), OLS (LOCF)	128.5 ± 1.0	125.0 ± 0.9	124.6 ± 1.0	124.4 ± 1.4
Adjusted mean change from baseline (mmHg) ± SE	-0.4 ± 0.7	-4.5 ± 0.7	-5.2 ± 0.7	-1.8 ± 1.2†
Adjusted mean difference vs placebo (mmHg) ± SE		-4.1 ± 1.0	-4.8 ± 1.0	
[95% CI]		[-6.2, -2.1]	[-6.9, -2.7]	
P value		<0.0001	<0.0001	

† mean change from baseline (non-adjusted)
CI = confidence interval; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; MDG = mean daily glucose; OLS = open label set; SBP = systolic blood pressure; SE = standard error

Figure 15: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.23 - metformin only) – FAS (LOCF), OLS (LOCF)

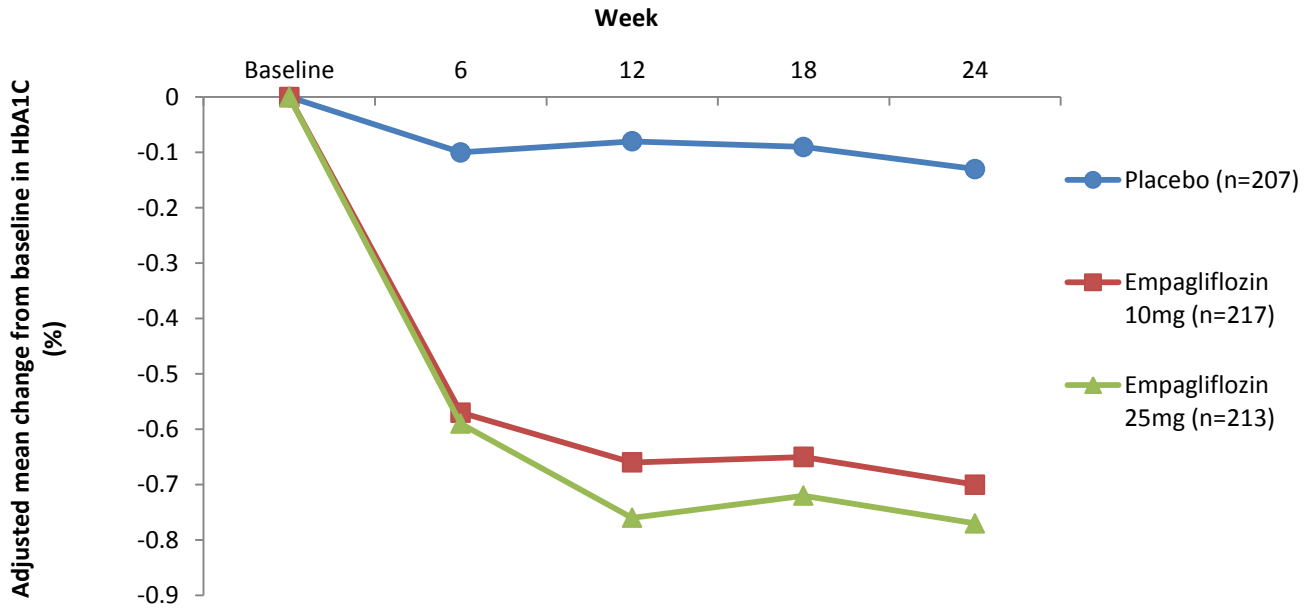


Table 18: Summary of primary and secondary endpoints in study 1245.23 (metformin plus SU)

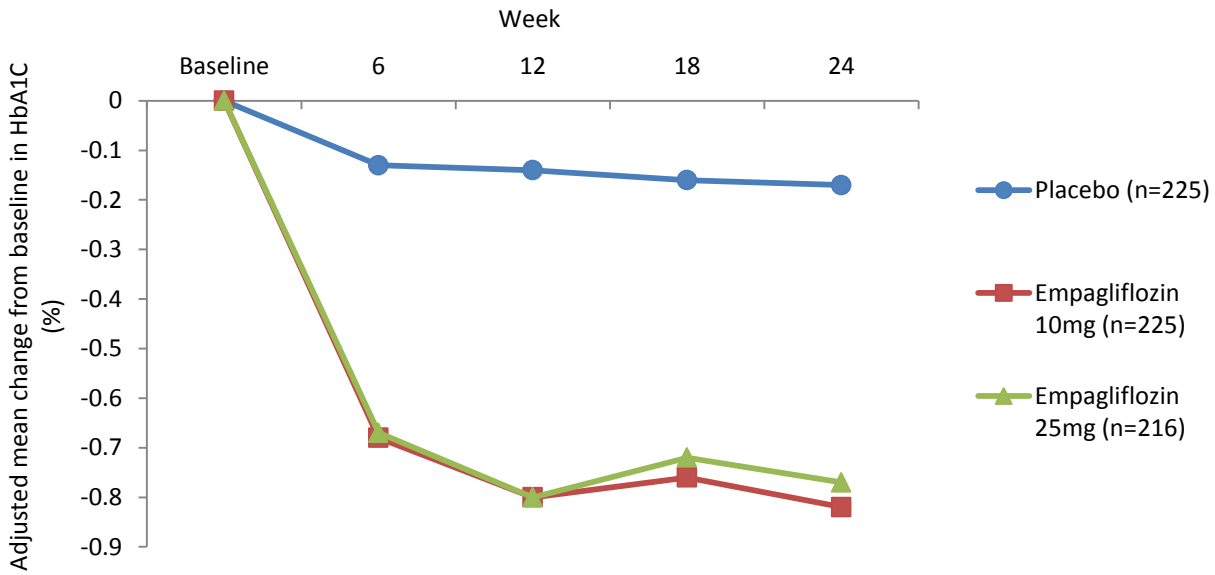
Efficacy Results				
	Placebo (n=225)	**Empagliflozin 10 mg (n=225)**	**Empagliflozin 25 mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline HbA_{1C} ± SE	8.15 ± 0.06	8.07 ± 0.05	8.10 ± 0.06	11.18 ± 0.12
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF), OLS (LOCF)	7.97 ± 0.07	7.26 ± 0.05	7.33 ± 0.06	8.65 ± 0.14
Adjusted mean change from baseline (%) ± SE	-0.17 ± 0.05	-0.82 ± 0.05	-0.77 ± 0.05	-2.53 ± 0.15†
Adjusted mean difference vs placebo (%) ± SE		-0.64	-0.59	
[97.5% CI]		[-0.79 to -0.49]	[-0.74 to -0.44]	
P value		<0.001	<0.001	
	Placebo (n=225)	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline body weight (kg) ± SE	76.23 ± 1.13	77.08 ± 1.22	77.50 ± 1.28	76.43 ± 1.81
Mean body weight at week 24 (kg) ± SE – FAS (LOCF), OLS (LOCF)	75.86 ± 1.12	74.91 ± 1.22	75.10 ± 1.26	75.15 ± 1.78
Adjusted mean change from baseline (kg) ± SE	-0.39 ± 0.15	-2.16 ± 0.15	-2.39 ± 0.16	-1.29 ± 0.30†
Adjusted mean difference vs placebo (kg) ± SE		-1.76	-1.99	
[97.5% CI]		[-2.25 to -1.28]	[-2.48 to -1.50]	
P value		<0.0001	<0.0001	
	Placebo (n=151)	**Empagliflozin 10mg (n=148)**	**Empagliflozin 25mg (n=117)**	**Open-label empagliflozin 25mg (n=52)**
Mean baseline MDG (mg/dL) ± SE	170.45 ± 2.47	170.28 ± 2.39	172.72 ± 3.49	233.07 ± 8.78
Mean MDG at week 24 (mg/dL) ± SE – FAS (LOCF), OLS (LOCF)	170.95 ± 2.48	160.53 ± 2.66	158.68 ± 3.15	203.72 ± 8.36
Adjusted mean change from baseline (mg/dL) ± SE	0.00 (1.78)	-10.01 ± 1.80	-13.06 ± 2.03	-29.34 ± 6.58†
Adjusted mean difference vs placebo (mg/dL) ± SE		-10.02 ± 2.53	-13.06 ± 2.70	
[97.5% CI]		[-15.72 to -4.32]	[-19.15 to -6.98]	

P value		<0.001	<0.001	
	Placebo (n=225)	**Empagliflozin 10mg (n=225)**	**Empagliflozin 25mg (n=216)**	**Open-label empagliflozin 25mg (n=101)**
Mean baseline SBP (mmHg) ± SE	128.8 ± 1.0	128.7 ± 0.9	129.3 ± 1.0	126.4 ± 1.2
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF), OLS (LOCF)	127.4 ± 0.9	124.7 ± 1.0	125.7 ± 0.8	122.7 ± 1.3
Adjusted change from baseline (mmHg) ± SE	-1.4 ± 0.7	-4.1 ± 0.7	-3.5 ± 0.7	-3.6 ± 1.0†
Adjusted difference vs placebo (mmHg) ± SE		-2.7	-2.1	
[95% CI]		[-4.6 to -0.8]	[-4.0 to -0.2]	
P value		0.0049	0.0321	

† mean change from baseline (non-adjusted)

CI = confidence interval; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; MDG = mean daily glucose; OLS = open label set; SBP = systolic blood pressure; SE = standard error

Figure 16: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time in study 1245.23 (metformin plus SU) – FAS (LOCF), OLS (LOCF)



Empagliflozin versus glimepiride as add-on to metformin (1245.28 – EMPA-REG H2H-SU)

The primary endpoint of study 1245.28 was the change from baseline in HbA_{1C} after 104 weeks of treatment. The key secondary endpoints included change from baseline in body weight, occurrence of confirmed hypoglycaemic AEs, change from baseline in SBP and change from baseline in DBP, all after 104 weeks of treatment.

After 104 weeks, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.66 ± 0.03% in the empagliflozin group and -0.55 ± 0.03% in the group. The adjusted mean ± SE treatment difference for empagliflozin compared with glimepiride was -0.11 ± 0.04% (97.5% CI: -0.20 to -0.01; p<0.0001 for non-inferiority).

At week 104, adjusted mean ± SE treatment differences from baseline in body weight were -3.12 ± 0.13kg in the empagliflozin group and 1.34 ± 0.13kg in the glimepiride group. The adjusted mean ± SE treatment difference for empagliflozin

compared with glimepiride was -4.46 ± 0.18kg (97.5% CI: -4.87 to -4.05; p<0.0001).

At week 104 adjusted mean ± SE treatment differences from baseline in SBP were -3.1 ± 0.4mmHg in the empagliflozin group and 2.5 ± 0.4mmHg in the glimepiride group. The adjusted mean ± SE treatment difference for empagliflozin compared with glimepiride was -5.6 ± 0.6 (97.5% CI: -7.04 to -4.2; p<0.0001).

At week 104 adjusted mean ± SE treatment differences from baseline in DBP were -1.8 ± 0.3mmHg in the empagliflozin group and 0.9 ± 0.3mmHg in the glimepiride group. The adjusted mean ± SE treatment difference for empagliflozin compared with glimepiride for DBP was -2.7 ± 0.4mmHg (97.5% CI: -3.5 to -1.8; p<0.0001)

A summary of the primary and secondary endpoints for study 1245.28 can be seen in Table 19. . A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 17.

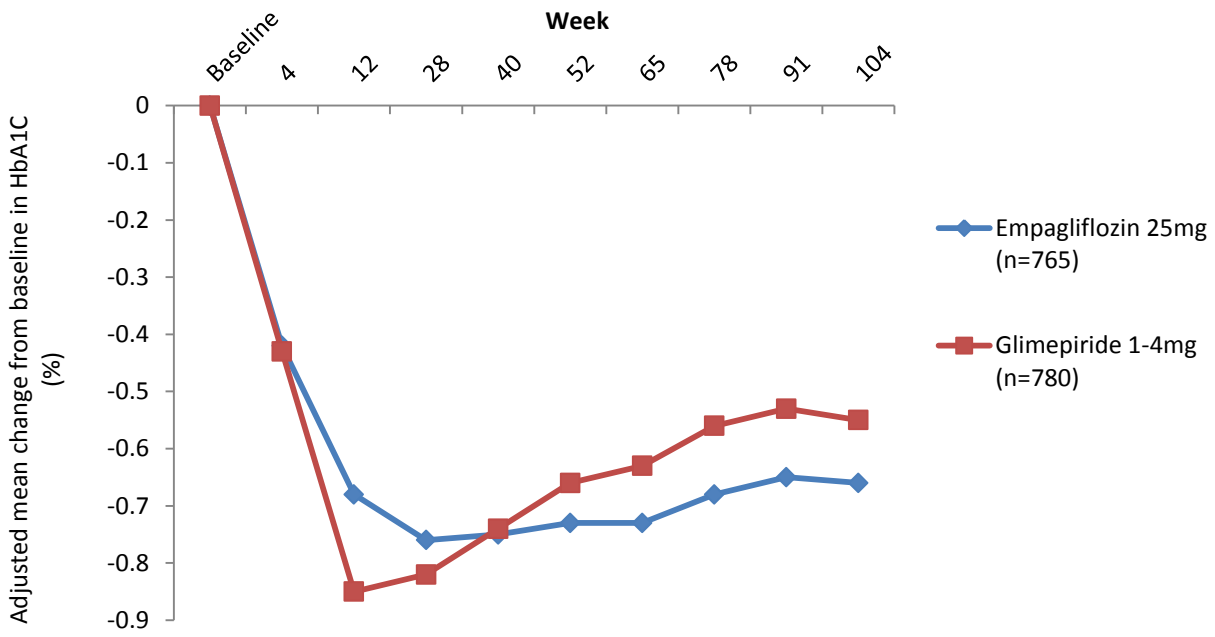
Table 19: Summary of primary and secondary endpoints in study 1245.28

Efficacy Results		
	Empagliflozin 25mg (N=765)	**Glimepiride 1-4mg (N=780)**
Mean baseline HbA_{1C} (%) ± SE	7.92 ± 0.03	7.92 ± 0.03
Mean HbA_{1C} at week 104 (%) ± SE – FAS (LOCF)	7.26 ± 0.03	7.37 ± 0.04
Adjusted mean change from baseline (%) ± SE	-0.66 ± 0.03	-0.55 ± 0.03
Adjusted mean difference *vs* glimepiride (%) ± SE	-0.11 ± 0.04	
[97.5% CI]	-0.20, -0.01	
P value (non-inferiority)	<0.0001	
	Empagliflozin 25mg (N=765)	**Glimepiride 1-4mg (N=780)**
Mean baseline body weight (kg) ± SE	82.52 ± 0.69	83.03 ± 0.69
Mean body weight at week 104 (kg) ± SE – FAS (LOCF)	79.41 ± 0.67	84.37 ± 0.70
Adjusted mean change from baseline (kg) ± SE	-3.11 ± 0.13	1.33 ± 0.13
Adjusted mean difference *vs* glimepiride (kg) ± SE	-4.46 ± 0.18	
[97.5% CI]	-4.87, -4.05	
P value	<0.0001	
	Empagliflozin 25mg (N=765)	**Glimepiride 1-4mg (N=780)**
Mean baseline SBP (mmHg) ± SE	133.4 ± 0.6	133.5 ± 0.6
Mean SBP at week 104 (mmHg) ± SE – FAS (LOCF-H)	130.3 ± 0.6	136.0 ± 0.6
Adjusted mean change from baseline (mmHg) ± SE	-3.1 ± 0.5	2.5 ± 0.5

Adjusted mean difference *vs* glimepiride (mmHg) ± SE	-5.6 ± 0.6	
[95% CI]	-7.0, -4.2	
P value	<0.0001	
	Empagliflozin 25mg (N=765)	**Glimepiride 1-4mg (N=780)**
Mean baseline DBP (mmHg) ± SE	79.5 ± 0.3	79.4 ± 0.3
Mean DBP at week 104 (mmHg) ± SE – FAS (LOCF-H)	77.7 ± 0.4	80.3 ± 0.3
Adjusted mean change from baseline (mmHg) ± SE	-1.8 ± 0.3	0.9 ± 0.3
Adjusted mean difference *vs* glimepiride (mmHg) ± SE	-2.7 ± 0.4	
[97.5% CI]	-3.5, -1.8	
P value	<0.0001	

CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; OLS = open label set; SBP = systolic blood pressure; SE = standard error

Figure 17: Adjusted mean change from baseline in HbA_{1C} (%) ANCOVA results over time in study 1245.28 – FAS (LOCF)



Long-term efficacy and safety of empagliflozin (1245.31 – EMPA-REG EXTEND)

The main objective of the 1245.31 extension study was the long-term safety and tolerability of empagliflozin 10mg and 25mg. No primary endpoint had been specified in the study; however key secondary endpoints included the long-term efficacy of empagliflozin compared with sitagliptin or placebo as monotherapy, placebo on a background of pioglitazone, placebo on a background of metformin and placebo on a background of metformin plus SU. These secondary efficacy endpoints can be seen in Table 20. HbA_{1C} changes over time can be seen in Figure 18, Figure 19, Figure 20 and Figure 21.

Table 20: Summary of efficacy endpoints in 1245.31 extension study

Efficacy Results				
Monotherapy (1245.20 roll-over)				
	Placebo (N=228)	**Empagliflozin 10mg (N=224)**	**Empagliflozin 25mg (N=224)**	**Sitagliptin 100ng (N=223)**
Mean baseline HbA_{1C} (%) ± SE	7.91 ± 0.05	7.87 ± 0.06	7.86 ± 0.06	7.85 ± 0.05
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.03 ± 0.07	7.22 ± 0.06	7.11 ± 0.06	7.33 ± 0.07
Adjusted mean change from baseline (%) ± SE	0.13 ± 0.06	-0.65 ± 0.06	-0.76 ± 0.06	-0.53 ± 0.06
Adjusted mean difference *vs* placebo (%) ± SE		-0.78 ± 0.08	-0.89 ± 0.08	-0.66 ± 0.08
[95% CI]		-0.94, -0.63	-1.04, -0.73	-0.82, -0.51
P value		<0.0001	<0.0001	<0.0001
Adjusted mean difference *vs* sitagliptin (%) ± SE		-0.12 ± 0.08	-0.22 ± 0.08	
[95% CI]		-0.28, 0.04	-0.38, -0.07	
P value		0.1310	0.0050	
	Placebo (N=228)	**Empagliflozin 10mg (N=224)**	**Empagliflozin 25mg (N=224)**	**Sitagliptin 100ng (N=223)**
Mean baseline body weight (kg) ± SE	78.23 ± 1.32	78.35 ± 1.25	77.80 ± 1.20	79.31 ± 1.37
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	77.79 ± 1.29	76.10 ± 1.21	75.36 ± 1.17	79.41 ± 1.37
Adjusted mean change from baseline (kg) ± SE	-0.43 ± 0.20	-2.24 ± 0.20	-2.45 ± 0.20	0.10 ± 0.20
Adjusted mean difference *vs* placebo (kg) ± SE		-1.81 ± 0.28	-2.02 ± 0.28	0.54 ± 0.28
[95% CI]		-2.35, -1.26	-2.56, -1.48	-0.01, 1.08
P value		<0.0001	<0.0001	0.0546
Adjusted mean difference *vs* sitagliptin (kg) ± SE		-2.34 ± 0.28	-2.56 ± 0.28	
[95% CI]		-2.89, -1.80	-3.10, -2.01	

P value		-	-	
	Placebo (N=228)	**Empagliflozin 10mg (N=224)**	**Empagliflozin 25mg (N=224)**	**Sitagliptin 100ng (N=223)**
Mean baseline SBP (mmHg) ± SE	130.4 ± 1.1	133.0 ± 1.1	129.9 ± 1.2	132.5 ± 1.1
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	130.0 ± 1.1	128.2 ± 1.0	126.4 ± 1.0	131.8 ± 1.1
Adjusted mean change from baseline (mmHg) ± SE	-0.7 ± 0.8	-4.1 ± 0.8	-4.2 ± 0.8	-0.3 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.4 ± 1.1	-3.4 ± 1.1	0.4 ± 1.1
[95% CI]		-5.5, -1.2	-5.6, -1.2	-1.8, 2.6
P value		0.025	0.0021	0.7241
Adjusted mean difference *vs* sitagliptin (mmHg) ± SE		-3.7 ± 1.1	-3.8 ± 1.1	
[95% CI]		-5.9, -1.6	-6.0, -1.6	
P value		-	-	
Background of pioglitazone (1245.19 roll-over)				
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**	
Mean baseline HbA_{1C} (%) ± SE	8.16 ± 0.07	8.07 ± 0.07	8.06 ± 0.06	
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.11 ± 0.09	7.47 ± 0.08	7.37 ± 0.07	
Adjusted mean change from baseline (%) ± SE	-0.01 ± 0.07	-0.61 ± 0.07	-0.70	
Adjusted mean difference *vs* placebo (%) ± SE		-0.59 ± 0.10	-0.69 ± 0.10	
[95% CI]		-0.79, -0.40	-0.88, -0.50	
P value		<0.0001	<0.0001	
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**	
Mean baseline body weight (kg) ± SE	78.10 ± 1.57	77.97 ± 1.49	78.93 ± 1.54	
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	78.60 ± 1.57	76.52 ± 1.47	77.71 ± 1.50	

Adjusted mean change from baseline (kg) ± SE	0.50 ± 0.26	-1.47 ± 0.26	-1.21 ± 0.26
Adjusted mean difference *vs* placebo (kg) ± SE		-1.97 ± 0.37	-1.71 ± 0.37
[95% CI]		-2.69, -1.24	-2.43, -0.99
P value		<0.0001	<0.0001
	Placebo (N=165)	**Empagliflozin 10mg (N=165)**	**Empagliflozin 25mg (N=168)**
Mean baseline SBP (mmHg) ± SE	125.7 ± 0.9	126.5 ± 1.1	125.9 ± 1.1
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	126.2 ± 1.1	124.7 ± 1.1	122.6 ± 1.0
Adjusted mean change from baseline (mmHg) ± SE	0.3 ± 0.9	-1.7 ± 0.9	-3.4 ± 0.9
Adjusted mean difference *vs* placebo (mmHg) ± SE		-2.0 ± 1.2	-3.7 ± 1.2
[95% CI]		-4.5, 0.4	-6.1, -1.3
P value		0.0987	0.0028
Background of metformin (1245.23 roll-over)			
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline HbA_{1C} (%) ± SE	7.90 ± 0.06	7.94 ± 0.05	7.86 ± 0.06
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	7.89 ± 0.07	7.30 ± 0.05	7.14 ± 0.06
Adjusted mean change from baseline (%) ± SE	-0.01 ± 0.05	-0.62 ± 0.05	-0.74 ± 0.05
Adjusted mean difference *vs* placebo (%) ± SE		-0.61 ± 0.07	-0.73 ± 0.07
[95% CI]		-0.75, -0.46	-0.88, -0.58
P value		<0.0001	<0.0001
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline body weight (kg) ± SE	79.73 ± 1.29	81.59 ± 1.26	82.21 ± 1.32
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	79.34 ± 1.30	79.19 ± 1.20	79.49 ± 1.25
Adjusted mean change from baseline (kg) ± SE	-0.46 ± 0.22	-2.39 ± 0.21	-2.65 ± 0.21

Adjusted mean difference *vs* placebo (kg) ± SE		-1.93 ± 0.30	-2.19 ± 0.30
[95% CI]		-2.52, -1.34	-2.79, -1.60
P value		<0.0001	<0.0001
	Placebo (N=207)	**Empagliflozin 10mg (N=217)**	**Empagliflozin 25mg (N=213)**
Mean baseline SBP (mmHg) ± SE	128.6 ± 1.0	129.6 ± 1.0	130.0 ± 1.0
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	128.1 ± 1.0	124.2 ± 0.9	125.3 ± 1.1
Adjusted mean change from baseline (mmHg) ± SE	-0.8 ± 0.8	-5.2 ± 0.8	-4.5 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-4.4 ± 1.1	-3.7 ± 1.1
[95% CI]		-6.6, -2.3	-5.9, -1.5
P value		<0.0001	0.0008
Background of metformin plus SU (1245.23 roll-over)			
	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline HbA_{1C} (%) ± SE	8.15 ± 0.06	8.07 ± 0.05	8.10 ± 8.10
Mean HbA_{1C} at week 76 (%) ± SE – FAS (LOCF)	8.11 ± 0.08	7.34 ± 0.06	7.38 ± 0.06
Adjusted mean change from baseline (%) ± SE	-0.03 ± 0.06	-0.74 ± 0.06	-0.72 ± 0.06
Adjusted mean difference *vs* placebo (%) ± SE		-0.72 ± 0.08	-0.69 ± 0.08
[95% CI]		-0.87, -0.56	-0.85, -0.53
P value		<0.0001	<0.0001
	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline body weight (kg) ± SE	76.23 ± 1.13	77.08 ± 1.22	77.50 ± 1.28
Mean body weight at week 76 (kg) ± SE – FAS (LOCF)	75.63 ± 1.12	74.62 ± 1.22	75.20 ± 1.27
Adjusted mean change from baseline (kg) ± SE	-0.63 ± 0.19	-2.44 ± 0.19	-2.28 ± 0.20
Adjusted mean difference *vs* placebo (kg) ± SE		-1.81 ± 0.27	-1.64 ± 0.27

[95% CI]		-2.34, -1.27	-2.18, -1.11
P value		<0.0001	<0.0001
	Placebo (N=225)	**Empagliflozin 10mg (N=225)**	**Empagliflozin 25mg (N=216)**
Mean baseline SBP (mmHg) ± SE	128.8 ± 1.0	128.7 ± 0.9	129.3 ± 1.0
Mean SBP at week 76 (mmHg) ± SE – FAS (LOCF)	127.3 ± 0.9	125.0 ± 0.9	125.4 ± 0.9
Adjusted mean change from baseline (mmHg) ± SE	-1.6 ± 0.7	-3.8 ± 0.7	-3.7 ± 0.7
Adjusted mean difference *vs* placebo (mmHg) ± SE		-2.2 ± 1.0	-2.1 ± 1.0
[95% CI]		-4.1, -0.3	-4.1, -0.2
P value		0.0213	0.0288

CI = confidence interval; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; SBP = systolic blood pressure; SE = standard error

Figure 18: Adjusted mean change from baseline (MMRM) in HbA1C (%) over time (1245.31 – monotherapy roll-over) – FAS (OC)

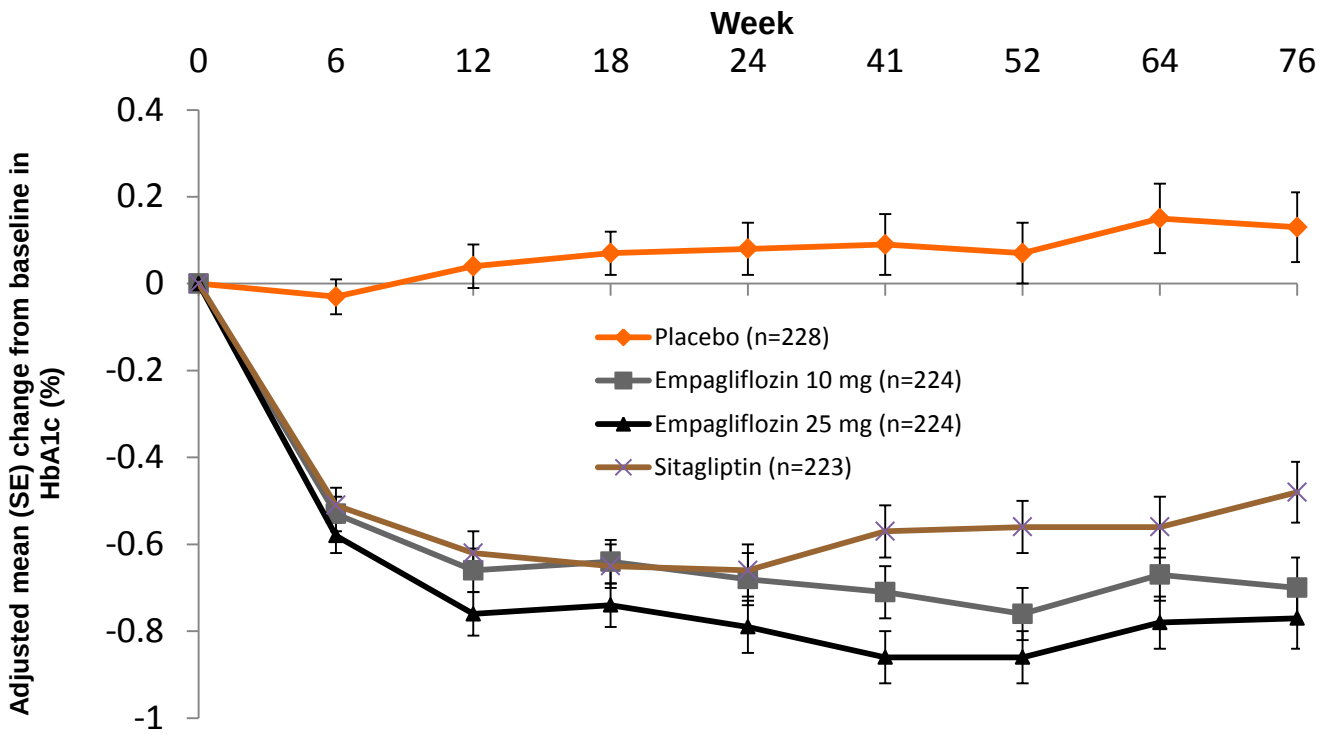


Figure 19: Adjusted mean change from baseline (MMRM) in HbA1C (%) over time (1245.31 – pioglitazone background roll-over) – FAS (OC)

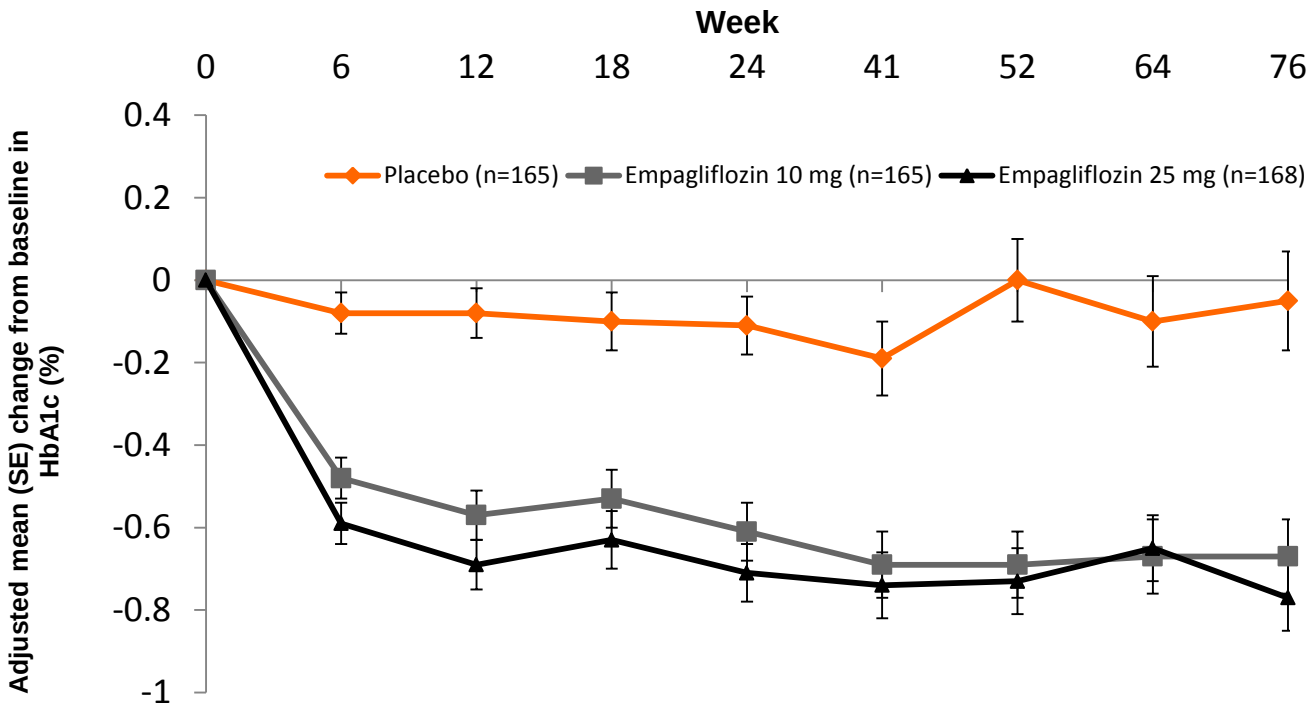


Figure 20: Adjusted mean change from baseline (MMRM) in HbA1C (%) over time (1245.31 – metformin background roll-over) – FAS (OC)

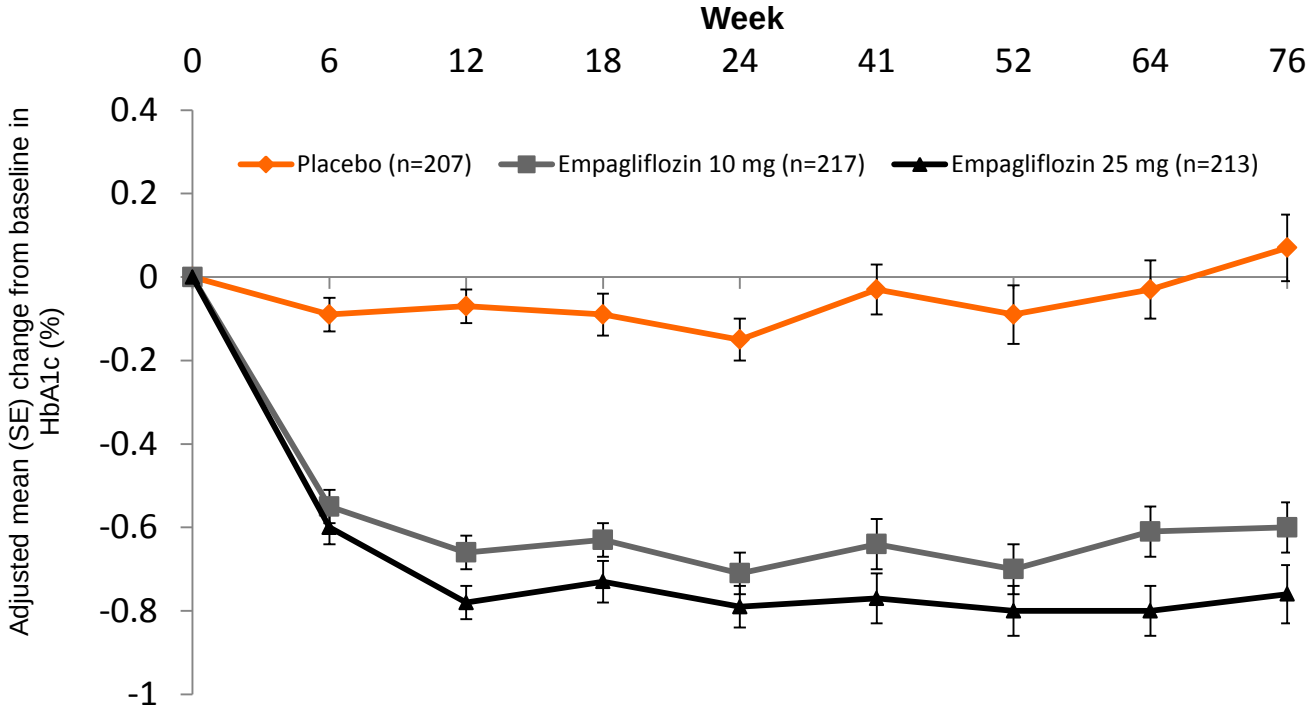
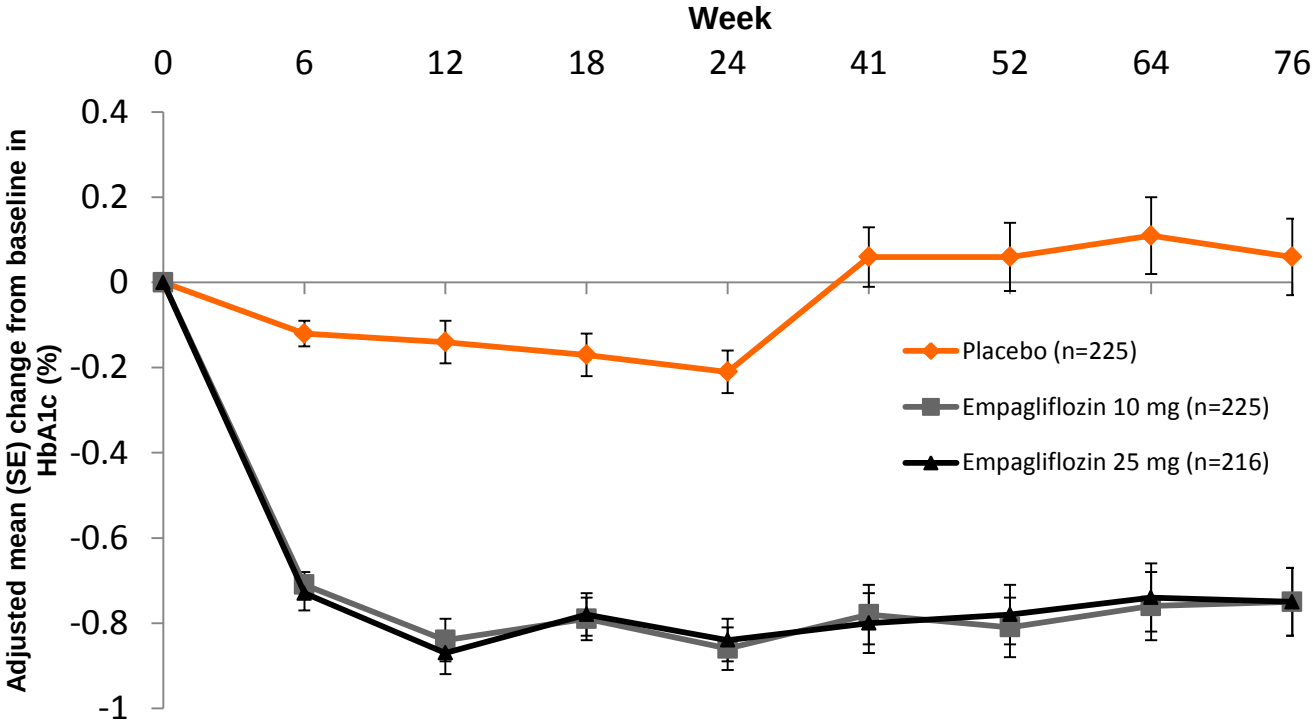


Figure 21: Adjusted mean change from baseline (MMRM) in HbA1C (%) over time (1245.31 – metformin plus SU background roll-over) – FAS (OC)



Empagliflozin as add-on combination to basal insulin with or without metformin and/or sulphonylureas (1245.33 – EMPA-REG BASAL)

The primary endpoint of study 1245.33 was the change from baseline in HbA_{1C} after 18 weeks of treatment. Key secondary endpoints included change from baseline in HbA_{1C} and basal insulin dose after 78 weeks. Change from baseline in FPG and body weight at weeks 18 and 78 were also measured. The changes from baseline in SBP and DBP at weeks 18 and 78 were included as exploratory endpoints (Table 21).

After 18 weeks, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.57 ± 0.07% in the empagliflozin 10 mg group and -0.71 ± 0.07% in the empagliflozin 25 mg group compared with -0.01 ± 0.07% in the placebo group. The adjusted mean ± SE treatment differences compared with placebo in HbA_{1C} were -0.56 ± 0.10% (95% CI: -0.78 to -0.33) and -0.70 ± 0.10% (95% CI: -0.93 to -0.47) in the empagliflozin 10 mg and 25 mg groups, respectively (P<0.0001 for both doses).

After 78 weeks, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.48 ± 0.08% and -0.64 ± 0.09% in the empagliflozin 10 mg and 25 mg groups, respectively. The adjusted mean ± SE treatment differences compared with placebo in HbA_{1C} were -0.46 ± 0.12% (97.5% CI: -0.73 to -0.19; P=0.0001) in the empagliflozin 10mg group and -0.62 ± 0.12% (97.5% CI: -0.90 to -0.34; P<0.0001) in the empagliflozin 25 mg group.

At week 78, adjusted mean ± SE treatment differences from baseline in basal insulin dose were -1.21 ± 1.48IU in the empagliflozin 10 mg group and -0.47 ± 1.59IU in the empagliflozin 25 mg group. The adjusted mean ± SE treatment differences compared with placebo in basal insulin dose were -6.66 ± 2.18IU (97.5% CI: -11.56 to -1.77; P=0.0024) and -5.92 ± 2.25 IU (97.5% CI: -11.00 to -0.85; P=0.0090) in the empagliflozin 10 mg and 25 mg groups, respectively.

A summary of the primary and secondary endpoints for study 1245.33 can be seen in Table 21. A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 22.

Table 21: Summary of primary and secondary endpoints in study 1245.33

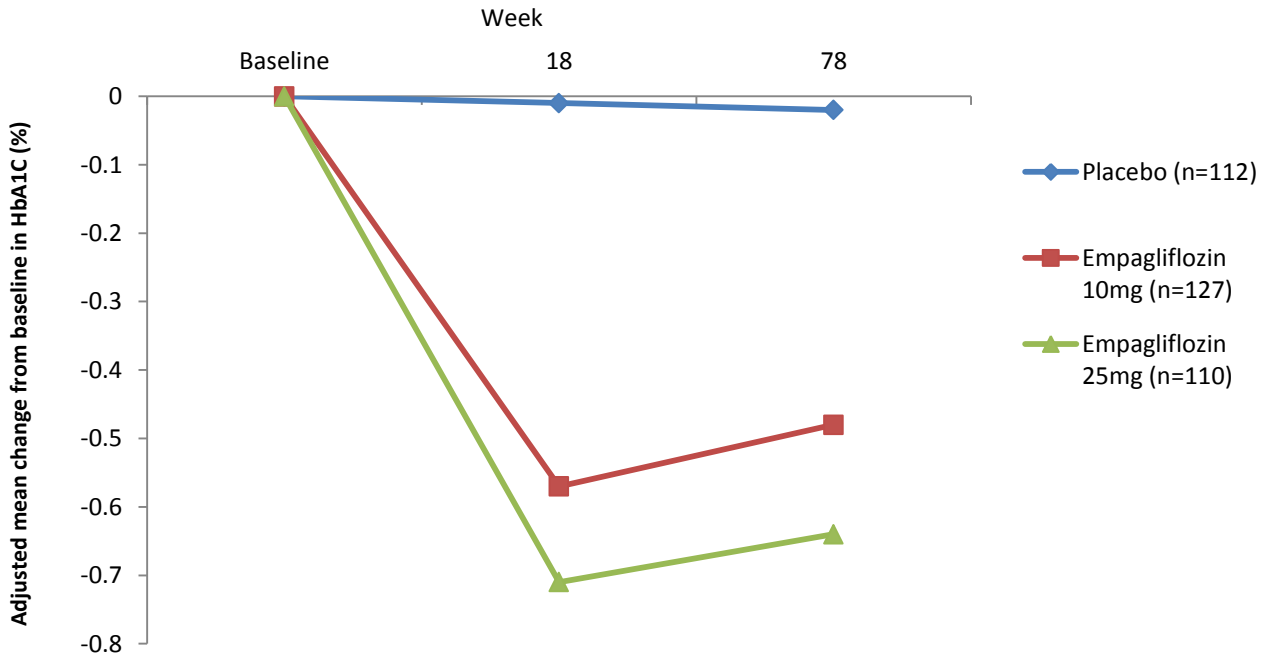
Efficacy Results			
	Placebo (n=125)	**Empagliflozin 10mg (n=132)**	**Empagliflozin 25mg (n=117)**
Mean baseline HbA_{1C} (%) ± SE	8.10 ± 0.07	8.26 ± 0.07	8.34 ± 0.08
Mean HbA_{1C} at week 18 (%) ± SE – FAS18-completers (LOCF-18)	8.13 ± 0.10	7.68 ± 0.09	7.59 ± 0.08
Adjusted mean change from baseline (%) ± SE	-0.01 ± 0.07	-0.57 ± 0.07	-0.71 ± 0.07
Adjusted mean difference *vs* placebo (%) ± SE		-0.56 ± 0.10	-0.70 ± 0.10
[97.5% CI]		[-0.78, -0.33]	[-0.93, -0.47]
P value		<0.0001	<0.0001
	Placebo (n=112)	**Empagliflozin 10mg (n=127)**	**Empagliflozin 25mg (n=110)**
Mean baseline basal insulin dose (IU) ± SE	47.84 ± 3.11	45.13 ± 2.62	48.43 ± 2.79
Mean basal insulin dose at week 78 (IU) ± SE – FAS78-completers (LOCF-78)	52.63 ± 2.97	44.43 ± 2.27	48.04 ± 2.83
Adjusted mean change from baseline (IU) ± SE	5.45 ± 1.58	-1.21 ± 1.48	-0.47 ± 1.59
Adjusted mean difference *vs* placebo (IU) ± SE		-6.66 ± 2.18	-5.92 ± 2.25
[97.5% CI]		[-11.56, -1.77]	[-11.00, -0.85]
P value		0.0024	0.0090
	Placebo (n=112)	**Empagliflozin 10mg (n=127)**	**Empagliflozin 25mg (n=110)**
Mean baseline HbA_{1C} (%) ± SE	8.09 ± 0.07	8.27 ± 0.07	8.29 ± 0.08
Mean HbA_{1C} at week 78 (%) ± SE – FAS78-completers (LOCF-78)	8.14 ± 0.11	7.76 ± 0.08	7.62 ± 0.09
Adjusted mean change from baseline (%) ± SE	-0.02 ± 0.09	-0.48 ± 0.08	-0.64 ± 0.09
Adjusted mean difference *vs* placebo (%) ± SE		-0.46 ± 0.12	-0.62 ± 0.12
[97.5% CI]		[-0.73, -0.19]	[-0.90, -0.34]
P value		0.0001	<0.0001

	Placebo (n=141)	Empagliflozin 10mg (n=148)	Empagliflozin 25mg (n=125)
Mean baseline body weight (kg) ± SE	90.53 ± 1.81	91.63 ± 1.57	94.69 ± 1.77
Mean body weight at week 18 (kg) ± SE – FAS (OC)	90.03 ±1.91	89.41 ± 1.62	93.42 ± 2.49
Adjusted† mean change from baseline (kg) ± SE	-0.05 ± 0.68	-2.09 ± 0.66	-0.92 ± 0.72
Adjusted mean difference *vs* placebo (kg) ± SE		-2.04 ± 0.95	-0.87 ± 0.99
[95% CI]		[-3.90, 0.18]	[-2.81, 1.08]
P value		0.0320	0.3818
	Placebo (n=100)	**Empagliflozin 10mg (n=113)**	**Empagliflozin 25mg (n=96)**
Mean body weight at week 78 (kg) ± SE – FAS (OC)	86.90 ± 2.54	88.22 ± 1.85	92.22 ± 2.17
Adjusted† mean change from baseline (kg) ± SE	1.16 ± 0.80	-2.47 ± 0.76	-1.96 ± 0.82
Adjusted mean difference *vs* placebo (kg) ± SE		-3.63 ± 1.10	-3.12 ± 1.15
[95% CI]		[-5.81, -1.45]	[-5.39, -0.85]
P value		0.0012	0.0073
	Placebo (n=170)	**Empagliflozin 10mg (n=169)**	**Empagliflozin 25mg (n=155)**
Mean baseline SBP (mmHg) ± SE	133.9 ± 1.3	132.4 ± 1.2	132.8 ± 1.2
Mean SBP at week 18 (mmHg) ± SE – FAS (LOCF)	133.2 ± 1.2	129.0 ± 1.0	129.6 ± 1.2
Adjusted mean change from baseline (mmHg) ± SE	-0.3 ± 0.9	-3.7 ± 0.9	-3.3 ± 1.0
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.4 ± 1.3	-3.0 ± 1.4
[95% CI]		[6.0, -0.8]	[-5.7, -0.4]
P value		0.0111	0.0267

	Placebo (n=170)	Empagliflozin 10mg (n=169)	Empagliflozin 25mg (n=155)
Mean SBP at week 78 (mmHg) ± SE – FAS (LOCF)	133.5 ± 1.3	128.6 ± 1.1	130.6 ± 1.3
Adjusted mean change from baseline (mmHg) ± SE	0.1 ± 1.0	-4.1 ± 1.0	-2.4 ± 1.1
Adjusted mean difference *vs* placebo (mmHg) ± SE		-4.2 ± 1.4	-2.4 ± 1.5
[95% CI]		[-7.0, -1.3]	[-5.4, 0.5]
P value		0.0040	0.0987

† MMRM adjusted results over time
CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; IU = international units; LOCF = last observation carried forward; MDG = mean daily glucose; MMRM = mixed model repeated measures; OC = observed cases; SBP = systolic blood pressure; SE = standard error

Figure 22: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.33) – FAS (LOCF)



Empagliflozin in patients with renal impairment (1245.36 – EMPA-REG RENAL)

The primary endpoint of study 1245.36 was the change from baseline in HbA_{1C} at 24 weeks in patients with T2DM and renal impairment.

At week 24, adjusted mean ± SE treatment differences from baseline in HbA_{1C} for subjects with mild renal impairment were -0.46 ± 0.07% in the empagliflozin 10 mg group and -0.63 ± 0.07% in the empagliflozin 25 mg group, compared with 0.06 ± 0.07% in the placebo group. The difference to placebo for the adjusted mean ± SE change in HbA1c from baseline at Week 24 was -0.52 ± 0.10% (95% CI: -0.72, -0.32) for the empagliflozin 10 mg group and -0.68 ± 0.10% (95% CI: -0.88, -0.49) for the empagliflozin 25 mg group (p<0.0001 for both doses) (Table 22). A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 23 .

At week 24 in the moderate renal impairment sub group, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.37 ± 0.05% in the empagliflozin 25mg group, compared with 0.05 ± 0.05% in the placebo group. The difference to placebo for the adjusted mean ± SE change in HbA_{1C} from baseline at week 24 was -0.42 ± 0.07% (95% CI: -0.56, -0.28; P<0.0001) (Table 23). A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 24.

Table 22: Summary of primary and secondary endpoints in study 1245.36 (mild renal impairment)

Efficacy Results			
	Placebo (n=95)	**Empagliflozin 10 mg (n=98)**	**Empagliflozin 25 mg (n=97)**
Mean baseline HbA_{1C} (%) ± SE	8.09 ± 0.08	8.02 ± 0.09	7.96 ± 0.07
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF)	8.13 ± 0.12	7.57 ± 0.08	7.35 ± 0.08
Adjusted mean change from baseline (%) ± SE	0.06 ± 0.07	-0.46 ± 0.07	-0.63 ± 0.07
Adjusted mean difference vs placebo (%) ± SE		-0.52 ± 0.10	-0.68 ± 0.10
[95% CI]		[-0.72, -0.32]	[-0.88, -0.49]
P value		<0.0001	<0.0001
	Placebo (n=95)	**Empagliflozin 10 mg (n=98)**	**Empagliflozin 25 mg (n=97)**
Mean HbA_{1C} at week 52 (%) ± SE – FAS (LOCF)	8.12 ± 0.12	7.46 ± 0.09	7.38 ± 0.09
Adjusted mean change from baseline (%) ± SE	0.06 ± 0.08	-0.57 ± 0.08	-0.60 ± 0.08
Adjusted mean difference vs placebo (%) ± SE		-0.62 ± 0.12	-0.65 ± 0.12
[97.5% CI]		[-0.85, -0.39]	[-0.88, -0.42]
P value		<0.0001	<00.0001

	Placebo (n=95)	Empagliflozin 10 mg (n=98)	Empagliflozin 25 mg (n=97)
Mean baseline body weight (kg) ± SE	86.00 ± 2.05	92.05 ± 2.16	88.06 ± 2.20
Mean body weight at week 24 (kg) ± SE – FAS (LOCF)	85.72 ± 2.00	90.24 ± 2.13	85.72 ± 2.19
Adjusted mean change from baseline (kg) ± SE	-0.33 ± 0.24	-1.76 ± 0.23	-2.33 ± 0.23
Adjusted mean difference *vs* placebo (kg) ± SE		-1.43 ± 0.34	-2.00 ± 0.33
[95% CI]		[-2.09, -0.77]	[-2.66, -1.34]
P value		<0.0001	<0.0001
	Placebo (n=95)	**Empagliflozin 10 mg (n=98)**	**Empagliflozin 25 mg (n=97)**
Mean body weight at week 52 (kg) ± SE – FAS (LOCF)	85.64 ± 2.05	90.00 ± 2.12	85.43 ± 2.18
Adjusted mean change from baseline (kg) ± SE	-0.44 ± 0.32	-2.00 ± 0.32	-2.60 ± 0.32
Adjusted mean difference *vs* placebo (kg) ± SE		-1.56 ± 0.45	-2.16 ± 0.45
[95% CI]		[-2.45, -0.67]	[-3.05, -1.28]
P value			
	Placebo (n=95)	**Empagliflozin 10 mg (n=98)**	**Empagliflozin 25 mg (n=97)**
Mean baseline SBP (mmHg) ± SE	134.69 ± 1.75	137.37 ± 1.51	133.68 ± 1.80
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF)	135.51 ± 1.66	133.73 ± 1.43	129.77 ± 1.68
Adjusted mean change from baseline (mmHg) ± SE	0.65 ± 1.19	-2.92 ± 1.17	-4.47 ± 1.18
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.57 ± 1.67	-5.12 ± 1.67
[95% CI]		[-6.86, -0.29]	[-8.41, -1.82]
P value		0.0333	0.0024

	Placebo (n=95)	Empagliflozin 10 mg (n=98)	Empagliflozin 25 mg (n=97)
Mean SBP at week 52 (mmHg) ± SE – FAS (LOCF)	136.51 ± 1.60	134.69 ± 1.46	128.20 ± 1.68
Adjusted mean change from baseline (mmHg) ± SE	1.57 ± 1.32	-1.74 ± 1.30	-6.18 ± 1.30
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.31 ± 1.85	-7.75 ± 1.85
[95% CI]		[-6.96, 0.33]	[-11.40, -4.10]
P value		0.0745	<0.0001

CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; MDG = mean daily glucose; SBP = systolic blood pressure; SE = standard error

Figure 23: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.36 – mild renal impairment) – FAS (LOCF)

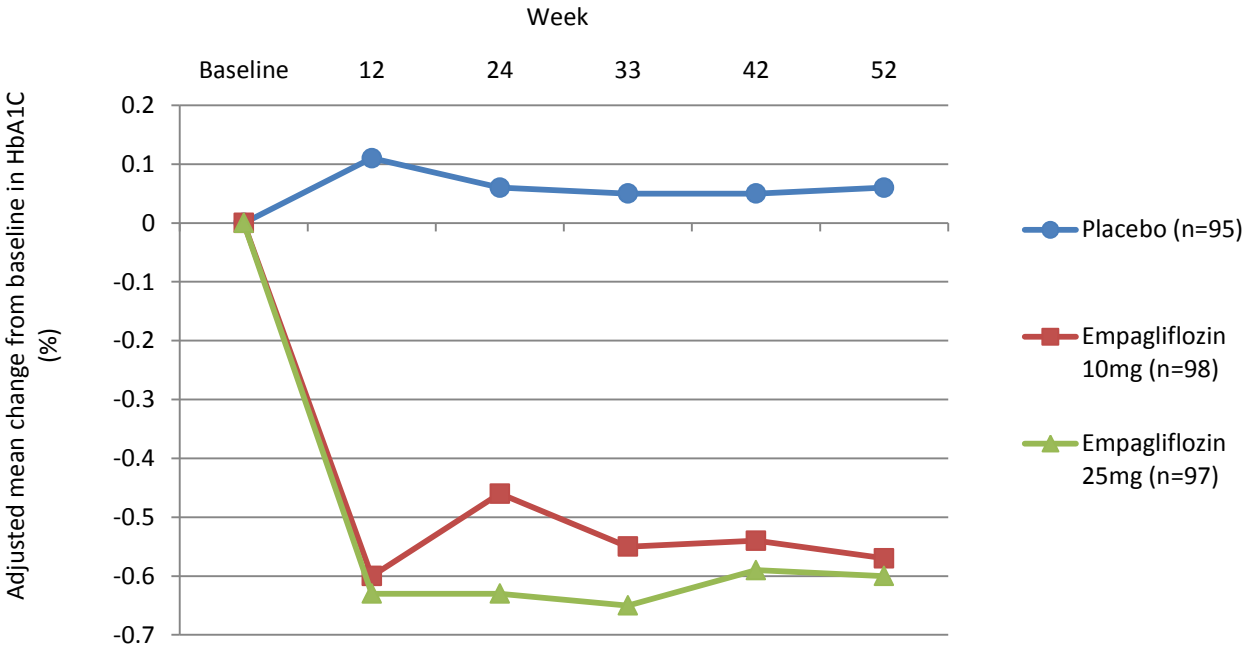


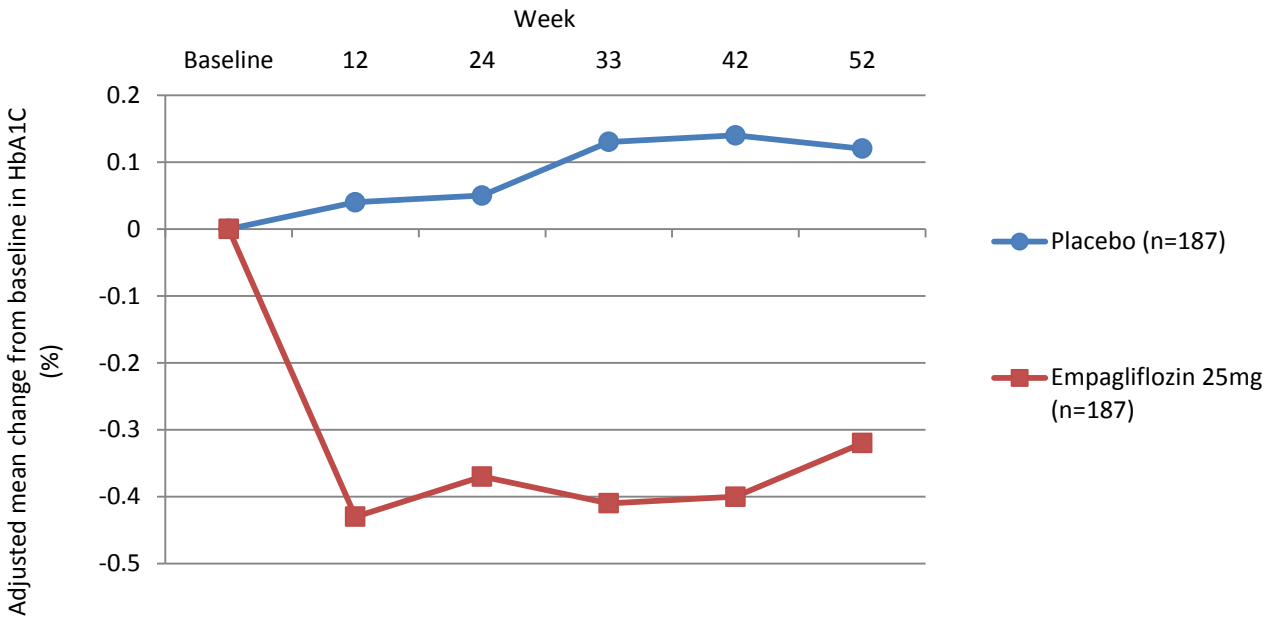
Table 23: Summary of primary and secondary endpoints in study 1245.36 (moderate renal impairment)

Efficacy Results		
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean baseline HbA_{1C} (%) ± SE	8.04 ± 0.06	8.03 ± 0.06
Mean HbA_{1C} at week 24 (%) ± SE – FAS (LOCF)	8.09 ± 0.07	7.66 ± 0.06
Adjusted mean change from baseline (%) ± SE	0.05 ± 0.05	-0.37 ± 0.05
Adjusted mean difference vs placebo (%) ± SE		-0.42 ± 0.07
[95% CI]		[-0.56, -0.28]
P value		<0.0001
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean HbA_{1C} at week 52 (%) ± SE – FAS (LOCF)	8.16 ± 0.07	7.71 ± 0.07
Change from baseline (%) ± SE	0.12 ± 0.06	-0.32 ± 0.06
Difference vs placebo (%) ± SE		-0.44 ± 0.08
[97.5% CI]		[-0.60, -0.29]
P value		<0.0001
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean baseline body weight (kg) ± SE	82.49 ± 1.32	83.22 ± 1.43
Mean body weight at week 24 (kg) ± SE – FAS (LOCF)	82.42 ± 1.33	82.23 ± 1.42
Adjusted mean change from baseline (kg) ± SE	-0.08 ± 0.18	-0.98 ± 0.18
Adjusted mean difference *vs* placebo (kg) ± SE		-0.91 ± 0.25
[95% CI]		[-1.41, -0.41]

P value		0.0004
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean body weight at week 52 (kg) ± SE – FAS (LOCF)	82.49 ± 1.32	82.04 ± 1.43
Adjusted mean change from baseline (kg) ± SE	0.00 ± 0.21	-1.17 ± 0.21
Adjusted mean difference *vs* placebo (kg) ± SE		-1.17 ± 0.30
[95% CI]		[-1.75, -0.59]
P value		<0.0001
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean baseline SBP (mmHg) ± SE	136.38 ± 1.34	136.64 ± 1.32
Mean SBP at week 24 (mmHg) ± SE – FAS (LOCF)	136.83 ± 1.28	132.71 ± 1.16
Adjusted mean change from baseline (mmHg) ± SE	0.40 ± 0.94	-3.88 ± 0.94
Adjusted mean difference *vs* placebo (mmHg) ± SE		-4.28 ± 1.32
[95% CI]		[-6.88, -1.68]
P *value*		0.0013
	Placebo (n=187)	**Empagliflozin 25 mg (n=187)**
Mean SBP at week 52 (mmHg) ± SE – FAS (LOCF)	135.38 ± 1.34	136.64 ± 1.32
Adjusted mean change from baseline (mmHg) ± SE	-0.79 ± 0.98	-5.06 ± 0.98
Adjusted mean difference *vs* placebo (mmHg) ± SE		-4.27 ± 1.39
[95% CI]		[-7.00, -1.53]
P *value*		0.0023

CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; MDG = mean daily glucose; SBP = systolic blood pressure; SE = standard error

Figure 24: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.36 – moderate renal impairment) – FAS (LOCF)



Empagliflozin in patients with hypertension (1245.48 – EMPA-REG BP)

The co-primary endpoints of study 1245.48 were changes from baseline in HbA_{1C} and mean 24-hour SBP after 12 weeks of treatment. The key secondary endpoint was the change from baseline in mean 24-hour DBP after 12 weeks. Other secondary endpoints included (all measured at 12 weeks): change from baseline in mean seated office SBP and DBP; proportion of patients with uncontrolled BP at baseline who had controlled BP (<130/80 mmHg); change from baseline in body weight.

At week 12, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.59 ± 0.04% in the empagliflozin 10mg group and -0.62 ± 0.04% in the empagliflozin 25 mg group, compared with 0.03 ± 0.04% in the placebo group. The difference compared to placebo for the adjusted mean ± SE change in baseline at 12 weeks was -0.62 ± 0.05% (95% CI: -0.72, -0.52) for the empagliflozin 10 mg group and -0.65 ± 0.05% (95% CI: -0.75 to -0.55) for the empagliflozin 25 mg group (P<0.0001 for both doses).

At week 12, the adjusted mean ± SE treatment difference from baseline in the co-primary endpoint of mean 24-hour SBP were -2.95 ± 0.48 mmHg in the empagliflozin 10 mg group and -3.68 ± 0.48 mmHg in the empagliflozin 25 mg group, compared with 0.48 ± 0.49mmHg in the placebo treatment group. Differences in the adjusted mean ± SE compared with placebo were -3.44 ± 0.69mmHg (95% CI: -4.78 to -2.09) and -4.16 ± 0.68 mmHg (95% CI: -5.50 to -2.83) in the empagliflozin 10 mg and empagliflozin 25 mg groups respectively (P<0.0001 for both doses).

A summary of the primary and secondary endpoints for study 1245.48 can be seen in Table 24. A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 25.

Table 24: Summary of primary and secondary endpoints in study 1245.48

Efficacy Results			
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline HbA_{1C} (%) ± SE	7.90 ± 0.04	7.87 ± 0.05	7.92 ± 0.04
Mean HbA_{1C} at week 12 (%) ± SE – FAS (LOCF)	7.93 ± 0.05	7.28 ± 0.04	7.29 ± 0.04
Adjusted mean change from baseline (%) ± SE	0.03 ± 0.04	-0.59 ± 0.04	-0.62 ± 0.04
Adjusted mean difference vs placebo (%) ± SE		-0.62 ± 0.05	-0.65 ± 0.05
[95% CI]		[-0.72, -0.52]	[-0.75, -0.55]
P value		<0.0001	<0.0001
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline 24-hour SBP (mmHg) ± SE	131.72 ± 0.72	131.34 ± 0.78	131.18 ± 0.73
Mean 24-hour SBP at week 12 (mmHg) ± SE – FAS (LOCF-H)	132.14 ± 0.71	128.35 ± 0.72	127.59 ± 0.68
Adjusted mean change from baseline (mmHg) ± SE	0.48 ± 0.49	-2.95 ± 0.48	-3.68 ± 0.48
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.44 ± 0.69	-4.16 ± 0.68
[95% CI]		[-4.78, -2.09]	[-5.50, -2.83]
P value		<0.0001	<0.0001
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline 24-hour DBP (mmHg) ± SE	75.16 ± 0.45	75.13 ± 0.50	74.64 ± 0.45
Mean 24-hour DBP at week 12 (mmHg) ± SE – FAS (LOCF-H)	75.46 ± 0.46	74.03 ± 0.48	73.33 ± 0.46
Adjusted mean change from baseline (mmHg) ± SE	0.32 ± 0.29	-1.04 ± 0.28	-1.40 ± 0.28
Adjusted mean difference *vs* placebo (mmHg) ± SE		-1.36 ± 0.40	-1.72 ± 0.40
[95% CI]		[-2.15, -0.56]	[-2.51, -0.93]
P value		0.0008	<0.0001

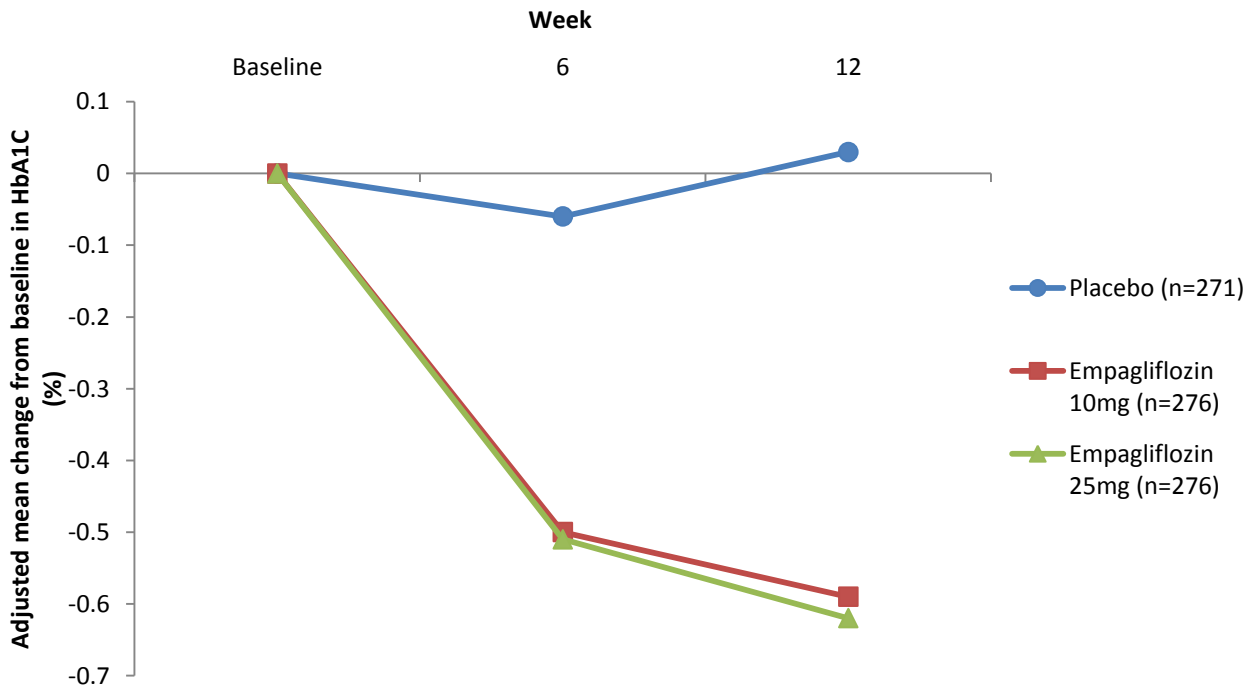
	Placebo (n=271)	Empagliflozin 10 mg (n=276)	Empagliflozin 25 mg (n=276)
Mean baseline body weight (kg) ± SE	95.22 ± 1.06	94.71 ± 1.19	95.59 ± 1.05
Mean body weight at week 12 (kg) ± SE – FAS (LOCF)	95.03 ± 1.07	93.04 ± 1.17	93.43 ± 1.02
Adjusted mean change from baseline (kg) ± SE	-0.18 ± 0.13	-1.68 ± 0.13	-2.16 ± 0.13
Adjusted mean difference *vs* placebo (kg) ± SE		-1.49 ± 0.18	-1.98 ± 0.18
[95% CI]		[-1.85, -1.13]	[-2.33, -1.62]
P value		<0.0001	<0.0001
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline daytime mean SBP (ABPM) (mmHg) ± SE	136.06 ± 0.73	135.25 ± 0.78	135.11 ± 0.74
Mean daytime mean SBP (ABPM) at week 12 (mmHg) ± SE – FAS (LOCF-H)	136.44 ± 0.74	131.85 ± 0.73	130.99 ± 0.70
Adjusted mean change from baseline (mmHg) ± SE	0.53 ± 0.51	-3.42 ± 0.51	-4.25 ± 0.51
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.94 ± 0.73	-4.78 ± 0.72
[95% CI]		[-5.37, -2.52]	[-6.20, -3.36]
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline daytime mean DBP (ABPM) (mmHg) ± SE	78.68 ± 0.47	78.37 ± 0.51	77.93 ± 0.48
Mean daytime mean DBP (ABPM) at week 12 (mmHg) ± SE – FAS (LOCF-H)	78.94 ± 0.49	77.09 ± 0.50	76.35 ± 0.49
Adjusted mean change from baseline (mmHg) ± SE	0.32 ± 0.31	-1.24 ± 0.31	-1.67 ± 0.31
Adjusted mean difference *vs* placebo (mmHg) ± SE		-1.56 ± 0.44	-1.98 ± 0.44
[95% CI]		[-2.42, -0.69]	[-2.84, -1.12]

	Placebo (n=271)	Empagliflozin 10 mg (n=276)	Empagliflozin 25 mg (n=276)
Mean baseline night-time mean SBP (ABPM) (mmHg) ± SE	123.09 ± 0.83	123.52 ± 0.88	123.30 ± 0.83
Mean night-time mean SBP (ABPM) at week 12 (mmHg) ± SE – FAS (LOCF-H)	123.60 ± 0.77	121.29 ± 0.83	120.83 ± 0.79
Adjusted mean change from baseline (mmHg) ± SE	0.41 ± 0.57	-2.10 ± 0.57	-2.50 ± 0.57
Adjusted mean difference *vs* placebo ± SE		-2.50 ± 0.81	-2.90 ± 0.81
[95% CI]		[-4.09, -0.91]	[-4.48, -1.32]
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline night-time mean DBP (ABPM) (mmHg) ± SE	68.17 ± 0.53	68.66 ± 0.57	68.04 ± 0.50
Mean night-time mean DBP (ABPM) at week 12 (mmHg) ± SE – FAS (LOCF-H)	68.54 ± 0.47	67.86 ± 0.54	67.30 ± 0.51
Adjusted mean change from baseline (mmHg) ± SE	0.31 ± 0.35	-0.65 ± 0.35	-0.84 ± 0.35
Adjusted mean difference *vs* placebo (mmHg) ± SE		-0.95 ± 0.50	-1.15 ± 0.50
[95% CI]		[-1.93, 0.03]	[-2.12, -0.18]
	Placebo (n=271)	**Empagliflozin 10 mg (n=276)**	**Empagliflozin 25 mg (n=276)**
Mean baseline trough mean sitting SBP (mmHg) ± SE	141.98 ± 0.75	142.32 ± 0.73	141.87 ± 0.76
Mean trough mean sitting SBP at week 12 (mmHg) ± SE – FAS (LOCF-H)	141.41 ± 0.91	137.59 ± 0.81	136.42 ± 0.86
Adjusted mean change from baseline (mmHg) ± SE	-0.67 ± 0.70	-4.60 ± 0.69	-5.47 ± 0.69
Adjusted mean difference *vs* placebo (mmHg) ± SE		-3.92 ± 0.99	-4.80 ± 0.98
[95% CI]		[-5.86, -1.98]	[-6.73, -2.87]
P value		<0.0001	<0.0001

	Placebo (n=271)	Empagliflozin 10 mg (n=276)	Empagliflozin 25 mg (n=276)
Mean baseline trough mean sitting DBP (mmHg) ± SE	83.67 ± 0.43	84.13 ± 0.44	83.82 ± 0.41
Mean trough mean sitting DBP at week 12 (mmHg) ± SE – FAS (LOCF-H)	82.65 ± 0.47	80.96 ± 0.48	80.80 ± 0.48
Adjusted mean change from baseline (mmHg) ± SE	-1.13 ± 0.39	-3.06 ± 0.39	-3.02 ± 0.39
Adjusted mean difference *vs* placebo (mmHg) ± SE		-1.93 ± 0.55	-1.89 ± 0.55
[95% CI]		[-3.01, -0.84]	[-2.97, -0.82]
P value		0.0005	0.0006

ABPM = ambulatory blood pressure monitoring; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; LOCF = last observation carried forward; LOCF-H = LOCF without values following a change in antihypertensive therapy; SBP = systolic blood pressure; SE = standard error

Figure 25: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.48) – FAS (LOCF)



Empagliflozin add-on to multiple daily injections of insulin (1245.49 EMPA-REG MDI)

The primary endpoint of study 1245.49 was the change from baseline in HbA_{1C} after 18 week of treatment. The key secondary endpoints (all measured after 52 weeks) were: the change from baseline in total daily insulin dose, change from baseline in body weight and change from baseline in HbA_{1C}.

At week 18, adjusted mean ± SE treatment differences from baseline in HbA_{1C} were -0.94 ± 0.05% in the empagliflozin 10mg group and -1.02 ± 0.05% in the empagliflozin 25 mg group, compared with -0.50 ± 0.05% in the placebo treatment group. The differences compared to placebo for the adjusted mean ± SE were -0.44 ± 0.08% (97.5% CI: -0.61 to -0.27) for empagliflozin 10 mg and -0.52 ± 0.07% (97.5% CI: -0.69 to -0.35) for empagliflozin 25 mg (P<0.0001 for both doses).

After 52 weeks, adjusted mean ± SE treatment differences from baseline in total daily insulin dose were 1.33 ± 2.13 IU/day in the empagliflozin 10 mg group and -1.06 ± 2.14 IU/day in the empagliflozin 25 mg group, compared with 10.16 ± 2.16 IU/day in the placebo group. Compared with placebo adjusted mean ± SE changes from baseline at week 52 in daily insulin dose for empagliflozin were -8.83 ±3.05 IU/day (97.5% CI: -15.69, -1.97; P=0.0040) in the empagliflozin 10 mg group and -11.22 ± 3.05 IU/day (97.5% CI: -18.09, -4.36, P=0.0003) in the empagliflozin 25 mg treatment group.

After 52 weeks, adjusted mean ± SE treatment differences from baseline in body weight were -1.95 ± 0.36 kg in the empagliflozin group 10 mg and -2.04 ± 0.36 kg in the empagliflozin 25 mg group, compared with 0.44 ± 0.36 kg in the placebo treatment group. The differences compared to placebo for the adjusted mean ± SE change in baseline at week 18 were -2.39 ± 0.51 kg (97.5% CI: -3.54 to -1.24) in the empagliflozin 10 mg group and -2.48 ± 0.51 kg (97.5% CI: -3.63 to -1.33) in the empagliflozin 25 mg group (P<0.0001 for both doses).

The adjusted mean ± SE treatment differences from baseline after 52 weeks in HbA_{1C} were -1.18 ± 0.08% in the empagliflozin 10mg group and -1.27 ± 0.08% in the empagliflozin 25 mg, compared with -0.81 ± 0.08% in the placebo treatment group. Compared with placebo adjusted mean ± SE changes from baseline at week 52 were -0.38 ± 0.11% (97.5% CI: -0.62 to -0.13) in the empagliflozin 10 mg group and -0.46 ± 0.11% (97.5% CI: -0.70 to -0.22) in the empagliflozin 25 mg group (P<0.0001 for non-inferiority testing for both doses).

A summary of the primary and secondary endpoints for study 1245.49 can be seen in Table 25. A graphical presentation of changes in HbA_{1C} over time can be seen in Figure 26.

Table 25: Summary of primary and secondary endpoints in study 1245.49

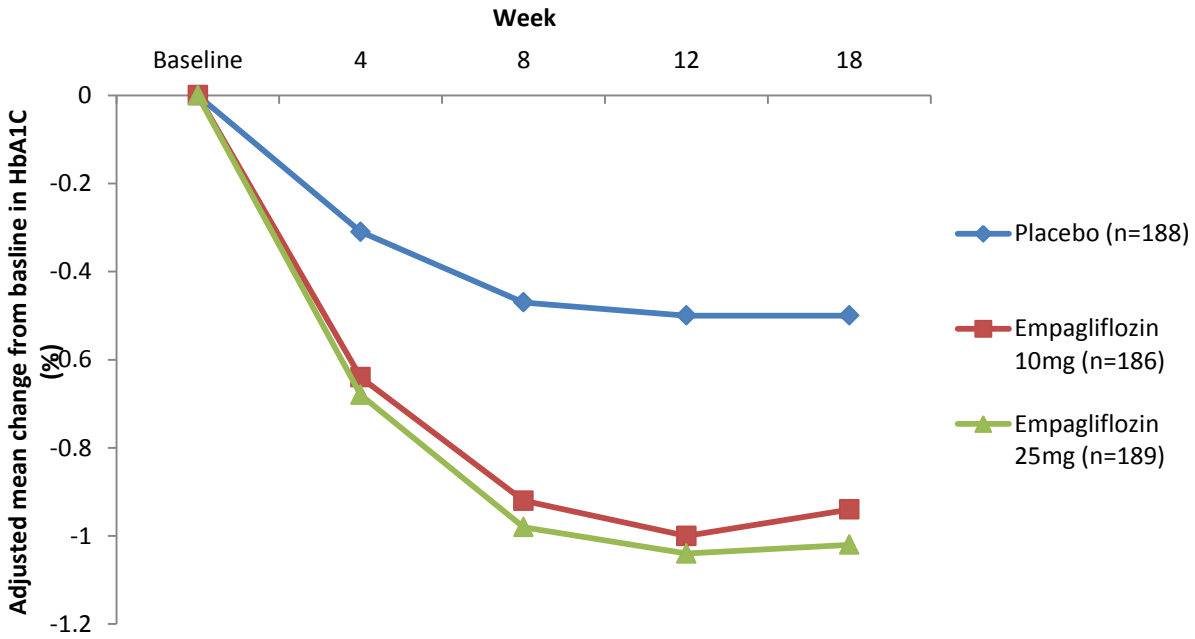
Efficacy Results			
	Placebo (n=188)	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Mean baseline HbA_{1C} (%) ± SE	8.33 ± 0.05	8.39 ± 0.05	8.29 ± 0.05
Mean HbA_{1C} at week 18 (%) ± SE – FAS (LOCF-18)	7.84 ± 0.07	7.44 ± 0.05	7.29 ± 0.06
Adjusted mean change from baseline (%) ± SE	-0.50 ± 0.06	-0.94 ± 0.06	-1.02 ± 0.06
Adjusted mean difference *vs* placebo (%) ± SE		-0.44 ± 0.08	-0.52 ± 0.07
[97.5% CI]		[-0.61, -0.27]	[-0.69, -0.35]
P value		<0.0001	<0.0001
	Placebo (n=115)	**Empagliflozin 10 mg (n=118)**	**Empagliflozin 25 mg (n=117)**
Mean baseline insulin total daily dose (IU) ± SE	89.94 ± 4.08	88.57 ± 90.43	90.38 ± 4.09
Mean insulin total daily dose at week 52 (IU) ± SE – PPS-completers-52 (LOCF-52)	99.48 ± 4.90	90.43 ± 4.03	89.38 ± 4.10
Adjusted mean change from baseline (IU) ± SE	10.16 ± 2.16	1.33 ± 2.13	-1.06 ± 2.14
Adjusted mean difference *vs* placebo (IU) ± SE		-8.83 ± 3.05	-11.22 ± 3.05
[97.5% CI]		[-15.69, -1.97]	[-18.09, -4.36]
P value		0.0040	0.0003
	Placebo (n=115)	**Empagliflozin 10 mg (n=119)**	**Empagliflozin 25 mg (n=118)**
Mean baseline body weight (kg) ± SE	96.34 ± 1.63	96.47 ± 1.53	95.37 ± 1.73
Mean body weight at week 52 (kg) ± SE – PPS-completers-52 (LOCF-52)	96.66 ± 1.72	94.57 ± 1.47	93.41 ± 1.72
Adjusted mean change from baseline (kg) ± SE	0.44 ± 0.36	-1.95 ± 0.36	-2.04 ± 0.36

Adjusted mean difference *vs* placebo (kg) ± SE		-2.39 ± 0.51	-2.48 ± 0.51
[97.5% CI]		[-3.54, -1.24]	[-3.63, -1.33]
P value		<0.0001	<0.0001
	Placebo (n=115)	**Empagliflozin 10 mg (n=119)**	**Empagliflozin 25 mg (n=118)**
Mean baseline HbA_{1C} (%) ± SE	8.25 ± 0.07	8.40 ± 0.07	8.37 ± 0.06
Mean HbA_{1C} at week 52 (%) ± SE – PPS-completers-52 (LOCF-52)	7.48 ± 0.09	7.19 ± 0.08	7.09 ± 0.08
Adjusted mean change from baseline (%) ± SE	-0.81 ± 0.08	-1.18 ± 0.08	-1.27 ± 0.08
Adjusted mean difference *vs* placebo (%) ± SE		-0.38 ± 0.11	-0.46 ± 0.11
[97.5% CI]		[-0.62, -0.13]	[-0.70, -0.22]
P value non-inferiority		<0.0001	<0.0001
	Placebo (n=188)	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Mean baseline SBP (mmHg) ± SE	132.6 ± 1.2	134.2 ± 1.2	132.9 ± 1.0
Mean SBP at week 18 (mmHg) ± SE – FAS (LOCF-18)	131.7 ± 1.1	130.2 ± 1.1	130.3 ± 1.0
Adjusted mean change from baseline (mmHg) ± SE	-1.2 ± 0.8	-3.6 ± 0.8	-2.9 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-2.4 ± 1.2	-1.7 ± 0.9
[95% CI]		[-4.7, -0.2]	[-3.9, 0.6]
P value		0.0366	0.1409
	Placebo (n=188)	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Mean SBP at week 52 (mmHg) ± SE – FAS (LOCF-52)	130.3 ± 1.0	129.8 ± 1.0	129.1 ± 1.0
Adjusted mean change from baseline (mmHg) ± SE	-2.6 ± 0.8	-3.9 ± 0.8	-4.0 ± 0.8
Adjusted mean difference *vs* placebo (mmHg) ± SE		-1.4 ± 1.1	-1.4 ± 1.1
[95% CI]		[-3.6, 0.9]	[-3.7, 0.8]
P value		0.2337	0.2097

CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; HbA_{1C} = glycated haemoglobin; IU = international units;

LOCF = last observation carried forward; PPS = per-protocol set; SBP = systolic blood pressure; SE = standard error

Figure 26: Adjusted mean change from baseline in HbA1C (%) ANCOVA results over time (1245.49) – FAS (LOCF)



Improvement in Health-Related Quality of Life (HRQoL)

Changes from baseline in EQ-5D and EQ-5D VAS were recorded in trials 1245.19, 20, 23, 28, 36 and 49. Analyses were performed in two phases using the trials with available data at the time of each analysis. In the first analysis (phase 1) the following four trials had available data and were included in the planned analyses: 1245.19, 1245.20, 1245.23, and 1245.36. The second analysis (phase 2), included trials 1245.28 and 1245.49, performed individual trial analyses and updated the pooled analyses that include all trials comparing empagliflozin with placebo.(42)

The mean EQ-5D utility index score at baseline was comparable across the six trials – ranging from 0.791 to 0.813 – with lowest values occurring in the add-on to MDI insulin trial (1245.49). The individual EQ-5D domain items were well balanced across all treatment arms in all studies. Baseline results indicate that across all six trial populations a considerable proportion of patients reported no problems (corresponding to a score of 1) with self-care or usual activities (95.7% to 97.4%). The most commonly reported problem was pain/discomfort, with 31% to 35% of patients reporting at least moderate pain or discomfort in each of the trials with a slightly higher percentage of patients in the dedicated renal impairment trial (1245.36).

Across all six trials the addition of empagliflozin did not result in clinically meaningful reductions in quality of life compared with placebo, with baseline EQ-5D utility index scores being maintained throughout the trials.(42) Changes from baseline in EQ-5D utility index scores at 24 weeks were negligible in all six trials and at 52 weeks in the dedicated renal impairment trial (1245.36) and the add-on to MDI insulin trial (1245.49). The results from the analysis of pooled data are presented in Table 26.

Table 26: Change from baseline EQ-5D utility index score by treatment and visit (pooled data)(42)

Study week	Change from baseline EQ-5D utility index score; mean (95% CI)			
	Placebo (*N*=1286)	Empagliflozin 10mg (*N*=1082)	Empagliflozin 25mg (*N*=1289)	Empagliflozin 10mg and 25mg (*N*=2371)
Week 4	-0.017 (-0.044, 0.010)	-0.011 (-0.035, 0.013)	-0.004 (-0.029, 0.021)	-0.008 (-0.025, 0.009)
Week 6	0.008 (-0.000, 0.017)	0.013 (0.004, 0.021)	0.011 (0.003, 0.019)	0.012 (0.006, 0.018)
Week 12	0.007 (-0.002, 0.015)	0.007 (-0.002, 0.017)	0.013 (0.004, 0.021)	0.010 (0.004, 0.016)
Week 18	0.011 (-0.017, 0.038)	0.020 (-0.002, 0.043)	-0.008 (-0.035, 0.018)	0.006 (-0.012, 0.023)
Week 24	0.0006 (-0.004, 0.015)	0.008 (-0.001, 0.018)	0.008 (-0.001, 0.018)	0.008 (0.002, 0.015)
Week 40	-0.010 (-0.044, 0.025)	-0.003 (-0.028, 0.021)	-0.016 (-0.045, 0.013)	-0.010 (-0.029, 0.009)
Week 52	-0.022 (-0.039, -0.004)	0.014 (-0.010, 0.037)	-0.007 (-0.025, 0.011)	0.000 (-0.014, 0.015)

Source data: Project 0303126: BI Empagliflozin QOL and HCRU Table 5.1
EQ-5D = EuroQoL 5 Dimensions; CI = Confidence Interval

No differences in EQ-5D utility index score were evident across the levels of any of the stratification variables assessed:

- Age
- Sex
- BMI
- Country
- Blood pressure
- HbA1c level at baseline
- eGFR at baseline
- Prior CV events
- Time since diagnosis of T2DM (years)
- Race
- CV risk predictor.

Similar results were found when HRQoL was assessed using the EQ-5D VAS. In all trials change from baseline EQ-5D VAS was similar across all treatment groups at all time points.(42)

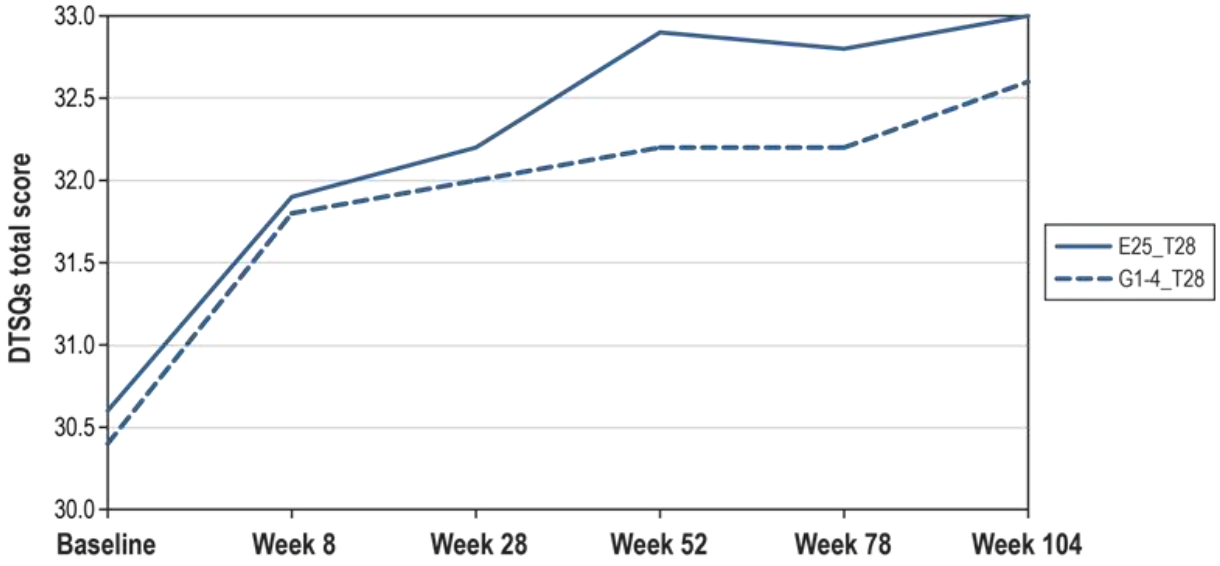
Diabetes Treatment Satisfaction Questionnaire

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is a diabetes-specific instrument designed to assess a patient's satisfaction with treatment, in contrast to the EQ-5D, which is a general health instrument measuring the impact of any disease on a patient's quality of life. The DTSQ consists of a six-item scale assessing treatment satisfaction, with possible total scores ranging from 0 (very dissatisfied) to 36 (very satisfied). Two additional items assess perceived frequency of hyperglycaemia and hypoglycaemia, with scores ranging from 0 (never) to 6 (always).(43)

Together with the Well-Being Questionnaire, the DTSQ has been recommended by the World Health Organisation (WHO) and the IDF as useful in assessing outcomes of diabetes care.(44) The DTSQ results were captured and analysed descriptively (no statistical tests were conducted) in study 1245.28.

At baseline, patients reported a relatively high treatment satisfaction (DTSQ total score >30). The mean baseline DTSQ score was 30.6 in the empagliflozin group and 30.4 in the glimepiride group. Only minor changes in mean DTSQ score from baseline to week 104 were observed (Figure 27). The change from baseline in DTSQ score was slightly larger for empagliflozin than glimepiride, suggesting an increased treatment satisfaction with empagliflozin over glimepiride.(42)

Figure 27: Observed mean DTSQ total score from baseline to week 104(42)



DTSQ = Diabetes Treatment Satisfaction Questionnaire; E25_T28: empagliflozin; G1-4_T28 = glimepiride.

6.6 Meta-analysis

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

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

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

A network meta-analysis was conducted for this submission and presented in Section 6.7.

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

N/A

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

N/A

6.7 *Indirect and mixed treatment comparisons*

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

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

Given the absence of head to head comparisons with treatments outlined within the decision problem it was necessary to conduct an indirect comparison.

The objective of the analysis was to estimate the effectiveness of empagliflozin in combination with metformin, metformin and SU, metformin and TZD and insulin. The main comparators for each background treatment are identified in Table 27. The rationales for the choices are outlined in section A. The doses included are the licensed doses for the full populations.

Table 27: Treatments included in NMA

Background Treatment	Comparator
• Metformin	• Dapagliflozin 10mg • Canagliflozin 100mg • Canagliflozin 300mg • Sitagliptin 100mg
• Metformin and SU	• Canagliflozin 100mg • Canagliflozin 300mg • Sitagliptin 100mg
• Metformin and TZD	• Canagliflozin 100mg • Canagliflozin 300mg • Sitagliptin 100mg
• Insulin	• Dapagliflozin 10mg • Canagliflozin 100mg • Canagliflozin 300mg • Sitagliptin 100mg

SU = sulphonylureas; TZD = thiazolidinediones

The search will also include all DPP-4is to identify any additional data on outcomes.

The empagliflozin trial program collected mainly data from 24 weeks (1245.19, 1245.23, and 1245.36). However, in an attempt to identify all relevant data for comparisons this was changed to 24 ± 4 weeks. In addition, comparisons at 52 ± 4 weeks were also included. It should be noted that the search was conducted until December 2013. Therefore, data from the 1245.31 and 41 trials would not normally be included; however, this was the only long term data available.

The outcomes identified for inclusion were based on the needs of the economic model and also from previous indirect comparisons conducted for the dapagliflozin appraisal. A summary of the outcomes extracted from the studies are presented in Table 28. Change in high- and low-density lipoprotein was not included as an outcome because a pilot search indicated that this outcome was not available and there has been no indication that the identified treatments had any clinical significant impact on this outcome measure. The change in body weight from baseline was measured in kilograms rather than change in BMI due to the structure of the model and availability of this outcome measure.

Table 28: Outcomes extracted

Background Treatment	Outcomes
Clinical	• HbA_{1C} change from baseline • SBP change from baseline • Body weight change from baseline
Safety	• Hypoglycaemia (non-severe) • Hypoglycaemiea (severe) • UTIs • Genital infections

HbA_{1C} = glycated haemoglobin; SBP = systolic blood pressure; UTIs=urinary tract infections;

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

Details of the identification of the studies used to carry out the indirect treatment comparison can be seen in Section 6.1.

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

The studies included in the NMA along with the baseline characteristics of patients included in the can be seen in Table 29 and Table 30.

Table 29 lists studies with duration of at least 24 ± 4 weeks while Table 30 lists studies of at least 52 ± 4 weeks. Section 9.6, Appendix 6 shows the studies excluded from the NMA following full-text review. Data extraction tables can be found in Section 9.7, Appendix 7.

Network diagrams for the NMA can be seen below in Figure 28, Figure 29, Figure 30, Figure 31 and Figure 32.

Figure 28: Treatment network of RCTs comparing the considered interventions for T2DM patients no longer responding adequately to metformin

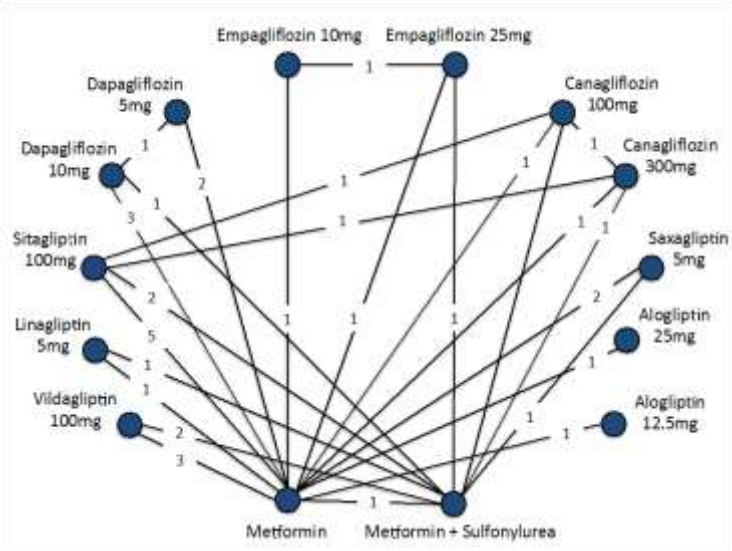


Figure 29: Treatment network of RCTs comparing the considered interventions for T2DM patients no longer responding adequately to metformin plus SU

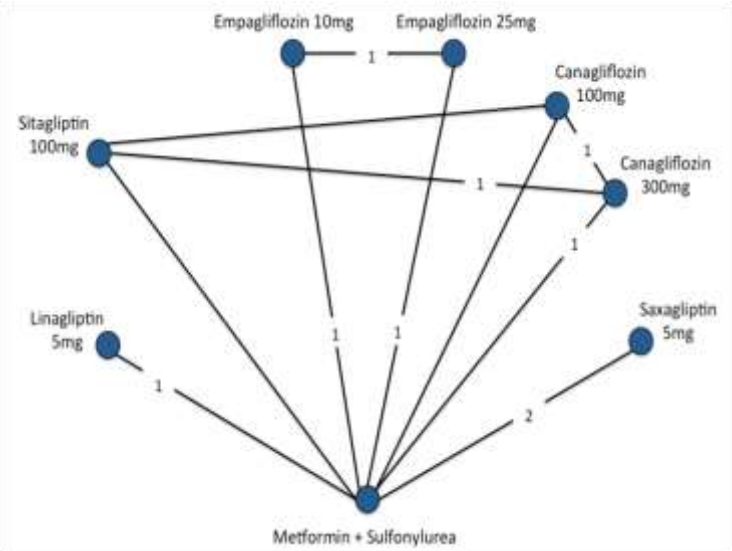
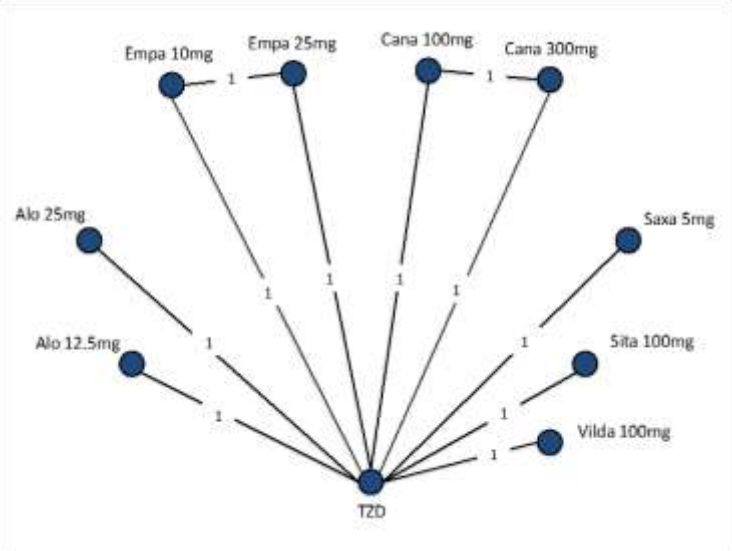
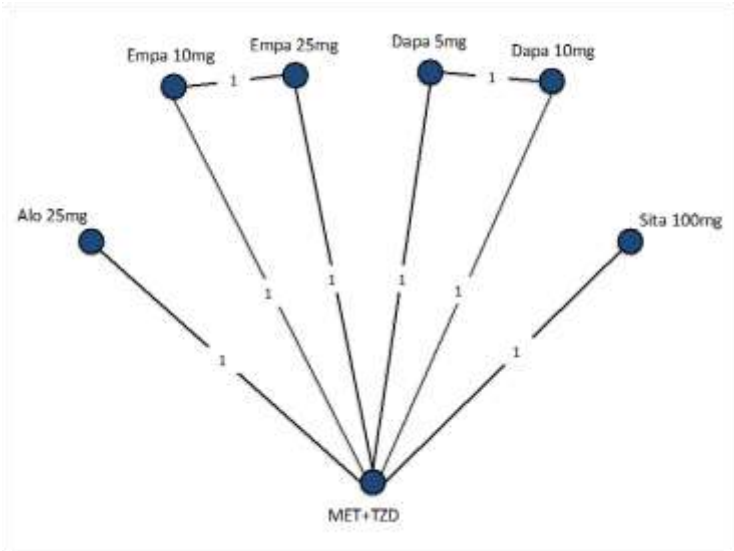


Figure 30: Treatment network of RCTs comparing the considered interventions for T2DM patients no longer responding adequately to TZDs



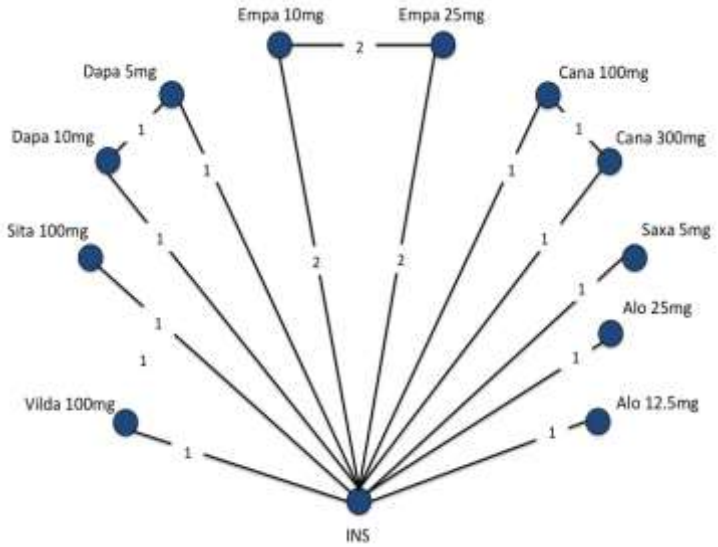
Alo = alogliptin; Empa = empagliflozin; Cana = canagliflozin; Saxa = saxagliptin; Sita = sitagliptin; TZD = thiazolidinediones; Vilda = vildagliptin

Figure 31: Treatment network of RCTs comparing the considered interventions for T2DM patients no longer responding adequately to TZDs and metformin



Alo = alogliptin; Dapa = dapagliflozin; Empa = empagliflozin; MET = metformin; Sita = sitagliptin; TZD = thiazolidinediones

Figure 32: Treatment network of RCTs comparing the considered interventions for T2DM patients no longer responding adequately to backbone insulin therapy plus other OADs



Alo = alogliptin; Cana = canagliflozin; Dapa = dapagliflozin; Empa = empagliflozin; INS = insulin therapy; MET = metformin; Saxa = saxagliptin; Sita = sitagliptin; Vilda = vildagliptin

Table 29: Study and patient characteristics of included trials (24 weeks)

Study	Interventions/Comparators	Age (years)	Male (%)	Mean Baseline HbA_{1C} (%)	Mean Body Weight (kg)	Total Sample Size
Second line						
BI GMBH (1245-23) 2012 (9)	Empagliflozin 10 mg + Met	55.5	57.6	7.9	81.6	638
	Empagliflozin 25 mg + Met	55.6	56.3	7.9	82.2	
	Placebo + Met	56	56	7.9	79.7	
BI GMBH (1245-28) 2013 (11)	Empagliflozin 25 mg + Met	NR	56.6	7.9	82.5	1545
	Placebo + Met +SU	NR	54	7.9	83	
Gallwitz et al. 2012 (45)	Linagliptin + Met	-	-	7.7	-	1551
	Met + SU	-	-	7.7	-	
Taskinen et al. 2011 (46)	Linagliptin + Met	56.5	53	8.1	82.2	701
	Placebo + Met	56.6	57	8	83.3	
Defronzo et al. 2009 (47)	Saxagliptin + Met	54.7	53.9	8.1	87.3	562
	Placebo + Met	54.8	53.6	8.1	87.1	
Goke et al. 2010(48)	Saxagliptin + Met	57.5	49.5	7.7	88.7	858
	Met + SU	57.6	54	7.7	88.6	
Yang et al. 2011 (49)	Saxagliptin + Met	53.8	48.1	7.9	68.9	570
	Placebo + Met	54.4	48.4	7.9	69	
Arechavaleta et al. 2011 (50)	Sitagliptin + Met	56.3	55	7.5	80.6	1,035
	Met + SU	56.2	53.8	7.5	82	
Charbonnel et al. 2006 (51)	Sitagliptin + Met	54.4	55.8	8	86.7	701
	Placebo + Met	54.7	59.5	8.9	89.6	
Nauck et al. 2007 (52)	Sitagliptin + Met	56.8	57.1	7.7	89.5	1091
	Met + SU	56.6	61.3	7.6	89.7	
Raz et al. 2008 (53)	Sitagliptin + Met	53.6	51	9.3	81.5	190
	Placebo + Met	56.1	41.5	9.1	81.2	
Scott et al. 2008 (54)	Sitagliptin + Met	55.2	55	7.8	83.1	273
	Placebo + Met	55.3	45	7.7	84.6	
Yang et al. 2012 (55)	Sitagliptin + Met	54.1	47	8.5	67.9	395
	Placebo + Met	55.1	55	8.5	68.9	
Charpentier et al. 2001 (56)	Met + SU	58.8	41	7.6	90.8	372
	Placebo + Met	60.7	54	7.6	83.1	
Bosi et al. 2007 (57)	Vildagliptin + Met	53.9	61.5	8.4	95.3	367
	Met	54.5	53.1	8.3	94.8	
Ferrannini et al 2009 (58)	Vildagliptin + Met	57.5	52.8	7.3	89	2789
	Met + SU	57.5	54.1	7.3	88.6	

Filozof et al 2010 (59)	Vildagliptin + Met	59.2	52.2	8.5	85.7	1007
	Met + SU	59.7	51.8	8.5	84.2	
Goodman et al 2009 (60)	Vildagliptin + Met	55	52.8	8.5	NR	372
	Met	54.5	67.2	8.7	NR	
Pan et al 2012 (61)	Vildagliptin + Met	54.2	50	8.1	71.6	290
	Met	54.5	45.8	8	69.8	
Janssen (DIA3009) 2013 (62)	Met + SU	56.2	52.1	7.8	86.6	1452
	Canagliflozin 100 mg + Met	56.2	52.1	7.8	86.6	
	Canagliflozin 300 mg + Met	56.2	52.1	7.8	86.6	
Janssen (DIA3006) 2013 (63)	Met	55.4	47.1	8	87	1284
	Sitagliptin + Met	55.4	47.1	8	87	
	Canagliflozin 100 mg + Met	55.4	47.1	8	87	
	Canagliflozin 300 mg + Met	55.4	47.1	8	87	
Bolinder et al 2012 (64)	Met	60.8	56	7.2	90.9	182
	Dapagliflozin 10 mg + Met	60.6	55.1	7.2	92.1	
Henry et al 2012a (65)	Met	52.7	46.6	9.1	87.2	419
	Dapagliflozin 10 mg + Met	51	50.2	9.1	88.4	
Henry et al 2012b (65)	Met	51.8	47.3	9.2	85.6	395
	Dapagliflozin 5 mg + Met	51.7	40.2	9.2	84.1	
Bailey et al 2010 (66)	Met	53.7	55	8.1	N/A	409
	Dapagliflozin 5 mg + Met	54.3	50	8.2	N/A	
	Dapagliflozin 10 mg + Met	52.7	57	7.9	N/A	
Nauck et al 2011 (67)	Met + SU	59	54.9	7.7	N/A	814
	Dapagliflozin 10 mg + Met	58	55.3	7.7	N/A	
Third Line						
Haring et al. 2013 (9)	Empagliflozin 10 mg + Met + SU	57	50.2	8.07	77.1	669
	Empagliflozin 25 mg + Met + SU	57.4	52.8	8.1	77.5	
	Placebo + Met + SU	56.9	49.8	8.15	76.2	
Owens et al. 2011 (68)	Linagliptin + Met + SU	58.3	46.8	8.15	76.5	1058
	Placebo + Met + SU	57.6	48.3	8.14	76.8	
Hermansen et al. 2007 (69)	Sitagliptin + Met + SU	55.6	52.7	8.34	86.5	882
	Placebo + Met + SU	56.5	53.4	8.34	85.9	
Moses et al. 2013 (70)	Saxagliptin + Met + SU	57.2	80	8.38	NR	257
	Placebo + Met + SU	56.8	74	8.19	NR	
Janssen (DIA3015) 2013 (63)	Sitagliptin + Met + SU	56.7	55.9	8.1	88.3	756
	Canagliflozin 300 mg + Met	56.7	51	8.1	88.3	
Janssen (DIA3002) 2013 (63)	Canagliflozin 100 mg + Met	56.7	51	8.13	92.6	469
	Canagliflozin 300 mg + Met	56.7	51	8.13	92.6	
	Placebo + Met + SU	56.7	51	8.13	92.6	

TZD failure						
Kovacs et al. 2012 (7)	TZD	54.6	44.2	8.2	74	499
	Met + TZD	54.6	44.2	8.2	79.5	
	Empagliflozin 10 mg + TZD	54.7	50.3	8.1	73.4	
	Empagliflozin 25 mg + TZD	54.2	50.6	7.9	72.6	
	Empagliflozin 10 mg + Met + TZD	54.7	50.3	8.1	79.4	
	Empagliflozin 25 mg + Met + TZD	54.2	50.6	8.1	81	
Rosenstock et al. 2012 (71)	TZD	53.5	51.1	8.3	86.4	420
	Dapagliflozin 5 mg + TZD	53.2	55.3	8.4	87.8	
	Dapagliflozin 10 mg + TZD	53.8	42.1	8.4	84.8	
Janssen (DIA3012) 2013 (63)	Met + TZD	57.4	63.2	7.9	94.1	344
	Canagliflozin 300 mg + Met	56.7	51	8.1	92.6	
	Placebo + Met + SU	56.7	51	8.1	92.6	
Pratley et al 2009 (72)	TZD	55.2	54.6	8	NR	493
	Alogliptin 12.5 mg + TZD	55.5	55.3	8.1	NR	
	Alogliptin 25 mg + TZD	55.4	62.8	8	NR	
Hollander et al 2009 (73)	TZD	54	46.2	8.2	80.9	565
	Saxagliptin 2.5 mg + TZD	54.9	54.4	8.3	82.1	
	Saxagliptin 5 mg + TZD	53.2	47.8	8.4	80.4	
Derosa et al 2010 (74)	MET + TZD	58	51.3	8.4	77.3	151
	Sitagliptin 100 mg + TZD	57	49.3	8.5	78.7	
Garber et al 2007 (75)	TZD	54.8	50.7	8.7	NR	463
	Vildagliptin 50 mg + TZD	54	54.8	8.6	NR	
	Vildagliptin 100 mg + TZD	54	44.9	8.7	NR	
Bosi et al 2011 (76)	MET + TZD	55.9	51.1	8.1	88	803
	Alogliptin 25 mg + MET + TZD	54.3	52	8.2	88.2	
Insulin failure						
BI GMBH (1245-49) 2013 (40)	INS	55.3	39.9	8.33	95.5	566
	Empagliflozin 10 mg + INS	56.7	52.2	8.39	96.7	
	Empagliflozin 25 mg + INS	58	44.2	8.29	95.9	
BI GMBH (1245-33) 2013 (12)	INS	58.1	52.9	8.18	90.46	494
	Empagliflozin 10 mg + INS	58.6	55	8.27	91.59	
	Empagliflozin 25 mg + INS	59.9	60	8.27	94.71	
Janssen (DIA3008) 2013 (63)	INS	62.8	66.5	8.3	NR	1718
	Canagliflozin 100 mg + INS	62.8	66.5	8.3	NR	
	Canagliflozin 300 mg + INS	62.8	66.5	8.3	NR	
	INS	58.8	49.2	8.47	94.5	807

Wilding et al 2012 (77)	Dapagliflozin 2.5 mg + INS	59.8	49.5	8.46	93	
	Dapagliflozin 5 mg + INS	59.3	47.4	8.62	93.3	
	Dapagliflozin 10 mg + INS	59.3	44.8	8.57	94.5	
	INS	55	48	9.3	91	390
Rosenstock et al 2009 (78)	Alogliptin 12.5 mg + INS	55.4	42	9.3	87.9	
	Alogliptin 25 mg + INS	55.9	34	9.3	86.7	
Barnett et al 2012 (79)	INS	57.3	45	8.6	86.2	455
	Saxagliptin + INS	57.2	40	8.7	87.7	
Vilsboll et al 2010 (80)	INS + Met	57.2	53	8.6	87.3	641
	Sitagliptin + INS	58.3	49	8.7	86.5	
Fonseca et al 2007 (81)	INS	58.9	54.6	8.4	95.1	296
	Vildagliptin + INS	59.6	47.9	8.4	94.5	

INS = insulin therapy; Met = metformin; SU = sulphonylurea; TZD = thiazolidinediones

Table 30: Study and patient characteristics of included trials (52 weeks)

Study	Interventions/Comparators	Age (years)	Male (%)	Mean Baseline HbA_{1C} (%)	Mean Body Weight (kg)	Sample Size
Second line						
BI GMBH (1245-28) 2013 (11)	Empagliflozin 25 mg + Met	NR	56.6	7.9	82.5	1545
	Placebo + Met +SU	NR	54	7.9	83	
Gallwitz et al. 2012 (45)	Linagliptin + Met	-	-	7.7	-	1551
	Met + SU	-	-	7.7	-	
Goke et al. 2010 (48)	Saxagliptin + Met	57.5	49.5	7.7	88.7	858
	Met + SU	57.6	54	7.7	88.6	
Nauck et al. 2007 (52)	Sitagliptin + Met	56.8	57.1	7.7	89.5	1091
	Met + SU	56.6	61.3	7.6	89.7	
Ferrannini et al 2009 (58)	Vildagliptin + Met	57.5	52.8	7.3	89	2789
	Met + SU	57.5	54.1	7.3	88.6	
Filozof et al 2010 (59)	Vildagliptin + Met	59.2	52.2	8.5	85.7	1007
	Met + SU	59.7	51.8	8.5	84.2	
Janssen (DIA3009) 2013	Met + SU	56.2	52.1	7.8	86.6	1452
	Canagliflozin 100 mg + Met	56.2	52.1	7.8	86.6	
	Canagliflozin 300 mg + Met	56.2	52.1	7.8	86.6	
Janssen (DIA3006) 2013 (82)	Met	55.4	47.1	8	87	1284
	Sitagliptin + Met	55.4	47.1	8	87	
	Canagliflozin 100 mg + Met	55.4	47.1	8	87	
	Canagliflozin 300 mg + Met	55.4	47.1	8	87	
Nauck et al 2011 (67)	Met + SU	59	54.9	7.7	N/A	814

	Dapagliflozin 10 mg + Met	58	55.3	7.7	N/A	
Third line						
Janssen (DIA3015) 2013 (63)	Sitagliptin + Met + SU	56.7	55.9	8.1	88.3	756
	Canagliflozin 300 mg + Met	56.7	51	8.1	88.3	
Janssen (DIA3002) 2013 (63)	Canagliflozin 100 mg + Met	56.7	51	8.13	92.6	469
	Canagliflozin 300 mg + Met	56.7	51	8.13	92.6	
	Placebo + Met + SU	56.7	51	8.13	92.6	
TZD failure						
Kovacs et al. 2012 (7)	TZD	54.6	44.2	8.2	74	499
	Met + TZD	54.6	44.2	8.2	79.5	
	Empagliflozin 10 mg + TZD	54.7	50.3	8.1	73.4	
	Empagliflozin 25 mg + TZD	54.2	50.6	7.9	72.6	
	Empagliflozin 10 mg + Met + TZD	54.7	50.3	8.1	79.4	
	Empagliflozin 25 mg + Met + TZD	54.2	50.6	8.1	81	
Rosenstock et al. 2012 (71)	TZD	53.5	51.1	8.3	86.4	420
	Dapagliflozin 5 mg + TZD	53.2	55.3	8.4	87.8	
	Dapagliflozin 10 mg + TZD	53.8	42.1	8.4	84.8	
Janssen (DIA3012) 2013 (63)	Met + TZD	57.4	63.2	7.9	94.1	344
	Canagliflozin 300 mg + Met	56.7	51	8.1	92.6	
	Placebo + Met + SU	56.7	51	8.1	92.6	
Pratley et al 2009 (72)	TZD	55.2	54.6	8	NR	493
	Alogliptin 12.5 mg + TZD	55.5	55.3	8.1	NR	
	Alogliptin 25 mg + TZD	55.4	62.8	8	NR	
Hollander et al 2009 (73)	TZD	54	46.2	8.2	80.9	565
	Saxagliptin 2.5 mg + TZD	54.9	54.4	8.3	82.1	
	Saxagliptin 5 mg + TZD	53.2	47.8	8.4	80.4	
Derosa et al 2010 (74)	MET + TZD	58	51.3	8.4	77.3	151
	Sitagliptin 100 mg + TZD	57	49.3	8.5	78.7	
Garber et al 2007 (75)	TZD	54.8	50.7	8.7	NR	463
	Vildagliptin 50 mg + TZD	54	54.8	8.6	NR	
	Vildagliptin 100 mg + TZD	54	44.9	8.7	NR	
Bosi et al 2011 (76)	MET + TZD	55.9	51.1	8.1	88	803
	Alogliptin 25 mg + MET + TZD	54.3	52	8.2	88.2	
Insulin failure						
BI GMBH (1245-49) 2013 (40)	INS	55.3	39.9	8.33	95.5	566
	Empagliflozin 10 mg + INS	56.7	52.2	8.39	96.7	

	Empagliflozin 25 mg + INS	58	44.2	8.29	95.9	
BI GMBH (1245-33) 2013 (12)	INS	58.1	52.9	8.18	90.46	494
	Empagliflozin 10 mg + INS	58.6	55	8.27	91.59	
	Empagliflozin 25 mg + INS	59.9	60	8.27	94.71	
Janssen (DIA3008) 2013 (63)	INS	62.8	66.5	8.3	NR	1718
	Canagliflozin 100 mg + INS	62.8	66.5	8.3	NR	
	Canagliflozin 300 mg + INS	62.8	66.5	8.3	NR	
	INS	58.8	49.2	8.47	94.5	807
Wilding et al 2012 (83)	Dapagliflozin 2.5 mg + INS	59.8	49.5	8.46	93	
	Dapagliflozin 5 mg + INS	59.3	47.4	8.62	93.3	
	Dapagliflozin 10 mg + INS	59.3	44.8	8.57	94.5	
	INS	55	48	9.3	91	390
Rosenstock et al 2009 (78)	Alogliptin 12.5 mg + INS	55.4	42	9.3	87.9	
	Alogliptin 25 mg + INS	55.9	34	9.3	86.7	
Barnett et al 2012 (79)	INS	57.3	45	8.6	86.2	455
	Saxagliptin + INS	57.2	40	8.7	87.7	
Vilsboll et al 2010 (80)	INS + Met	57.2	53	8.6	87.3	641
	Sitagliptin + INS	58.3	49	8.7	86.5	
Fonseca et al 2007 (81)	INS	58.9	54.6	8.4	95.1	296
	Vildagliptin + INS	59.6	47.9	8.4	94.5	

INS = insulin therapy; Met = metformin; SU = sulphonylurea; TZD = thiazolidinediones

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

The data used from the studies listed in Table 29 and Table 30 for the NMA included:

- Change from baseline in HbA_{1C}
- Change from baseline in body weight
- Change from baseline in SBP
- Hypoglycaemia (non severe)
- Hypoglycaemia (severe)
- UTIs
- Genital infections

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

Bayesian network meta-analysis was performed for all outcomes where sufficient data was available. For all continuous outcomes (i.e., change from baseline), the mean differences and associated 95% credible intervals between all interventions were obtained using Bayesian network meta-analysis. For all dichotomous outcomes, the proportions of events were modelled in a logistic regression framework, and under this model relative risks and associated 95% credible intervals were estimated for all intervention comparisons. For both continuous and binary outcomes, placebo responses/risks were also pooled.

All models used conventional network meta-analysis models in accordance with the NICE technical support document 2. For the second line population, several trials were available for many of the informed comparisons, and for that reason and conventional uninformed random-effects model was applied. For the other three populations all comparisons were informed by only one trial (with the exception of empagliflozin vs placebo for insulin inadequate responders). For this reason, heterogeneity could not be estimates and a conventional fixed-effect model was therefore employed.

6.7.6 *Please present the results of the analysis*.

The results from the indirect comparison between empagliflozin, sitagliptin, dapagliflozin and canagliflozin all given against a background therapy of either: metformin, metformin and SU, metformin and TZD and insulin showed empagliflozin was in general comparable to the other SGLT2 inhibitors. Empagliflozin was more likely to result in reductions in body weight when compared to placebo and other therapies. Empagliflozin was statistically comparable to placebo and other therapies for AEs of UTIs and GTIs for both second and third line treatment.

Second Line

Table 31: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for the second line treatment of T2DM (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	**-0.83 (-0.97 to -0.69)**	--	--	--	--	--	--	--
Empagliflozin 10mg	**-0.60 (-0.92 to -0.28)**	0.23 (-0.11 to 0.56)	--	--	--	--	--	--
Empagliflozin 25mg	**-0.70 (-0.95 to -0.45)**	0.13 (-0.12 to 0.38)	-0.10 (-0.41 to 0.22)	--	--	--	--	--
Canagliflozin 100mg	**-0.66 (-0.91 to -0.41)**	0.17 (-0.08 to 0.42)	-0.06 (-0.46 to 0.34)	0.04 (-0.30 to 0.37)	--	--	--	--
Canagliflozin 300mg	**-0.78 (-1.04 to -0.53)**	0.04 (-0.20 to 0.29)	-0.19 (-0.59 to 0.21)	-0.09 (-0.43 to 0.25)	-0.12 (-0.37 to 0.12)	--	--	--
Dapagliflozin 5mg	**-0.47 (-0.73 to -0.21)**	**0.36 (0.07 to 0.65)**	0.13 (-0.28 to 0.54)	0.23 (-0.13 to 0.58)	0.19 (-0.17 to 0.55)	0.31 (-0.04 to 0.68)	--	--
Dapagliflozin 10mg	**-0.56 (-0.74 to -0.37)**	**0.27 (0.07 to 0.48)**	0.04 (-0.33 to 0.42)	0.14 (-0.16 to 0.44)	0.1 (-0.20 to 0.41)	0.23 (-0.07 to 0.53)	-0.09 (-0.37 to 0.20)	--
Alogliptin 12.5mg	**-0.50 (-0.92 to -0.10)**	0.33 (-0.12 to 0.75)	0.10 (-0.43 to 0.61)	0.19 (-0.30 to 0.67)	0.16 (-0.34 to 0.63)	0.28 (-0.21 to 0.76)	-0.03 (-0.53 to 0.45)	0.05 (-0.40 to 0.50)
Alogliptin 25mg	**-0.51 (-0.92 to -0.09)**	0.32 (-0.11 to 0.76)	0.09 (-0.43 to 0.62)	0.19 (-0.29 to 0.67)	0.16 (-0.33 to 0.63)	0.28 (-0.21 to 0.76)	-0.04 (-0.53 to 0.46)	0.05 (-0.4 to 0.50)
Linagliptin 5mg	**-0.58 (-0.83 to -0.34)**	**0.24 (0.00 to 0.49)**	0.02 (-0.38 to 0.41)	0.12 (-0.23 to 0.45)	0.08 (-0.26 to 0.41)	0.20 (-0.14 to 0.53)	-0.11 (-0.47 to 0.24)	-0.03 (-0.33 to 0.27)
Saxagliptin 5mg	**-0.62 (-0.83 to -0.41)**	0.21 (-0.01 to 0.43)	-0.02 (-0.40 to 0.36)	0.08 (-0.23 to 0.39)	0.04 (-0.27 to 0.35)	0.16 (-0.15 to 0.48)	-0.15 (-0.49 to 0.18)	-0.06 (-0.34 to 0.20)
Sitagliptin 100mg	**-0.79 (-0.96 to -0.62)**	0.04 (-0.14 to 0.21)	-0.19 (-0.55 to 0.17)	-0.09 (-0.38 to 0.19)	-0.12 (-0.42 to 0.16)	0.00 (-0.30 to 0.28)	-0.31 (-0.63 to -0.01)	-0.23 (-0.48 to 0.01)
Vildagliptin 100mg	**-0.77 (-0.95 to -0.60)**	0.06 (-0.12 to 0.24)	-0.17 (-0.54 to 0.19)	-0.07 (-0.37 to 0.21)	-0.11 (-0.40 to 0.18)	0.02 (-0.28 to 0.30)	-0.30 (-0.62 to 0.01)	-0.21 (-0.46 to 0.03)

Mean reduction in body weight, kg (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	**2.37 (1.89 to 2.75)**	--	--	--	--	--	--	--
Empagliflozin 10mg	**-1.76 (-2.50 to -1.04)**	**-4.13 (-4.86 to -3.32)**	--	--	--	--	--	--
Empagliflozin 25mg	**-2.26 (-2.83 to -1.71)**	**-4.64 (-5.12 to -4.05)**	-0.51 (-1.21 to 0.22)	--	--	--	--	--
Canagliflozin 100mg	**-2.02 (-2.67 to -1.43)**	**-4.39 (-4.98 to -3.78)**	-0.27 (-1.21 to 0.64)	0.25 (-0.55 to 0.98)	--	--	--	--
Canagliflozin 300mg	**-2.72 (-3.37 to -2.12)**	**-5.09 (-5.68 to -4.47)**	**-0.96 (-1.90 to -0.06)**	-0.45 (-1.24 to 0.27)	**-0.69 (-1.24 to -0.16)**	--	--	--
Dapagliflozin 5mg	**-1.79 (-2.37 to -1.20)**	**-4.15 (-4.82 to -3.41)**	-0.03 (-0.95 to 0.91)	0.47 (-0.32 to 1.29)	0.24 (-0.61 to 1.11)	**0.93 (0.08 to 1.82)**	--	--
Dapagliflozin 10mg	**-2.03 (-2.47 to -1.59)**	**-4.4 (-4.87 to -3.84)**	-0.27 (-1.08 to 0.58)	0.23 (-0.43 to 0.90)	-0.01 (-0.69 to 0.73)	**0.69 (0.00 to 1.44)**	-0.25 (-0.88 to 0.41)	--
Linagliptin 5mg	0.13 (-1.26 to 1.49)	**-2.23 (-3.66 to -0.76)**	**1.89 (0.31 to 3.40)**	**2.40 (0.90 to 3.87)**	**2.16 (0.66 to 3.68)**	**2.86 (1.33 to 4.39)**	**1.93 (0.40 to 3.39)**	**2.16 (0.72 to 3.60)**
Saxagliptin 5mg	-0.06 (-0.61 to 0.51)	**-2.43 (-3.08 to -1.66)**	**1.69 (0.80 to 2.63)**	**2.20 (1.42 to 3.02)**	**1.96 (1.16 to 2.84)**	**2.65 (1.85 to 3.55)**	**1.73 (0.92 to 2.54)**	**1.97 (1.26 to 2.68)**
Sitagliptin 100mg	0.34 (-0.23 to 0.85)	**-2.02 (-2.51 to -1.54)**	**2.10 (1.21 to 2.95)**	**2.62 (1.88 to 3.25)**	**2.37 (1.62 to 3.09)**	**3.07 (2.30 to 3.79)**	**2.13 (1.31 to 2.88)**	**2.38 (1.70 to 2.96)**
Vildagliptin 100mg	**0.74 (0.28 to 1.20)**	**-1.64 (-2.21 to -0.95)**	**2.49 (1.65 to 3.36)**	**3.00 (2.29 to 3.74)**	**2.76 (2.02 to 3.56)**	**3.45 (2.72 to 4.26)**	**2.53 (1.78 to 3.27)**	**2.77 (2.14 to 3.40)**

Mean reduction in SBP, mmHg (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	0.20 (-1.50 to 1.83)	--	--	--	--	--	--	--
Empagliflozin 10mg	**-4.31 (-6.98 to -1.57)**	**-4.45 (-7.43 to -1.55)**	--	--	--	--	--	--
Empagliflozin 25mg	**-5.11 (-7.21 to -2.94)**	**-5.30 (-7.33 to -3.16)**	-0.85 (-3.49 to 1.94)	--	--	--	--	--
Canagliflozin 100mg	**-4.11 (-6.39 to -2.00)**	**-4.32 (-6.5 to -2.27)**	0.15 (-3.27 to 3.44)	1.00 (-1.94 to 3.66)	--	--	--	--
Canagliflozin 300mg	**-5.37 (-7.75 to -3.31)**	**-5.56 (-7.82 to -3.54)**	-1.12 (-4.57 to 2.09)	-0.24 (-3.21 to 2.33)	-1.28 (-3.21 to 0.6)	--	--	--
Dapagliflozin 5mg	-2.33 (-4.82 to 0.24)	-2.52 (-5.34 to 0.38)	1.97 (-1.66 to 5.66)	2.80 (-0.42 to 5.98)	1.78 (-1.37 to 5.13)	**3.06 (0.00 to 6.49)**	--	--
Dapagliflozin 10mg	**-3.77 (-5.51 to -1.97)**	**-3.96 (-5.86 to -1.91)**	0.52 (-2.59 to 3.70)	1.33 (-1.18 to 3.98)	0.34 (-2.13 to 3.07)	1.63 (-0.88 to 4.36)	-1.46 (-4.27 to 1.42)	--
Saxagliptin 5mg	0.78 (-3.31 to 4.91)	0.61 (-3.82 to 5.13)	**5.12 (0.19 to 10.04)**	**5.97 (1.30 to 10.6)**	**4.92 (0.25 to 9.68)**	**6.21 (1.56 to 11.01)**	3.21 (-1.74 to 7.84)	**4.61 (0.13 to 9.06)**
Sitagliptin 100mg	-2.13 (-5.09 to 0.97)	-2.37 (-5.73 to 1.26)	2.12 (-1.88 to 6.25)	2.90 (-0.78 to 6.78)	1.94 (-1.58 to 5.9)	3.22 (-0.29 to 7.17)	0.19 (-3.63 to 4.24)	1.62 (-1.86 to 5.19)
Vildagliptin 100mg	-1.72 (-4.44 to 1.08)	-1.88 (-5.10 to 1.36)	2.63 (-1.27 to 6.46)	3.47 (-0.07 to 6.82)	2.45 (-1.12 to 6.04)	3.71 (0.21 to 7.26)	0.62 (-3.01 to 4.22)	2.07 (-1.26 to 5.28)
Hypoglycaemia, RR (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	1.20 (0.36 to 5.10)	--	--	--	--	--	--	--
Empagliflozin 10mg	4.52 (0.47 to 30.5)	3.66 (0.24 to 36.03)	--	--	--	--	--	--
Empagliflozin 25mg	3.52 (0.30 to 29.8)	2.88 (0.17 to 33.02)	0.77 (0.11 to 4.60)	--	--	--	--	--

Canagliflozin 100mg	N/A	N/A	N/A	N/A	--	--	--	--
Canagliflozin 300mg	N/A	N/A	N/A	N/A	N/A	--	--	--
Dapagliflozin 5mg	2.09 (0.63 to 8.33)	1.71 (0.30 to 10.5)	0.45 (0.05 to 6.25)	0.59 (0.06 to 9.27)	N/A	N/A	--	--
Dapagliflozin 10mg	1.22 (0.43 to 3.84)	1.02 (0.17 to 4.98)	0.28 (0.03 to 3.04)	0.34 (0.04 to 4.88)	N/A	N/A	0.58 (0.13 to 2.17)	--
Alogliptin 12.5mg	0.20 (0.01 to 1.98)	0.17 (0.01 to 2.01)	0.05 (0.00 to 1.01)	0.06 (0.00 to 1.39)	N/A	N/A	0.10 (0.01 to 1.26)	0.17 (0.01 to 2.05)
Linagliptin 5mg	0.19 (0.02 to 1.25)	0.15 (0.01 to 1.46)	**0.04 (0.00 to 0.79)**	0.06 (0.00 to 1.32)	N/A	N/A	**0.09 (0.01 to 0.81)**	0.16 (0.01 to 1.39)
Saxagliptin 5mg	1.03 (0.32 to 3.40)	0.86 (0.13 to 4.57)	0.23 (0.02 to 2.77)	0.29 (0.02 to 5.06)	N/A	N/A	0.49 (0.08 to 2.59)	0.84 (0.18 to 4.03)
Sitagliptin 100mg	0.53 (0.12 to 2.08)	0.43 (0.05 to 2.48)	0.12 (0.01 to 1.61)	0.16 (0.01 to 2.51)	N/A	N/A	0.25 (0.03 to 1.54)	0.43 (0.07 to 2.37)
Vildagliptin 100mg	2.51 (0.34 to 16.7)	1.99 (0.19 to 18.37)	0.55 (0.03 to 10.5)	0.73 (0.03 to 15.9)	N/A	N/A	1.17 (0.10 to 10.8)	2.07 (0.20 to 16.4)
Hypoglycaemia (non-severe), RR (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	1.05 (0.33 to 4.27)	--	--	--	--	--	--	--
Empagliflozin 10mg	4.17 (0.42 to 32.8)	3.87 (0.26 to 38.2)	--	--	--	--	--	--
Empagliflozin 25mg	2.87 (0.26 to 25.5)	2.69 (0.17 to 30.6)	0.71 (0.11 to 4.55)	--	--	--	--	--
Canagliflozin 100mg	N/A	N/A	N/A	N/A	--	--	--	--
Canagliflozin 300mg	N/A	N/A	N/A	N/A	N/A	--	--	--
Dapagliflozin 5mg	2.27 (0.67 to 8.49)	2.18 (0.34 to 11.9)	0.56 (0.05 to 8.14)	0.8 (0.07 to 11.4)	N/A	N/A	--	--
Dapagliflozin 10mg	1.38 (0.49 to 3.88)	1.29 (0.23 to 6.06)	0.33 (0.03 to 4.21)	0.48 (0.04 to 6.63)	N/A	N/A	0.60 (0.14 to 2.34)	--
Linagliptin	0.19	0.17	**0.05**	0.07	N/A	N/A	**0.08**	0.14

5mg	(0.02 to 1.13)	(0.02 to 1.46)	**(0.00 to 0.83)**	(0.00 to 1.26)			**(0.01 to 0.75)**	(0.01 to 1.12)
Saxagliptin 5mg	1.04 (0.31 to 3.26)	0.98 (0.15 to 4.71)	0.25 (0.02 to 3.25)	0.36 (0.03 to 4.93)	N/A	N/A	0.45 (0.08 to 2.36)	0.75 (0.16 to 3.58)
Sitagliptin 100mg	0.5 (0.11 to 1.85)	0.48 (0.06 to 2.63)	0.12 (0.01 to 1.64)	0.17 (0.01 to 2.55)	N/A	N/A	0.22 (0.03 to 1.31)	0.36 (0.06 to 1.9)
Vildagliptin 100mg	2.67 (0.34 to 17.1)	2.43 (0.21 to 22.8)	0.64 (0.03 to 12.3)	0.92 (0.05 to 17.5)	N/A	N/A	1.13 (0.11 to 11.2)	1.91 (0.2 to 15.8)
UTIs, RR (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.15 (0.06 to 16.5)	--	--	--	--	--	--	--
Empagliflozin 25mg	1.09 (0.06 to 15.5)	N/A	0.96 (0.06 to 15.2)	--	--	--	--	--
Canagliflozin 100mg	N/A	N/A	N/A	N/A	--	--	--	--
Canagliflozin 300mg	N/A	N/A	N/A	N/A	N/A	--	--	--
Dapagliflozin 5mg	0.99 (0.05 to 14.9)	N/A	0.87 (0.02 to 43.3)	0.91 (0.02 to 43.1)	N/A	N/A	--	--
Dapagliflozin 10mg	2.21 (0.26 to 19.9)	N/A	N/A	N/A	N/A	N/A	N/A	--
Linagliptin 5mg	0.80 (0.04 to 12.4)	N/A	0.70 (0.01 to 34.4)	0.72 (0.01 to 36.0)	N/A	N/A	0.78 (0.02 to 40.5)	0.36 (0.01 to 9.79)
Saxagliptin 5mg	1.43 (0.17 to 10.4)	N/A	1.24 (0.05 to 40.6)	1.30 (0.05 to 40.7)	N/A	N/A	1.45 (0.05 to 47.4)	0.64 (0.03 to 10.7)
Sitagliptin 100mg	0.87 (0.05 to 13.1)	N/A	0.76 (0.02 to 37.8)	0.79 (0.02 to 37.6)	N/A	N/A	0.87 (0.02 to 46.9)	0.40 (0.01 to 10.4)
Vildagliptin 100mg	0.91 (0.04 to 12.5)	N/A	0.81 (0.02 to 34.9)	0.83 (0.02 to 36.9)	N/A	N/A	0.92 (0.02 to 40.8)	0.42 (0.01 to 11.2)

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row).
Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Table 32: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for the second line treatment of T2DM (52 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	**-0.59 (-0.90 to -0.25)**	--	--	--	--	--	--	--
Empagliflozin 10mg	**-0.63 (-0.87 to -0.39)**	-0.04 (-0.37 to 0.28)	--	--	--	--	--	--
Empagliflozin 25mg	**-0.66 (-0.91 to -0.40)**	-0.07 (-0.28 to 0.14)	-0.03 (-0.27 to 0.22)	--	--	--	--	--
Canagliflozin 100mg	**-0.60 (-0.95 to -0.21)**	0.00 (-0.18 to 0.17)	0.04 (-0.32 to 0.39)	0.07 (-0.20 to 0.34)	--	--	--	--
Canagliflozin 300mg	**-0.72 (-1.08 to -0.33)**	-0.13 (-0.30 to 0.04)	-0.09 (-0.45 to 0.27)	-0.06 (-0.33 to 0.21)	-0.13 (-0.28 to 0.03)	--	--	--
Dapagliflozin 5mg	N/A	N/A	N/A	N/A	N/A	N/A	--	--
Dapagliflozin 10mg	**-0.60 (-0.97 to -0.19)**	0.00 (-0.21 to 0.22)	0.04 (-0.34 to 0.43)	0.07 (-0.23 to 0.37)	0.00 (-0.28 to 0.29)	0.13 (-0.14 to 0.41)	N/A	--
Linagliptin 5mg	-0.38 (-0.76 to 0.02)	0.21 (0.00 to 0.42)	0.25 (-0.13 to 0.64)	0.28 (-0.01 to 0.58)	0.21 (-0.06 to 0.49)	**0.34 (0.07 to 0.62)**	N/A	0.21 (-0.09 to 0.51)
Saxagliptin 5mg	**-0.53 (-0.91 to -0.12)**	0.06 (-0.16 to 0.28)	0.10 (-0.28 to 0.49)	0.13 (-0.17 to 0.44)	0.06 (-0.21 to 0.35)	0.19 (-0.09 to 0.47)	N/A	0.06 (-0.25 to 0.37)
Sitagliptin 100mg	**-0.59 (-0.94 to -0.20)**	0.00 (-0.16 to 0.17)	0.04 (-0.31 to 0.41)	0.07 (-0.19 to 0.34)	0.01 (-0.16 to 0.19)	0.13 (-0.04 to 0.31)	N/A	0.00 (-0.27 to 0.27)
Vildagliptin 100mg	**-0.67 (-1.01 to -0.28)**	-0.08 (-0.22 to 0.09)	-0.04 (-0.38 to 0.33)	-0.01 (-0.26 to 0.26)	-0.08 (-0.30 to 0.17)	0.05 (-0.17 to 0.29)	N/A	-0.08 (-0.34 to 0.19)
Mean reduction in body weight, kg (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	**2.52 (0.87 to 4.09)**	--	--	--	--	--	--	--
Empagliflozin 10mg	**-1.69 (-2.87 to -0.51)**	**-4.2 (-5.83 to -2.57)**	--	--	--	--	--	--

Empagliflozin 25mg	**-2.30 (-3.51 to -1.13)**	**-4.82 (-5.93 to -3.69)**	-0.62 (-1.84 to 0.62)	--	--	--	--	--
Canagliflozin 100mg	**-2.67 (-4.54 to -0.85)**	**-5.19 (-6.15 to -4.20)**	-0.99 (-2.88 to 0.90)	-0.36 (-1.85 to 1.08)	--	--	--	--
Canagliflozin 300mg	**-3.12 (-4.99 to -1.27)**	**-5.65 (-6.61 to -4.66)**	-1.44 (-3.34 to 0.46)	-0.83 (-2.27 to 0.64)	-0.46 (-1.31 to 0.41)	--	--	--
Dapagliflozin 5mg	N/A	N/A	N/A	N/A	N/A	N/A	--	--
Dapagliflozin 10mg	**-2.14 (-4.21 to -0.15)**	**-4.66 (-5.84 to -3.47)**	-0.46 (-2.50 to 1.55)	0.16 (-1.48 to 1.78)	0.52 (-0.99 to 2.03)	0.99 (-0.57 to 2.50)	N/A	--
Linagliptin 5mg	-0.08 (-2.11 to 1.88)	**-2.60 (-3.73 to -1.48)**	1.60 (-0.4 to 3.55)	**2.21 (0.64 to 3.79)**	**2.59 (1.11 to 4.05)**	**3.05 (1.56 to 4.50)**	N/A	**2.06 (0.39 to 3.69)**
Saxagliptin 5mg	0.32 (-1.70 to 2.24)	**-2.20 (-3.37 to -1.03)**	2.00 (-0.02 to 3.99)	**2.62 (1.01 to 4.21)**	**2.99 (1.46 to 4.46)**	**3.45 (1.92 to 4.93)**	N/A	**2.47 (0.75 to 4.13)**
Sitagliptin 100mg	-0.14 (-2.03 to 1.67)	**-2.68 (-3.63 to -1.71)**	1.53 (-0.38 to 3.41)	**2.14 (0.68 to 3.61)**	**2.51 (1.56 to 3.49)**	**2.97 (2.00 to 3.93)**	N/A	**1.98 (0.46 to 3.52)**
Vildagliptin 100mg	**4.17 (2.25 to 5.83)**	**1.64 (0.72 to 2.39)**	**5.84 (3.91 to 7.58)**	**6.46 (4.98 to 7.75)**	**6.82 (5.46 to 8.00)**	**7.29 (5.91 to 8.45)**	N/A	**6.30 (4.75 to 7.66)**
Mean reduction in SBP, mmHg (95% credible interval)								
intervention/ comparator	**Metformin**	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Metformin +SU	0.89 (-1.61 to 3.39)	--	--	--	--	--	--	--
Empagliflozin 10mg	**-3.30 (-5.37 to -1.20)**	**-4.18 (-6.69 to -1.69)**	--	--	--	--	--	--
Empagliflozin 25mg	**-4.90 (-7.1 to -2.73)**	**-5.8 (-7.18 to -4.40)**	-1.63 (-3.69 to 0.47)	--	--	--	--	--

Canagliflozin 100mg	-2.64 (-5.70 to 0.29)	**-3.51 (-5.08 to -1.96)**	0.67 (-2.28 to 3.62)	2.30 (0.17 to 4.36)	--	--	--	--
Canagliflozin 300mg	**-3.90 (-6.97 to -0.96)**	**-4.79 (-6.37 to -3.24)**	-0.61 (-3.54 to 2.31)	1.01 (-1.10 to 3.06)	-1.29 (-2.82 to 0.29)	--	--	--
Dapagliflozin 5mg	N/A	N/A	N/A	N/A	N/A	N/A	--	--
Dapagliflozin 10mg	**-4.22 (-7.20 to -1.28)**	**-5.11 (-6.68 to -3.53)**	-0.93 (-3.87 to 2.02)	0.68 (-1.42 to 2.79)	-1.60 (-3.80 to 0.64)	-0.32 (-2.51 to 1.90)	N/A	--
Saxagliptin 5mg	-2.02 (-5.00 to 1.04)	**-2.90 (-4.54 to -1.26)**	1.28 (-1.68 to 4.33)	**2.91 (0.71 to 5.05)**	0.63 (-1.68 to 2.84)	1.91 (-0.36 to 4.14)	N/A	2.20 (-0.05 to 4.47)
Sitagliptin 100mg	0.31 (-3.14 to 3.73)	-0.59 (-2.85 to 1.68)	**3.60 (0.28 to 6.95)**	**5.21 (2.55 to 7.85)**	**2.93 (1.30 to 4.60)**	**4.21 (1.94 to 6.45)**	N/A	**4.53 (1.76 to 7.30)**

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row). Note, no 52-week randomized trial data available for Dapagliflozin.

Third Line

Table 33: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for the third line treatment of T2DM (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-0.65 (-0.79 to -0.51)**	--	--	--	--
Empagliflozin 25mg	**-0.60 (-0.74 to -0.46)**	0.05 (-0.09 to 0.19)	--	--	--
Canagliflozin 100mg	**-0.76 (-0.97 to -0.55)**	-0.11 (-0.36 to 0.13)	-0.16 (-0.41 to 0.09)	--	--
Canagliflozin 300mg	**-1.01 (-1.18 to -0.85)**	**-0.36 (-0.58 to -0.15)**	**-0.41 (-0.63 to -0.20)**	**-0.25 (-0.46 to -0.04)**	--
Linagliptin 5mg	**-0.62 (-0.73 to -0.50)**	0.03 (-0.15 to 0.21)	-0.02 (-0.20 to 0.16)	0.14 (-0.09 to 0.38)	**0.40 (0.19 to 0.59)**
Saxagliptin 5mg	**-0.66 (-0.86 to -0.45)**	-0.01 (-0.26 to 0.24)	-0.06 (-0.31 to 0.19)	0.10 (-0.19 to 0.40)	**0.35 (0.09 to 0.62)**
Sitagliptin 100mg	**-0.81 (-0.98 to -0.65)**	-0.16 (-0.38 to 0.05)	-0.21 (-0.43 to 0.01)	-0.05 (-0.27 to 0.17)	**0.20 (0.10 to 0.30)**
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-1.77 (-2.18 to -1.35)**	--	--	--	--
Empagliflozin 25mg	**-2.00 (-2.43 to -1.57)**	-0.23 (-0.66 to 0.20)	--	--	--
Canagliflozin 100mg	**-1.26 (-1.88 to -0.62)**	0.51 (-0.24 to 1.26)	0.74 (-0.03 to 1.51)	--	--
Canagliflozin 300mg	**-1.69 (-2.23 to -1.16)**	0.07 (-0.60 to 0.75)	0.31 (-0.39 to 0.99)	-0.43 (-1.06 to 0.20)	--

Linagliptin 5mg	0.34 (-0.03 to 0.70)	**2.11** **(1.54 to 2.66)**	**2.34** **(1.77 to 2.9)**	**1.59** **(0.87 to 2.32)**	**2.03** **(1.39 to 2.67)**
Saxagliptin 5mg	**0.80** **(0.3 to 1.31)**	**2.57** **(1.91 to 3.24)**	**2.80** **(2.13 to 3.48)**	**2.06** **(1.24 to 2.87)**	**2.50** **(1.75 to 3.23)**
Sitagliptin 100mg	**0.97** **(0.41 to 1.53)**	**2.74** **(2.05 to 3.43)**	**2.97** **(2.27 to 3.67)**	**2.23** **(1.54 to 2.92)**	**2.66** **(2.32 to 3)**
Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-2.72** **(-4.66 to -0.79)**	--	--	--	--
Empagliflozin 25mg	**-2.10** **(-4.05 to -0.19)**	0.60 (-1.36 to 2.55)	--	--	--
Canagliflozin 100mg	-2.35 (-4.99 to 0.27)	0.37 (-2.88 to 3.63)	-0.24 (-3.46 to 3.07)	--	--
Canagliflozin 300mg	-1.77 (-4.36 to 0.86)	0.94 (-2.29 to 4.24)	0.35 (-2.84 to 3.64)	0.58 (-2.10 to 3.27)	--
Linagliptin 5mg	-0.94 (-2.60 to 0.74)	1.78 (-0.80 to 4.34)	1.18 (-1.38 to 3.76)	1.38 (-1.70 to 4.57)	0.81 (-2.27 to 3.9)
Sitagliptin 100mg	**4.21** **(1.09 to 7.33)**	**6.93** **(3.26 to 10.61)**	**6.31** **(2.70 to 10.1)**	**6.55** **(3.38 to 9.73)**	**5.96** **(4.17 to 7.79)**
Hypoglycaemia, RR (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**1.68** **(1.02 to 2.73)**	--	--	--	--
Empagliflozin 25mg	1.29 (0.75 to 2.18)	0.77 (0.47 to 1.22)	--	--	--
Canagliflozin 100mg	**2.27** **(1.41 to 3.61)**	1.35 (0.70 to 2.63)	1.76 (0.87 to 3.57)	--	--
Canagliflozin 300mg	**2.76** **(1.81 to 4.23)**	1.64 (0.88 to 3.12)	**2.15** **(1.11 to 4.22)**	1.22 (0.84 to 1.79)	--
Linagliptin 5mg	**1.59** **(1.15 to 2.24)**	0.95 (0.54 to 1.73)	1.24 (0.67 to 2.31)	0.71 (0.40 to 1.23)	**0.58** **(0.34 to 0.98)**
Sitagliptin 100mg	1.62 (0.71 to 3.60)	0.97 (0.37 to 2.44)	1.26 (0.48 to 3.26)	0.72 (0.28 to 1.77)	0.59 (0.24 to 1.40)

Hypoglycaemia (non-severe), RR (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**1.68 (1.02 to 2.73)**	--	--	--	--
Empagliflozin 25mg	1.29 (0.75 to 2.18)	0.77 (0.47 to 1.22)	--	--	--
Canagliflozin 100mg	**2.27 (1.41 to 3.61)**	1.35 (0.70 to 2.63)	1.76 (0.87 to 3.57)	--	--
Canagliflozin 300mg	**2.76 (1.81 to 4.23)**	1.64 (0.88 to 3.12)	**2.15 (1.11 to 4.22)**	1.22 (0.84 to 1.79)	--
Linagliptin 5mg	**1.64 (1.18 to 2.32)**	0.99 (0.55 to 1.81)	1.24 (0.70 to 2.44)	0.72 (0.41 to 1.29)	0.59 (0.35 to 1.01)
Sitagliptin 100mg	1.62 (0.71 to 3.60)	0.97 (0.37 to 2.44)	1.26 (0.48 to 3.26)	0.72 (0.28 to 1.77)	0.59 (0.24 to 1.40)
UTIs, RR (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	1.30 (0.71 to 2.35)	--	--	--	--
Empagliflozin 25mg	1.04 (0.54 to 1.99)	0.80 (0.43 to 1.47)	--	--	--
Canagliflozin 100mg	--	--	--	--	--
Canagliflozin 300mg	--	--	--	--	--
Linagliptin 5mg	0.62 (0.33 to 1.20)	0.48 (0.20 to 1.16)	0.6 (0.25 to 1.51)	--	--
Sitagliptin 100mg	0.48 (0.12 to 1.51)	0.36 (0.08 to 1.37)	0.45 (0.10 to 1.73)	--	--
Genital infections, RR (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	3.01 (0.62 to 14.8)	--	--	--	--
Empagliflozin 25mg	2.59 (0.51 to 13.2)	--	--	--	--

Canagliflozin 100mg	--	--	--	--	--
Canagliflozin 300mg	--	--	--	--	--

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).
Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).
Note that with the exception of one randomised clinical trials comparing linagliptin 5mg with placebo, the data for non-severe hypoglycaemic events was the same as the data for all hypoglycaemic events

Table 34: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for the third line treatment of T2DM (52 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-0.71 (-0.88 to -0.54)**	--	--	--	--
Empagliflozin 25mg	**-0.69 (-0.86 to -0.53)**	0.02 (-0.15 to 0.18)	--	--	--
Canagliflozin 100mg	-0.75 (-1.94 to 0.41)	-0.04 (-1.24 to 1.14)	-0.06 (-1.25 to 1.12)	--	--
Canagliflozin 300mg	**-0.97 (-1.19 to -0.75)**	-0.26 (-0.54 to 0.02)	-0.28 (-0.56 to 0.00)	-0.22 (-1.39 to 0.96)	--
Sitagliptin 100mg	**-0.6 (-0.86 to -0.34)**	0.11 (-0.2 to 0.42)	0.09 (-0.22 to 0.40)	0.15 (-1.05 to 1.35)	**0.37 (0.23 to 0.51)**
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-2.00 (-2.49 to -1.52)**	--	--	--	--
Empagliflozin 25mg	**-2.05 (-2.55 to -1.56)**	-0.05 (-0.60 to 0.48)	--	--	--

Canagliflozin 100mg	**-1.28 (-2.12 to -0.45)**	0.72 (-0.26 to 1.70)	0.77 (-0.20 to 1.75)	--	--
Canagliflozin 300mg	**-2.28 (-3.11 to -1.44)**	-0.28 (-1.24 to 0.68)	-0.23 (-1.20 to 0.74)	**-1.00 (-1.87 to -0.15)**	--
Sitagliptin 100mg	0.37 (-0.53 to 1.28)	**2.37 (1.34 to 3.41)**	**2.42 (1.38 to 3.45)**	**1.65 (0.71 to 2.58)**	**2.65 (2.28 to 3.01)**
Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Metformin +SU**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-2.81 (-4.89 to -0.69)**	--	--	--	--
Empagliflozin 25mg	**-2.71 (-4.91 to -0.53)**	0.09 (-2.03 to 2.14)	--	--	--
Canagliflozin 100mg	**-3.8 (-6.78 to -0.88)**	-1.01 (-4.66 to 2.65)	-1.08 (-4.77 to 2.59)	--	--
Canagliflozin 300mg	**-2.99 (-5.81 to -0.22)**	-0.2 (-3.68 to 3.3)	-0.29 (-3.87 to 3.25)	0.82 (-2.05 to 3.61)	--
Sitagliptin 100mg	2.99 (-0.36 to 6.32)	**5.79 (1.85 to 9.71)**	**5.69 (1.65 to 9.66)**	**6.80 (3.43 to 10.18)**	**5.99 (4.15 to 7.80)**

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row). Note, no 52-week randomized trial data available for Dapagliflozin.

TZD failure

Table 35: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing TZD monotherapy (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-0.55 (-0.93 to -0.16)**	--	--	--	--
Empagliflozin 25mg	**-0.67 (-1.05 to -0.28)**	-0.12 (-0.51 to 0.27)	--	--	--

Dapagliflozin 5mg	**-0.40 (-0.62 to -0.18)**	0.15 (-0.30 to 0.60)	0.27 (-0.18 to 0.72)	--	--
Dapagliflozin 10mg	**-0.55 (-0.77 to -0.33)**	0.00 (-0.45 to 0.44)	0.12 (-0.33 to 0.57)	-0.15 (-0.37 to 0.07)	--
Alogliptin 12.5mg	**-0.47 (-0.77 to -0.17)**	0.08 (-0.41 to 0.57)	0.20 (-0.29 to 0.69)	-0.07 (-0.44 to 0.30)	0.08 (-0.28 to 0.45)
Alogliptin 25mg	**-0.61 (-0.90 to -0.32)**	-0.06 (-0.55 to 0.43)	0.06 (-0.43 to 0.55)	-0.21 (-0.58 to 0.16)	-0.06 (-0.43 to 0.31)
Saxagliptin 5mg	**-0.64 (-0.84 to -0.45)**	-0.09 (-0.53 to 0.34)	0.03 (-0.40 to 0.46)	-0.24 (-0.54 to 0.06)	-0.09 (-0.39 to 0.21)
Sitagliptin 100mg	-0.21 (-0.57 to 0.16)	0.35 (-0.01 to 0.71)	**0.47 (0.10 to 0.83)**	0.20 (-0.21 to 0.63)	0.35 (-0.06 to 0.78)
Vildagliptin 50mg	**-0.50 (-0.78 to -0.22)**	0.05 (-0.43 to 0.52)	0.17 (-0.31 to 0.64)	-0.10 (-0.45 to 0.25)	0.05 (-0.30 to 0.41)
Vildagliptin 100mg	**-0.70 (-0.98 to -0.42)**	-0.15 (-0.63 to 0.32)	-0.03 (-0.50 to 0.44)	-0.30 (-0.65 to 0.05)	-0.15 (-0.50 to 0.20)
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-1.35 (-2.56 to -0.14)**	--	--	--	--
Empagliflozin 25mg	**-1.35 (-2.56 to -0.14)**	0.01 (-1.20 to 1.22)	--	--	--
Dapagliflozin 5mg	**-1.54 (-2.32 to -0.78)**	-0.19 (-1.63 to 1.24)	-0.20 (-1.62 to 1.22)	--	--
Dapagliflozin 10mg	**-1.78 (-2.56 to -1.00)**	-0.43 (-1.86 to 1.01)	-0.44 (-1.85 to 0.98)	-0.23 (-1.02 to 0.54)	--
Saxagliptin 5mg	0.50 (-0.20 to 1.19)	**1.85 (0.46 to 3.24)**	**1.84 (0.46 to 3.20)**	**2.04 (1.01 to 3.08)**	**2.27 (1.24 to 3.32)**
Sitagliptin 100mg	0.52 (-0.97 to 2.02)	**1.87 (0.38 to 3.39)**	**1.86 (0.37 to 3.35)**	**2.06 (0.39 to 3.75)**	**2.30 (0.62 to 3.98)**
Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	-2.64 (-7.43 to 2.29)	--	--	--	--

Empagliflozin 25mg	**-6.91 (-11.66 to -2.08)**	-4.32 (-9.08 to 0.55)	--	--	--
Dapagliflozin 5mg	-2.09 (-5.33 to 1.30)	0.56 (-5.49 to 6.38)	4.85 (-1.08 to 10.65)	--	--
Dapagliflozin 10mg	**-4.70 (-8.01 to -1.39)**	-2.06 (-8.10 to 3.80)	2.24 (-3.71 to 8.05)	-2.60 (-5.96 to 0.68)	--
Hypoglycaemia, RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.90 (0.00 to 44.93)	--	--	--	--
Empagliflozin 25mg	1.87 (0.01 to 43.89)	N/A	--	--	--
Dapagliflozin 5mg	2.62 (0.40 to 22.69)	N/A	N/A	--	--
Dapagliflozin 10mg	0.20 (0.00 to 4.87)	N/A	N/A	0.08 (0.00 to 1.14)	--
Alogliptin 12.5mg	1.01 (0.35 to 3.37)	N/A	N/A	0.39 (0.04 to 3.63)	N/A
Alogliptin 25mg	1.45 (0.54 to 4.58)	N/A	N/A	0.56 (0.05 to 5.02)	N/A
Saxagliptin 5mg	1.00 (0.00 to 110.70	N/A	N/A	0.37 (0.00 to 81.79)	N/A
Sitagliptin 100mg	0.91 (0.00 to 109.70)	N/A	N/A	0.34 (0.00 to 80.10)	N/A
Vildagliptin 50mg	0.08 (0.00 to 1.25)	0.04 (0.00 to 27.54)	0.04 (0.00 to 29.15)	**0.03 (0.00 to 0.92)**	N/A
Vildagliptin 100mg	0.37 (0.03 to 2.56)	N/A	N/A	0.13 (0.01 to 2.04)	N/A
Hypoglycaemia (non-severe), RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	0.04 (0.00 to 19.36)	--	--	--	--
Empagliflozin 25mg	0.05 (0.00 to 18.17)	N/A	--	--	--

Dapagliflozin 5mg	4.16 (0.46 to 44.69)	N/A	N/A	--	--
Dapagliflozin 10mg	0.02 (0.00 to 2.73)	N/A	N/A	**0.00 (0.00 to 0.51)**	--
Alogliptin 12.5mg	0.02 (0.00 to 4.93)	N/A	N/A	**0.01 (0.00 to 1.96)**	N/A
Alogliptin 25mg	2.20 (0.05 to 25.62)	N/A	N/A	0.47 (0.01 to 15.46)	N/A
Saxagliptin 5mg	0.03 (0.00 to 5.57)	N/A	N/A	0.01 (0.00 to 2.23)	N/A
Sitagliptin 100mg	1.07 (0.00 to 330.90)	N/A	N/A	0.24 (0.00 to 176.60)	N/A
Vildagliptin 50mg	**0.01 (0.00 to 0.64)**	N/A	N/A	**0.00 (0.00 to 0.28)**	N/A
Vildagliptin 100mg	0.27 (0.01 to 2.55)	N/A	N/A	0.06 (0.00 to 1.54)	N/A
UTIs, RR (95% credible interval)					
intervention/ comparator	**Control (TZD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	6.57 (0.88 to 66.34)	--	--	--	--
Empagliflozin 25mg	**9.00 (1.37 to 75.85)**	1.34 (0.50 to 4.24)	--	--	--
Dapagliflozin 5mg	1.08 (0.00 to 74.80)	0.16 (0.00 to 17.95)	0.11 (0.00 to 12.05)	--	--
Dapagliflozin 10mg	1.00 (0.00 to 75.03)	0.15 (0.00 to 18.06)	0.10 (0.00 to 11.73)	N/A	--
Alogliptin 12.5mg	0.99 (0.00 to 75.98)	0.14 (0.00 to 18.12)	0.10 (0.00 to 12.26)	N/A	N/A
Alogliptin 25mg	1.01 (0.00 to 74.07)	0.14 (0.00 to 17.84)	0.10 (0.00 to 11.59)	N/A	N/A
Saxagliptin 5mg	0.99 (0.42 to 2.23)	0.15 (0.01 to 1.31)	**0.11 (0.01 to 0.84)**	N/A	N/A
Sitagliptin 100mg	1.05 (0.00 to 73.86)	0.15 (0.00 to 17.96)	0.11 (0.00 to 11.85)	N/A	N/A
Vildagliptin 50mg	1.75 (0.27 to 12.79)	0.26 (0.02 to 4.02)	0.19 (0.01 to 2.65)	N/A	N/A

Vildagliptin 100mg	**4.49 (1.11 to 24.97)**	0.69 (0.05 to 8.30)	0.50 (0.04 to 5.29)	N/A	N/A

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).
Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Table 36: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing TZD plus metformin therapy (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-0.44 (-0.66 to -0.22)**	--	--	--	--
Empagliflozin 25mg	**-0.59 (-0.80 to -0.38)**	-0.15 (-0.36 to 0.06)	--	--	--
Canagliflozin 100mg	**-0.63 (-0.82 to -0.44)**	-0.19 (-0.49 to 0.10)	-0.04 (-0.32 to 0.24)	--	--
Canagliflozin 300mg	**-0.77 (-0.93 to -0.61)**	**-0.33 (-0.61 to -0.06)**	-0.18 (-0.44 to 0.08)	-0.14 (-0.30 to 0.02)	--
Alogliptin 25mg	**-0.47 (-0.58 to -0.36)**	-0.03 (-0.28 to 0.21)	0.12 (-0.12 to 0.35)	0.16 (-0.06 to 0.39)	**0.30 (0.11 to 0.49)**
Sitagliptin 100mg	**-0.7 (-0.84 to -0.56)**	-0.26 (-0.52 to 0.00)	-0.11 (-0.36 to 0.14)	-0.07 (-0.31 to 0.17)	0.07 (-0.14 to 0.28)
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-2.14 (-2.82 to -1.45)**	--	--	--	--
Empagliflozin 25mg	**-1.98 (-2.68 to -1.28)**	0.15 (-0.54 to 0.86)	--	--	--
Canagliflozin 100mg	**-2.55 (-3.36 to -1.74)**	-0.41 (-1.48 to 0.64)	-0.57 (-1.64 to 0.49)	--	--
Canagliflozin 300mg	**-3.49 (-4.29 to -2.69)**	**-1.35 (-2.41 to -0.30)**	**-1.51 (-2.56 to -0.45)**	**-0.94 (-1.74 to -0.13)**	--

Alogliptin 25mg	**-0.79 (-1.25 to -0.33)**	**1.34 (0.52 to 2.17)**	**1.19 (0.34 to 2.02)**	**1.76 (0.82 to 2.69)**	**2.70 (1.76 to 3.61)**
Sitagliptin 100mg	0.20 (-0.40 to 0.80)	**2.33 (1.42 to 3.24)**	**2.18 (1.26 to 3.09)**	**2.75 (1.76 to 3.75)**	**3.69 (2.69 to 4.69)**
Mean reduction in SBP, mmHg (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	**-4.24 (-6.91 to -1.54)**	--	--	--	--
Empagliflozin 25mg	**-4.06 (-6.72 to -1.36)**	0.18 (-2.54 to 2.82)	--	--	--
Canagliflozin 100mg	**-4.11 (-6.98 to -1.22)**	0.10 (-3.87 to 4.13)	-0.05 (-4.02 to 3.93)	--	--
Canagliflozin 300mg	**-3.54 (-6.46 to -0.54)**	0.69 (-3.29 to 4.68)	0.50 (-3.48 to 4.53)	0.59 (-2.39 to 3.55)	--
Hypoglycaemia, RR (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	0.63 (0.11 to 2.63)	--	--	--	--
Empagliflozin 25mg	1.51 (0.54 to 5.29)	2.4 (0.74 to 13.10)	--	--	--
Canagliflozin 100mg	0.1 (0.00 to 36.55)	0.17 (0.00 to 67.43)	0.07 (0.00 to 20.36)	--	--
Canagliflozin 300mg	0.11 (0.00 to 35.60)	0.19 (0.00 to 69.34)	0.07 (0.00 to 19.62)	N/A	--
Alogliptin 25mg	**2.29 (1.21 to 5.53)**	3.67 (0.87 to 24.54)	1.51 (0.44 to 5.26)	N/A	N/A
Sitagliptin 100mg	1.34 (0.58 to 3.11)	2.13 (0.42 to 14.08)	0.90 (0.20 to 3.11)	N/A	N/A
Hypoglycaemia (non-severe), RR (95% credible interval)					
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	0.47 (0.06 to 2.43)	--	--	--	--

Empagliflozin 25mg	1.5 (0.44 to 5.85)	3.18 (0.75 to 23.82)	--	--	--
Canagliflozin 100mg	0.08 (0.00 to 73.06)	N/A	0.05 (0.00 to 44.10)	--	--
Canagliflozin 300mg	0.08 (0.00 to 69.75)	N/A	0.05 (0.00 to 44.64)	N/A	--
Alogliptin 25mg	**2.46 (1.10 to 6.26)**	5.32 (0.88 to 48.38)	1.65 (0.36 to 7.12)	N/A	N/A

Hypoglycaemia (severe), RR (95% credible interval)

intervention/ comparator	**Control (TZD+MET)**
Empagliflozin 10mg	0.96 (0.00 to 197.10)
Empagliflozin 25mg	1.08 (0.00 to 197.1)
Canagliflozin 100mg	1.00 (0.00 to 193.90)
Canagliflozin 300mg	1.03 (0.00 to 194.00)
Sitagliptin 100mg	1.18 (0.38 to 3.85)
Alogliptin 25mg	4.11 (0.35 to 22.26)

UTIs, RR (95% credible interval)

intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	1.10 (0.62 to 2.00)	--	--	--	--
Empagliflozin 25mg	0.65 (0.31 to 1.25)	0.60 (0.28 to 1.11)	--	--	--
Canagliflozin 100mg	0.11 (0.00 to 13.06)	0.10 (0.00 to 11.31)	0.18 (0.00 to 21.79)	--	--
Canagliflozin 300mg	0.12 (0.00 to 13.36)	0.11 (0.00 to 11.66)	0.19 (0.00 to 23.29)	N/A	--
Alogliptin 25mg	1.46 (0.89 to 2.63)	1.33 (0.64 to 2.93)	**2.27 (1.02 to 5.85)**	N/A	N/A

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).
Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Table 37: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing TZD plus metformin therapy (52 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)			
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
Empagliflozin 10mg	**-0.56 (-0.77 to -0.35)**	--	--
Empagliflozin 25mg	**-0.63 (-0.84 to -0.42)**	-0.07 (-0.26 to 0.12)	--
Alogliptin 25mg	**-0.41 (-0.52 to -0.30)**	0.15 (-0.09 to 0.38)	0.22 (-0.02 to 0.46)

Mean reduction in body weight, kg (95% credible interval)			
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
Empagliflozin 10mg	**-2.08 (-2.76 to -1.39)**	--	--
Empagliflozin 25mg	**-2.02 (-2.67 to -1.36)**	0.06 (-0.66 to 0.77)	--
Alogliptin 25mg	-0.5 (-1.03 to 0.03)	**1.58 (0.71 to 2.44)**	**1.52 (0.68 to 2.36)**

Mean reduction in SBP, mmHg (95% credible interval)				
intervention/ comparator	**Control (TZD+MET)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 300mg**
Empagliflozin 10mg	-2.72 (-5.48 to 0.06)	--	--	--
Empagliflozin 25mg	**-4.10 (-6.73 to -1.46)**	-1.38 (-4.30 to 1.52)	--	--
Canagliflozin 300mg	-1.06 (-4.27 to 2.16)	1.66 (-2.57 to 5.89)	3.05 (-1.12 to 7.14)	--

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).

Insulin failure

Table 38: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4 inhibitors for treatment of T2DM patients who are failing insulin therapy plus other OADs (24 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-0.50 (-0.61 to -0.39)**	--	--	--	--	--	--
Empagliflozin 25mg	**-0.57 (-0.69 to -0.46)**	-0.07 (-0.19 to 0.04)	--	--	--	--	--
Canagliflozin 100mg	**-0.64 (-0.8 to -0.47)**	-0.14 (-0.34 to 0.06)	-0.07 (-0.27 to 0.14)	--	--	--	--
Canagliflozin 300mg	**-0.73 (-0.90 to -0.56)**	**-0.23 (-0.43 to -0.03)**	-0.16 (-0.36 to 0.05)	-0.09 (-0.26 to 0.08)	--	--	--
Dapagliflozin 5mg	**-0.50 (-0.66 to -0.35)**	0.00 (-0.19 to 0.19)	0.07 (-0.12 to 0.27)	0.14 (-0.09 to 0.36)	**0.23 (0.00 to 0.45)**	--	--
Dapagliflozin 10mg	**-0.57 (-0.73 to -0.42)**	-0.07 (-0.26 to 0.12)	0.00 (-0.19 to 0.19)	0.07 (-0.16 to 0.30)	0.16 (-0.07 to 0.38)	-0.07 (-0.21 to 0.07)	--
Alogliptin 12.5mg	-0.5 (-1.06 to 0.06)	0.00 (-0.57 to 0.56)	0.07 (-0.49 to 0.64)	0.14 (-0.45 to 0.72)	0.23 (-0.35 to 0.80)	0.00 (-0.58 to 0.57)	0.07 (-0.50 to 0.65)
Alogliptin 25mg	**-0.59 (-1.14 to -0.03)**	-0.09 (-0.65 to 0.48)	-0.01 (-0.58 to 0.56)	0.05 (-0.53 to 0.64)	0.15 (-0.44 to 0.73)	-0.08 (-0.66 to 0.49)	-0.01 (-0.59 to 0.57)
Saxagliptin 5mg	**-0.41 (-0.58 to -0.24)**	0.09 (-0.11 to 0.29)	0.17 (-0.03 to 0.37)	0.23 (-0.01 to 0.47)	**0.32 (0.08 to 0.56)**	0.10 (-0.14 to 0.32)	0.17 (-0.06 to 0.39)
Sitagliptin 100mg	**-0.60 (-0.80 to -0.41)**	-0.10 (-0.32 to 0.12)	-0.03 (-0.25 to 0.20)	0.04 (-0.22 to 0.29)	0.13 (-0.13 to 0.39)	-0.10 (-0.35 to 0.15)	-0.03 (-0.28 to 0.22)
Vildagliptin 100mg	**-0.31 (-0.58 to -0.03)**	0.20 (-0.10 to 0.50)	0.27 (-0.03 to 0.57)	**0.34 (0.01 to 0.66)**	**0.43 (0.11 to 0.75)**	0.20 (-0.12 to 0.52)	0.27 (-0.04 to 0.58)
Mean reduction in body weight, kg (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**

Empagliflozin 10mg	**-1.36 (-1.81 to -0.91)**	--	--	--	--	--	--
Empagliflozin 25mg	**-1.78 (-2.28 to -1.29)**	-0.42 (-0.93 to 0.09)	--	--	--	--	--
Canagliflozin 100mg	**-1.85 (-2.44 to -1.26)**	-0.49 (-1.22 to 0.25)	-0.06 (-0.83 to 0.71)	--	--	--	--
Canagliflozin 300mg	**-2.33 (-2.91 to -1.74)**	**-0.97 (-1.70 to -0.24)**	-0.55 (-1.31 to 0.23)	-0.48 (-1.02 to 0.04)	--	--	--
Dapagliflozin 5mg	**-1.43 (-1.97 to -0.89)**	-0.07 (-0.77 to 0.64)	0.35 (-0.38 to 1.08)	0.42 (-0.38 to 1.21)	**0.90 (0.10 to 1.69)**	--	--
Dapagliflozin 10mg	**-2.04 (-2.58 to -1.50)**	-0.67 (-1.39 to 0.02)	-0.26 (-1.00 to 0.47)	-0.19 (-0.99 to 0.60)	0.29 (-0.51 to 1.07)	**-0.61 (-1.15 to -0.07)**	--
Alogliptin 12.5mg	0.09 (-0.47 to 0.65)	**1.45 (0.74 to 2.18)**	**1.88 (1.12 to 2.63)**	**1.94 (1.14 to 2.77)**	**2.43 (1.62 to 3.23)**	**1.52 (0.74 to 2.30)**	**2.13 (1.36 to 2.91)**
Alogliptin 25mg	0.00 (-0.55 to 0.56)	**1.36 (0.65 to 2.07)**	**1.78 (1.05 to 2.53)**	**1.85 (1.05 to 2.66)**	**2.33 (1.53 to 3.13)**	**1.43 (0.66 to 2.20)**	**2.04 (1.28 to 2.81)**
Saxagliptin 5mg	0.21 (-0.29 to 0.71)	**1.57 (0.9 to 2.23)**	**1.99 (1.29 to 2.70)**	**2.06 (1.28 to 2.82)**	**2.54 (1.76 to 3.30)**	**1.63 (0.91 to 2.38)**	**2.25 (1.52 to 2.99)**
Vildagliptin 100mg	0.71 (-0.12 to 1.54)	**2.07 (1.13 to 3.01)**	**2.49 (1.53 to 3.47)**	**2.56 (1.53 to 3.58)**	**3.04 (2.02 to 4.06)**	**2.14 (1.14 to 3.15)**	**2.75 (1.75 to 3.75)**

Mean reduction in SBP, mmHg (95% credible interval)

intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-2.85 (-4.51 to -1.18)**	--	--	--	--	--	--
Empagliflozin 25mg	**-2.24 (-3.94 to -0.59)**	0.59 (-1.12 to 2.31)	--	--	--	--	--
Canagliflozin 100mg	-2.61 (-5.60 to 0.34)	0.26 (-3.16 to 3.64)	-0.36 (-3.81 to 3.08)	--	--	--	--
Canagliflozin 300mg	**-4.39 (-7.43 to -1.38)**	-1.55 (-5.01 to 1.94)	-2.14 (-5.60 to 1.34)	-1.78 (-4.74 to 1.13)	--	--	--
Dapagliflozin 5mg	-2.38 (-4.98 to 0.24)	0.45 (-2.60 to 3.57)	-0.13 (-3.23 to 3.02)	0.23 (-3.65 to 4.19)	2.01 (-1.92 to 5.98)	--	--
Dapagliflozin 10mg	**-3.12 (-5.76 to -0.42)**	-0.27 (-3.38 to 2.87)	-0.88 (-3.98 to 2.33)	-0.51 (-4.43 to 3.42)	1.27 (-2.76 to 5.28)	-0.74 (-3.32 to 1.84)	--

Hypoglycaemia, RR (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.09 (0.82 to 1.41)	--	--	--	--	--	--
Empagliflozin 25mg	1.24 (0.95 to 1.59)	1.14 (0.89 to 1.48)	--	--	--	--	--
Canagliflozin 100mg	**1.45 (1.23 to 1.69)**	1.34 (0.99 to 1.82)	1.17 (0.88 to 1.58)	--	--	--	--
Canagliflozin 300mg	**1.42 (1.20 to 1.66)**	1.31 (0.97 to 1.78)	1.15 (0.86 to 1.55)	0.98 (0.84 to 1.15)	--	--	--
Dapagliflozin 5mg	1.12 (0.83 to 1.48)	1.03 (0.70 to 1.53)	0.91 (0.61 to 1.33)	0.77 (0.55 to 1.07)	0.79 (0.56 to 1.09)	--	--
Dapagliflozin 10mg	1.05 (0.77 to 1.40)	0.97 (0.65 to 1.45)	0.85 (0.57 to 1.26)	0.73 (0.52 to 1.01)	0.74 (0.53 to 1.03)	0.94 (0.70 to 1.26)	--
Alogliptin 12.5mg	1.12 (0.72 to 1.64)	1.03 (0.62 to 1.65)	0.90 (0.55 to 1.43)	0.77 (0.48 to 1.17)	0.79 (0.49 to 1.20)	1.00 (0.59 to 1.63)	1.06 (0.63 to 1.73)
Alogliptin 25mg	1.13 (0.73 to 1.67)	1.04 (0.63 to 1.68)	0.91 (0.56 to 1.47)	0.78 (0.49 to 1.19)	0.80 (0.50 to 1.22)	1.01 (0.60 to 1.68)	1.08 (0.64 to 1.78)
Saxagliptin 5mg	1.45 (0.70 to 2.79)	1.33 (0.62 to 2.69)	1.17 (0.54 to 2.32)	1.00 (0.48 to 1.95)	1.02 (0.49 to 2.00)	1.29 (0.59 to 2.62)	1.38 (0.63 to 2.81)
Sitagliptin 100mg	**2.05 (1.68 to 2.46)**	**1.89 (1.38 to 2.62)**	**1.65 (1.22 to 2.26)**	**1.41 (1.10 to 1.80)**	**1.44 (1.13 to 1.84)**	**1.82 (1.31 to 2.59)**	**1.94 (1.38 to 2.77)**
Vildagliptin 100mg	0.75 (0.48 to 1.14)	0.70 (0.41 to 1.14)	**0.61 (0.36 to 0.99)**	**0.52 (0.32 to 0.81)**	**0.53 (0.33 to 0.82)**	0.67 (0.39 to 1.12)	0.72 (0.42 to 1.20)

Hypoglycaemia (non severe), RR (95% credible interval)							
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	1.06 (0.84 to 1.32)	--	--	--	--	--	--
Empagliflozin 25mg	1.07 (0.85 to 1.33)	1.01 (0.80 to 1.27)	--	--	--	--	--
Canagliflozin 100mg	**1.44 (1.22 to 1.68)**	**1.36 (1.04 to 1.79)**	**1.35 (1.03 to 1.77)**	--	--	--	--

Canagliflozin 300mg	**1.40 (1.19 to 1.63)**	**1.32 (1.01 to 1.74)**	**1.31 (1.00 to 1.73)**	0.97 (0.83 to 1.13)	--	--	--
Dapagliflozin 5mg	1.10 (0.82 to 1.45)	1.04 (0.72 to 1.49)	1.03 (0.71 to 1.48)	0.77 (0.55 to 1.05)	0.79 (0.57 to 1.08)	--	--
Dapagliflozin 10mg	1.02 (0.74 to 1.35)	0.96 (0.65 to 1.39)	0.95 (0.65 to 1.37)	**0.70 (0.50 to 0.98)**	0.73 (0.52 to 1.01)	0.92 (0.69 to 1.24)	--
Alogliptin 12.5mg	1.29 (0.80 to 1.92)	1.22 (0.72 to 1.93)	1.21 (0.72 to 1.92)	0.90 (0.55 to 1.37)	0.92 (0.56 to 1.41)	1.16 (0.69 to 1.92)	1.27 (0.74 to 2.10)
Alogliptin 25mg	1.34 (0.85 to 1.99)	1.27 (0.77 to 2.00)	1.26 (0.76 to 1.99)	0.93 (0.58 to 1.42)	0.96 (0.60 to 1.47)	1.22 (0.72 to 1.99)	1.32 (0.78 to 2.17)
Saxagliptin 5mg	1.46 (0.71 to 2.79)	1.38 (0.65 to 2.75)	1.37 (0.65 to 2.73)	1.02 (0.49 to 1.94)	1.05 (0.51 to 2.01)	1.33 (0.61 to 2.67)	1.44 (0.67 to 2.93)
Sitagliptin 100mg	0.97 (0.00 to 4.50)	0.92 (0.00 to 4.55)	0.92 (0.00 to 4.51)	0.67 (0.00 to 3.25)	0.69 (0.00 to 3.34)	0.87 (0.00 to 4.55)	0.96 (0.00 to 4.99)
Vildagliptin 100mg	0.99 (0.00 to 4.51)	0.93 (0.00 to 4.53)	0.93 (0.00 to 4.50)	0.69 (0.00 to 3.25)	0.71 (0.00 to 3.32)	0.90 (0.00 to 4.55)	0.97 (0.00 to 5.00)

Hypoglycaemia (severe), RR (95% credible interval)

intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	0.92 (0.07 to 8.16)	--	--	--	--	--	--
Empagliflozin 25mg	2.56 (0.41 to 16.46)	2.73 (0.41 to 33.79)	--	--	--	--	--
Canagliflozin 100mg	0.70 (0.30 to 1.59)	0.77 (0.07 to 12.07)	0.27 (0.04 to 2.04)	--	--	--	--
Canagliflozin 300mg	1.11 (0.54 to 2.30)	1.21 (0.12 to 18.93)	0.43 (0.06 to 3.07)	1.57 (0.72 to 3.64)	--	--	--
Dapagliflozin 5mg	0.91 (0.10 to 8.35)	1.00 (0.04 to 29.76)	0.35 (0.02 to 6.08)	1.30 (0.12 to 13.51)	0.82 (0.08 to 8.30)	--	--
Dapagliflozin 10mg	1.56 (0.24 to 13.03)	1.77 (0.10 to 47.44)	0.62 (0.04 to 9.32)	2.25 (0.29 to 20.75)	1.43 (0.19 to 12.86)	1.72 (0.27 to 14.86)	--
Alogliptin 12.5mg	0.11 (0.00 to 2.00)	0.12 (0.00 to 6.20)	0.04 (0.00 to 1.46)	0.16 (0.00 to 3.26)	0.10 (0.00 to 1.99)	0.11 (0.00 to 4.99)	0.07 (0.00 to 2.32)
Alogliptin 25mg	0.55 (0.04 to 4.55)	0.59 (0.02 to 17.69)	0.21 (0.01 to 3.59)	0.78 (0.05 to 7.60)	0.49 (0.03 to 4.67)	0.58 (0.02 to 13.27)	0.33 (0.01 to 5.90)

Saxagliptin 5mg	0.78 (0.12 to 6.31)	0.87 (0.05 to 24.25)	0.30 (0.02 to 4.86)	1.11 (0.14 to 10.85)	0.70 (0.09 to 6.49)	0.88 (0.05 to 17.95)	0.50 (0.03 to 8.11)
Vildagliptin 100mg	0.06 (0.00 to 0.85)	0.06 (0.00 to 2.96)	**0.02 (0.00 to 0.61)**	0.09 (0.00 to 1.40)	**0.06 (0.00 to 0.84)**	0.06 (0.00 to 2.20)	0.04 (0.00 to 1.04)

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).
Relative risks smaller than 1.00 represent superiority of the interventions (left column), and relative risks larger than 1.00 represent superiority of the comparators (first row).

Table 39: NMA results for the comparative efficacy and safety of empagliflozin versus other SGLT2is and DPP-4is for treatment of T2DM patients who are failing insulin therapy (52 ± 4 weeks)

Mean reduction in HbA_{1C}, % (95% credible interval)					
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-0.37 (-0.59 to -0.15)**	--	--	--	--
Empagliflozin 25mg	**-0.47 (-0.69 to -0.24)**	-0.09 (-0.31 to 0.13)	--	--	--
Dapagliflozin 5mg	**-0.51 (-0.68 to -0.34)**	-0.14 (-0.41 to 0.14)	-0.04 (-0.32 to 0.23)	--	--
Dapagliflozin 10mg	**-0.54 (-0.70 to -0.38)**	-0.17 (-0.44 to 0.11)	-0.07 (-0.35 to 0.2)	-0.03 (-0.2 to 0.14)	--
Mean reduction in body weight, kg (95% credible interval)					
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Empagliflozin 10mg	**-2.22 (-2.88 to -1.55)**	--	--	--	--
Empagliflozin 25mg	**-2.29 (-2.97 to -1.59)**	-0.07 (-0.76 to 0.62)	--	--	--
Dapagliflozin 5mg	**-2.01 (-2.77 to -1.25)**	0.20 (-0.80 to 1.21)	0.27 (-0.73 to 1.29)	--	--
Dapagliflozin 10mg	**-2.73 (-3.52 to -1.93)**	-0.52 (-1.56 to 0.53)	-0.45 (-1.48 to 0.61)	-0.71 (-1.50 to 0.08)	--

Mean reduction in SBP, mmHg (95% credible interval)			
intervention/ comparator	**Placebo (INS+OAD)**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
Empagliflozin 10mg	**-2.42 (-4.19 to -0.64)**	--	--
Empagliflozin 25mg	**-2.27 (-4.06 to -0.47)**	0.14 (-1.66 to 1.96)	--
Dapagliflozin 10mg	**-4.98 (-8.42 to -1.58)**	-2.57 (-6.45 to 1.27)	-2.72 (-6.56 to 1.14)

Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparators (first row).

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

Overall the trials were considered broadly comparable in terms of baseline characteristics, the only exception is that the empagliflozin trials have lower baseline BMI than the trials for the other SGLT2is. This could have potentially led to an underestimation of the potential weight reduction due to treatments generally having a greater effect the higher the baseline. However, it is unclear how much impact this could have on the results

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

Due to the limited selection of treatments all trials were considered relevant for inclusion

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

There were no comparisons where there was an inconsistency between comparisons

6.8 Non-RCT evidence

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

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

No non-RCT evidence was available for the cost effectiveness of empagliflozin.

6.9 Adverse events (AEs)

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

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

None of the trial presented in this empagliflozin submission were primarily designed to asses safety outcomes.

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

Empagliflozin as add-on to pioglitazone or pioglitazone plus metformin (1245.19 – EMPA-REG PIO)

The frequency of subjects with at least one reported AE was similar throughout treatment groups: 67.3%, 71.4% and 72.7% in the empagliflozin 10mg, empagliflozin 25mg and placebo treatment groups, respectively. The highest frequency of AEs was reported for UTIs, with frequencies of 14.5% in the

empagliflozin 10mg group, 10.7% in the empagliflozin 25mg group and 10.9% in the placebo treatment group.

A summary of AEs occurring in study 1245.19 can be seen in Table 40.

Table 40: Summary of AEs in study 1245.19

	Placebo (n=165)	Empagliflozin 10mg (n=165)	Empagliflozin 25mg (n=168)
One or more AE(s), n (%)	120 (72.7)	111 (67.3)	120 (71.4)
One or more drug-related AE(s), n (%)	31 (18.8)	24 (14.5)	31 (18.5)
AEs leading to discontinuation, n (%)	4 (2.4)	2 (1.2)	5 (3.0)
One or more serious AE(s), n (%)	7 (4.2)	7 (4.2)	6 (3.6)
Deaths, n (%)	1 (0.6)	0 (0.0)	2 (1.2)
AEs with frequency of ≥5% in any randomised group			
UTI, n (%)	18 (10.9)	24 (14.5)	18 (10.7)
Hyperglycaemia, n (%)	26 (15.8)	8 (4.8)	4 (2.4)
Dyslipidemia, n (%)	17 (10.3)	18 (10.9)	12 (7.1)
Hypertension, n (%)	9 (5.5)	3 (1.8)	2 (1.2)
Special interest categories			
Hypoglycaemia, n (%)	3 (1.8)	2 (1.2)	4 (2.4)
Events requiring assistance, n (%)	0	0	0
AEs belonging to BICMQ 'UTI', n (%)	27 (16.4)	28 (17.0)	20 (11.9)
AEs belonging to BICMQ 'genital infection', n (%)	4 (2.4)	14 (8.5)	6 (3.6)
Bone fractures, n (%)	4 (2.4)	2 (1.2)	1 (0.6)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; UTI = urinary tract infection

Empagliflozin as add-on to metformin plus sulphonylurea (1245.23 – EMPA-REG MET, EMPA-REG METSU)

Metformin only substudy

The frequency of subjects with at least one AE was 57.1%, 49.5% and 58.7% in the empagliflozin 10mg group, empagliflozin 25mg group and placebo group, respectively. The highest frequency of AEs was reported for the medical dictionary for drug regulatory activities (MedDRA) system organ class 'infections and infestations' with similar frequencies across all treatment groups (empagliflozin

10mg 21.2%, empagliflozin 23.4% and placebo 23.3%). The AE reported at the greatest frequency was nasopharyngitis, occurring at an incidence of 5.5%, 7.0% and 7.8% in the empagliflozin 10mg, empagliflozin 25mg and placebo groups, respectively.

A summary of AEs occurring in study 1245.23 (metformin only substudy) can be seen in Table 41.

Table 41: Summary of AEs in study 1245.23 (metformin only substudy)

	Placebo (n=206)	Empagliflozin 10mg (n=217)	Empagliflozin 25mg (n=214)	Open-label empagliflozin 25mg (n=69)
One or more AE(s), n (%)	121 (58.7)	124 (57.1)	106 (49.5)	38 (55.1)
One or more drug-related AE(s), n (%)	25 (12.1)	35 (16.1)	27 (12.6)	11 (15.9)
AEs leading to discontinuation, n (%)	7 (3.4)	2 (0.9)	5 (2.3)	1 (1.4)
One or more serious AE(s), n (%)	7 (3.4)	7 (3.2)	5 (2.3)	1 (1.4)
Deaths, n (%)	0	0	0	0
AEs with frequency of ≥5% in any randomised group				
Nasopharyngitis, n (%)	16 (7.8)	12 (5.5)	15 (7.0)	5 (7.2)
UTI, n (%)	8 (3.9)	9 (4.1)	9 (4.2)	5 (7.2)
URTI, n (%)	9 (4.4)	2 (0.9)	9 (4.2)	4 (5.8)
Hyperglycaemia, n (%)	23 (11.2)	5 (2.3)	2 (0.9)	2 (2.9)
Diarrhoea, n (%)	7 (3.4)	4 (1.8)	3 (1.4)	4 (5.8)
Special interest categories				
Hypoglycaemia, n (%)	1 (0.5)	4 (1.8)	3 (1.4)	2 (2.9)
Events requiring assistance, n (%)	0	0	0	0
AEs belonging to BICMQ 'UTI', n (%)	10 (4.9)	11 (5.1)	12 (5.6)	5 (7.2)
AEs belonging to BICMQ 'genital infection', n (%)	0	8 (3.7)	10 (4.7)	1 (1.4)
AEs belonging to BICMQ 'volume depletion', n (%)	0	2 (0.9)	0	0

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Metformin plus SU substudy

The frequency of subjects with at least one reported AE on treatment was 67.9% in the empagliflozin 10mg group, 64.1% in the empagliflozin 25mg group and 62.7% in the placebo group. The highest frequency of AEs was reported for the MedDRA system organ class 'infections and infestations' with similar frequencies across all treatment groups (empagliflozin 10mg 27.2%, empagliflozin 28.1% and placebo 24.0%). The AE reported with the highest incidence was hypoglycaemia, occurring at an incidence of 15.6% in the empagliflozin 10mg group, 12.9% in the empagliflozin 25mg group and 9.8% in the placebo group.

A summary of AEs occurring in study 1245.23 (metformin plus SU substudy) can be seen in Table 42.

Table 42: Summary of AEs in study 1245.23 (metformin plus SU substudy)

	Placebo (n=225)	Empagliflozin 10mg (n=224)	Empagliflozin 25mg (n=217)	Open-label empagliflozin 25mg (n=101)
One or more AE(s), n (%)	141 (62.7)	152 (67.9)	139 (64.1)	68 (67.3)
One or more drug-related AE(s), n (%)	34 (15.1)	54 (24.1)	43 (19.8)	19 (18.8)
AEs leading to discontinuation, n (%)	8 (3.6)	6 (2.7)	7 (3.2)	5 (5.0)
One or more serious AE(s), n (%)	14 (6.2)	11 (4.9)	1 (0.5)	5 (5.0)
Deaths, n (%)	0	1 (0.4)	0	0
AEs with frequency of ≥5% in any randomised group				
Nasopharyngitis, n (%)	11 (4.9)	18 (8.0)	13 (6.0)	5 (5.0)
UTI, n (%)	15 (6.7)	21 (9.4)	15 (6.9)	3 (3.0)
URTI, n (%)	12 (5.3)	7 (3.1)	11 (5.1)	3 (3.0)
Hyperglycaemia, n (%)	28 (12.4)	6 (2.7)	5 (2.3)	8 (7.9)
Hypoglycaemia, n (%)	22 (9.8)	35 (15.6)	28 (12.9)	9 (8.9)
Diarrhoea, n (%)	5 (2.2)	6 (2.7)	4 (1.8)	5 (5.0)
Dizziness, n (%)	12 (5.3)	6 (2.7)	9 (4.1)	2 (2.0)
Special interest categories				
Hypoglycaemia, n (%)	19 (8.4)	36 (16.1)	25 (11.5)	7 (6.9)
Events requiring assistance, n (%)	0	0	0	0

AEs belonging to BICMQ 'UTI', n (%)	18 (8.0)	23 (10.3)	18 (8.3)	3 (3.0)
AEs belonging to BICMQ 'genital infection', n (%)	2 (0.9)	6 (2.7)	5 (2.3)	2 (2.0)
AEs belonging to BICMQ 'volume depletion', n (%)	1 (0.4)	1 (0.4)	0 (0)	1 (1.0)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Empagliflozin versus glimepiride as add-on to metformin (1245.28 – EMPA-REG H2H-SU)

The frequency of subjects with AEs at week 104 was similar between the empagliflozin and glimepiride groups (86.4% vs 86.3%, respectively). The frequency of AEs leading to discontinuation of trial medication was small in both treatment groups (empagliflozin 5.1%, glimepiride 4.4%). SAEs occurred at an incidence of 15.6% of patients in the empagliflozin group and 11.4% in the glimepiride group. These included ten fatal SAEs up to week 104 (five from each treatment group).

AEs with a frequency of ≥5% in either treatment group occurred at a similar incidence (empagliflozin 86.4%, glimepiride 86.3%). However, metabolism and nutrition disorders were less frequent for patients treated with empagliflozin. Hyperglycaemia occurred less frequently in the empagliflozin group (13.7%) compared with the glimepiride group (21.5%), as was the frequency of hypoglycaemia (empagliflozin 4.2%, glimepiride 25.3%).

A summary of AEs occurring in study 1245.28 can be seen in Table 43.

Table 43: Summary of AEs in study 1245.28

	Empagliflozin 25mg (n=765)	**Placebo (n=780)**
One or more AE(s), n (%)	661 (86.4)	673 (86.3)
One or more drug-related AE(s), n (%)	190 (24.8)	252 (32.3)
AEs leading to discontinuation, n (%)	39 (5.1)	34 (4.4)
One or more serious AE(s), n (%)	119 (15.6)	89 (11.4)

	Empagliflozin 25mg (n=765)	Placebo (n=780)
Deaths, n (%)	5 (0.7)	5 (0.6)
AEs with frequency of ≥5% in any randomised group		
UTI, n (%)	95 (12.4)	99 (12.7)
Nasopharyngitis, n (%)	76 (9.9)	89 (11.4)
URTI, n (%)	79 (10.3)	74 (9.5)
Influenza, n (%)	51 (6.7)	51 (6.5)
Hyperglycaemia, n (%)	105 (13.7)	168 (21.5)
Hypoglycaemia, n (%)	32 (4.2)	197 (25.3)
Dyslipidemia, n (%)	41 (5.4)	39 (5.0)
Headache, n (%)	48 (6.3)	55 (7.1)
Dizziness, n (%)	49 (6.4)	49 (6.3)
Hypertension, n (%)	41 (5.4)	77 (9.9)
Cough n (%)	42 (5.5)	47 (6.0)
Diarrhoea, n (%)	39 (5.1)	51 (6.5)
Arthralgia, n (%)	44 (5.8)	66 (8.5)
Back pain, n (%)	63 (8.2)	64 (8.2)
Pain in extremity, n (%)	39 (5.1)	32 (4.1)
Special interest categories		
Hypoglycaemia, n (%)	19 (2.5)	189 (24.2)
AEs belonging to BICMQ 'UTI', n (%)	105 (13.7)	102 (13.1)
AEs belonging to BICMQ 'genital infection', n (%)	90 (11.8)	17 (2.2)
AEs belonging to BICMQ 'volume depletion', n (%)	11 (1.4)	8 (1.3)
AEs belonging to BICMQ 'bone fractures', n (%)	19 (2.5)	17 (2.2)
AEs belonging to BICMQ 'malignancies', n (%)	15 (2.0)	9 (1.2)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Long-term efficacy and safety of empagliflozin (1245.31 – EMPA-REG EXTEND)

A summary of each of the adverse events in the 1245.31 extension study can be seen in Table 44.

Table 44: Summary of AEs in study 1245.31

Monotherapy (1245.20 roll-over)				
	Placebo (n=229)	**Empagliflozin 10mg (n=224)**	**Empagliflozin 25mg (n=223)**	**Sitagliptin 100mg (n=223)**
One or more AE(s), n (%)	175 (76.4)	172 (76.8)	174 (78.0)	161 (72.2)
One or more drug-related AE(s), n (%)	36 (15.7)	49 (21.9)	52 (23.3)	31 (13.9)
AEs leading to discontinuation, n (%)	15 (6.6)	11 (4.9)	9 (4.0)	11 (4.9)
One or more serious AE(s), n (%)	23 (10.0)	25 (11.2)	16 (7.2)	18 (8.1)
Deaths, n (%)	1 (0.4)	0	0	1 (0.4)
AEs with frequency of ≥5% in any randomised group				
Nasopharyngitis, n (%)	27 (11.8)	32 (14.3)	25 (11.2)	27 (12.1)
UTI, n (%)	21 (9.2)	20 (8.9)	14 (6.3)	18 (8.1)
URTI, n (%)	12 (5.2)	17)7.6)	16 (7.2)	19 (8.5)
Bronchitis, n (%)	10 (4.4)	11 (4.9)	6 (2.7)	12 (5.4)
Hyperglycaemia, n (%)	63 (27.5)	20 (8.9)	11 (4.9)	28 (12.6)
Hypoglycaemia, n (%)	3 (1.3)	4 (1.8)	2 (0.9)	2 (0.9)
Dyslipidaemia, n (%)	15 (6.6)	16 (7.1)	14 (6.3)	14 (6.3)
Hypertension, n (%)	13 (5.7)	11 (4.9)	5 (2.2)	14 (6.3)
Diarrhoea, n (%)	9 (3.9)	12 (5.4)	6 (2.7)	8 (3.6)
Back pain, n (%)	12 (5.2)	7 (3.1)	7 (3.1)	19 (8.5)
Special interest categories				
Hypoglycaemia, n (%)	2 (0.9)	2 (0.9)	1 (0.4)	2 (0.9)
AEs belonging to BICMQ 'UTI', n (%)	25 (10.9)	21 (9.4)	20 (9.0)	20 (9.0)
AEs belonging to BICMQ 'genital infection', n (%)	4 (1.7)	13 (5.8)	14 (6.3)	2 (0.9)
AEs belonging to BICMQ 'volume depletion', n (%)	1 (0.4)	6 (2.7)	2 (0.9)	3 (1.3)
Background of pioglitazone (1245.19 roll-over)				
	Placebo (n=165)	**Empagliflozin 10mg (n=165)**	**Empagliflozin 25mg (n=168)**	
One or more AE(s), n (%)	136 (82.4)	126 (76.4)	138 (82.1)	
One or more drug-related AE(s), n (%)	41 (24.8)	33 (20.0)	39 (23.2)	
AEs leading to discontinuation, n (%)	7 (4.2)	5 (3.0)	8 (4.8)	
One or more serious	11 (6.7)	13 (7.9)	15 (8.9)	

AE(s), n (%)			
Deaths, n (%)	1 (0.6)	1 (0.6)	3 (1.8)
AEs with frequency of ≥5% in any randomised group			
UTI, n (%)	34 (20.6)	29 (17.6)	33 (19.6)
URTI, n (%)	11 (6.7)	9 (5.,5)	15 (8.9)
Nasopharyngitis, n (%)	7 (4.2)	10 (6.1)	9 (5.4)
Anaemia, n (%)	13 (7.9)	7 (4.2)	11 (6.5)
Hyperglycaemia, n (%)	49 (29.7)	27 (16.4)	23 (13.7)
Hypoglycaemia, n (%)	8 (4.8)	4 (2.4)	7 (4.2)
Dyslipidaemia, n (%)	26 (15.8)	23 (13.9)	21 (12.5)
Hypercholesterolaemia, n (%)	3 (1.8)	9 (5.5)	7 (4.2)
Dizziness, n (%)	6 (3.6)	6 (3.6)	14 (8.3)
Headache, n (%)	8 (4.8)	10 (6.1)	13 (7.7)
Hypertension, n (%)	16 (9.7)	6 (3.6)	3 (1.8)
Dyspepsia, n (%)	2 (1.2)	10 (6.1)	4 (2.4)
Arthralgia, n (%)	9 (5.5)	11 (6.7)	10 (6.0)
Back pain, n (%)	9 (5.5)	10 (6.1)	7 (4.2)
Special interest categories			
Hypoglycaemia, n (%)	7 (4.2)	3 (1.8)	5 (3.0)
AEs belonging to BICMQ 'UTI', n (%)	44 (26.7)	37 (22.4)	37 (22.0)
AEs belonging to BICMQ 'genital infection', n (%)	5 (3.0)	17 (10.3)	7 (4.2)
AEs belonging to BICMQ 'volume depletion', n (%)	0	0	2 (1.2)
AEs belonging to BICMQ 'bone fracture', n (%)	5 (3.0)	5 (3.0)	1 (0.6)
Background of metformin (1245.23 roll-over)			
	Placebo (n=206)	**Empagliflozin 10mg (n=217)**	**Empagliflozin 25mg (n=214)**
One or more AE(s), n (%)	160 (77.7)	174 (80.2)	154 (72.0)
One or more drug-related AE(s), n (%)	46 (22.3)	66 (30.4)	43 (20.1)
AEs leading to discontinuation, n (%)	10 (4.9)	7 (3.2)	12 (5.6)
One or more serious AE(s), n (%)	24 (11.7)	19 (8.8)	17 (7.9)
Deaths, n (%)	0	0	0
AEs with frequency of ≥5% in any randomised group			
Nasopharyngitis, n (%)	39 (18.9)	36 (16.6)	29 (13.6)
UTI, n (%)	23 (11.2)	25 (11.5)	18 (8.4)
URTI, n (%)	17 (8.3)	7 (3.2)	21 (9.8)
Hyperglycaemia, n (%)	56 (27.2)	25 (11.5)	14 (6.5)
Dyslipidaemia, n (%)	7 (3.4)	16 (7.4)	8 (3.7)
Hypoglycaemia, n (%)	8 (3.9)	15 (6.9)	10 (4.7)
Back pain, n (%)	10 (4.9)	9 (4.1)	11 (5.1)

Hypertension, n (%)	6 (2.9)	8 (3.7)	11 (5.1)
Special interest categories			
Hypoglycaemia, n (%)	7 (3.4)	9 (4.1)	9 (4.2)
AEs belonging to BICMQ 'UTI', n (%)	28 (13.6)	31 (14.3)	22 (10.3)
AEs belonging to BICMQ 'genital infection', n (%)	1 (0.5)	18 (8.3)	20 (9.3)
AEs belonging to BICMQ 'volume depletion', n (%)	0	2 (0.9)	1 (0.5)
Background of metformin plus SU (1245.23 roll-over)			
	Placebo (n=225)	**Empagliflozin 10mg (n=224)**	**Empagliflozin 25mg (n=217)**
One or more AE(s), n (%)	183 (81.3)	183 (81.7)	178 (82.0)
One or more drug-related AE(s), n (%)	59 (26.2)	80 (35.7)	69 (31.8)
AEs leading to discontinuation, n (%)	16 (7.1)	10 (4.5)	15 (6.9)
One or more serious AE(s), n (%)	31 (13.8)	29 (12.9)	24 (11.1)
Deaths, n (%)	0	1 (0.4)	0
AEs with frequency of ≥5% in any randomised group			
Nasopharyngitis, n (%)	24 (10.7)	36 (16.1)	34 (15.7)
UTI, n (%)	29 (12.9)	33 (14.7)	33 (15.2)
URTI, n (%)	24 (10.7)	18 (8.0)	21 (9.7)
Bronchitis, n (%)	8 (3.6)	12 (5.4)	8 (3.7)
Influenza, n (%)	4 (1.8)	7 (3.1)	11 (5.1)
Hyperglycaemia, n (%)	59 (26.2)	24 (10.7)	26 (12.0)
Hypoglycaemia, n (%)	40 (17.8)	53 (23.7)	46 (21.2)
Dizziness, n (%)	16 (7.1)	14 (6.3)	18 (8.3)
Headache, n (%)	13 (5.8)	17 (7.6)	10 (4.6)
Cough, n (%)	3 (1.3)	13 (5.8)	6 (2.8)
Back pain, n (%)	11 (4.9)	15 (6.7)	12 (5.5)
Glycosylated haemoglobin increased, n (%)	12 (5.3)	6 (2.7)	11 (5.1)
Special interest categories			
Hypoglycaemia, n (%)	35 (15.6)	53 (23.7)	42 (19.4)
AEs belonging to BICMQ 'UTI', n (%)	36 (16.0)	38 (17.0)	35 (16.1)
AEs belonging to BICMQ 'genital infection', n (%)	2 (0.9)	10 (4.5)	13 (6.0)
AEs belonging to BICMQ 'volume depletion', n (%)	1 (0.4)	2 (0.9)	1 (0.5)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Empagliflozin as add-on combination to basal insulin with or without metformin and/or sulphonylureas (1245.33 – EMPA-REG BASAL)

The incidence of AEs on treatment was similar across all treatment groups: 84.6% in the empagliflozin 10mg group, 87.1% in the 25mg group and 87.1% in the placebo treatment group. During the treatment period, the highest incidence of adverse events was reported for the MedDRA system organ class 'infections and infestations' reported at a higher incidence in the empagliflozin 10mg and 25mg groups (49.1% and 45.8%, respectively) compared with the placebo group (42.9%).

A summary of AEs occurring in study 1245.33 can be seen in Table 45.

Table 45: Summary of AEs in study 1245.33

	Placebo (n=170)	Empagliflozin 10mg (n=169)	Empagliflozin 25mg (n=155)
One or more AE(s), n (%)	148 (87.1)	143 (84.6)	135 (87.1)
One or more drug-related AE(s), n (%)	52 (30.6)	65 (38.5)	68 (43.9)
AEs leading to discontinuation, n (%)	13 (7.6)	19 (11.2)	20 (12.9)
One or more serious AE(s), n (%)	28 (16.5)	28 (16.6)	28 (18.1)
Deaths, n (%)	1 (0.6)	0	0
AEs with frequency of ≥5% in any randomised group			
URTI, n (%)	10 (5.9)	18 (10.7)	13 (8.4)
UTI, n (%)	13 (7.6)	21 (12.4)	16 (10.3)
Nasopharyngitis, n (%)	22 (12.9)	20 (11.8)	17 (11.0)
Hypoglycaemia, n (%)	56 (32.9)	56 (33.1)	55 (35.5)
Hyperglycaemia, n (%)	17 (10.0)	16 (9.5)	15 (9.7)
Back pain, n (%)	13 (7.6)	11 (6.5)	13 (8.4)
Dizziness, n (%)	12 (7.1)	18 (10.7)	7 (4.5)
Diarrhoea, n (%)	13 (7.6)	10 (5.9)	11 (7.1)
Nausea, n (%)	12 (7.1)	9 (5.3)	8 (5.2)
Arthralgia, n (%)	10 (5.9)	6 (3.6)	8 (5.2)
Cough n (%)	9 (5.3)	6 (3.6)	4 (2.6)
Headache, n (%)	5 (2.9)	5 (3.0)	8 (5.2)
Depression, n (%)	4 (2.4)	11 (6.5)	2 (1.3)
Vomiting, n (%)	5 (2.9)	4 (2.4)	8 (5.2)
Fatigue, n (%)	2 (1.2)	10 (5.9)	2 (2.6)

Hypertension, n (%)	12 (7.1)	1 (0.6)	3 (1.9)
Special interest categories			
Hypoglycaemia, n (%)	60 (35.3)	61 (36.1)	56 (36.1)
Events requiring assistance, n (%)	0	0	2 (1.3)
AEs belonging to BICMQ 'UTI', n (%)	15 (8.8)	25 (14.8)	18 (11.6)
AEs belonging to BICMQ 'genital infection', n (%)	3 (1.8)	13 (7.7)	8 (5.2)
AEs belonging to BICMQ 'volume depletion', n (%)	2 (1.2)	6 (3.6)	6 (3.9)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Empagliflozin in patients with renal impairment (1245.36 – EMPA-REG RENAL)

During the 52 week study 87.8% of subjects in the empagliflozin 10mg group, 83.5% of subjects in the empagliflozin 25mg group and 84.6% of subjects in the placebo treatment group reported ≥1 AE. The highest percentage of subjects with AEs was reported for the MedDRA system organ class 'infections and infestations' (50.0% of subjects in the empagliflozin 10mg group, 44.9% of subjects in the empagliflozin 25mg group and 42.6% of patients in the placebo group). This was followed by the MedDRA system organ class 'metabolism and nutrition' (34.7%, 39.9% and 44.5% in the empagliflozin 10mg, 25mg and placebo groups, respectively).

A summary of AEs occurring in study 1245.36 can be seen in Table 46.

Table 46: Summary of AEs in study 1245.36

	Placebo (n=319)	**Empagliflozin 10mg (n=98)**	**Empagliflozin 25mg (n=321)**
One or more AE(s), n (%)	270 (84.6)	86 (87.8)	268 (83.5)
One or more drug-related AE(s), n (%)	87 (27.3)	37 (37.8)	101 (31.5)
AEs leading to discontinuation, n (%)	17 (5.3)	4 (4.1)	21 (6.5)
One or more serious AE(s), n (%)	44 (13.8)	4 (4.1)	21 (6.5)
Deaths, n (%)	3 (0.9)	0	1 (0.3)
AEs with frequency of ≥5% in any randomised group			

UTI, n (%)	41 (12.9)	14 (14.3)	41 (12.8)
URTI, n (%)	25 (7.8)	14 (14.3)	35 (10.9)
Nasopharyngitis, n (%)	29 (9.1)	6 (6.1)	27 (8.4)
Influenza, n (%)	8 (2.5)	6 (6.1)	27 (8.4)
Balantis Candida, n (%)	0	5 (5.1)	0
Hypoglycaemia, n (%)	92 (28.8)	27 (27.6)	92 (28.7)
Hyperglycaemia, n (%)	41 (12.9)	4 (4.1)	25 (7.8)
Back pain, n (%)	20 (6.3)	8 (8.2)	19 (5.9)
Pain in extremity, n (%)	10 (3.1)	8 (8.2)	7 (2.2)
Arthralgia, n (%)	21 (6.6)	7 (7.1)	13 (4.0)
Headache, n (%)	13 (4.1)	5 (5.1)	16 (5.0)
Cough n (%)	25 (7.8)	2 (2.0)	11 (3.4)
Hypertension, n (%)	22 (6.9)	1 (1.0)	14 (4.4)
Special interest categories			
Hypoglycaemia, n (%)	73 (22.9)	23 (23.5)	71 (22.1)
Events requiring assistance, n (%)	5 (1.6)	1 (1.0)	5 (1.6)
AEs belonging to BICMQ 'UTI', n (%)	47 (14.7)	14 (14.3)	47 (14.6)
AEs belonging to BICMQ 'genital infection', n (%)	8 (2.5)	7 (7.1)	11 (3.4)
AEs belonging to BICMQ 'bone fracture', n (%)	12 (3.8)	2 (2.0)	3 (0.9)
AEs belonging to BICMQ 'volume depletion', n (%)	8 (2.5)	1 (1.0)	9 (2.8)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; URTI = upper respiratory tract infection; UTI = urinary tract infection

Empagliflozin in patients with hypertension (1245.48 – EMPA-REG BP)

The frequency of patients with ≥1 AE on treatment was 48.9% in the empagliflozin 10mg group, 51.4% in the empagliflozin 25mg group and 52.6% in the placebo group. The highest frequency of AEs was reported for the MedDRA system organ class 'infections and infestations' with similar frequencies across all treatment groups (empagliflozin 10mg: 20.3%, empagliflozin 25mg: 22.8%, placebo: 20.6%).

A summary of AEs occurring in study 1245.48 can be seen in Table 47.

Table 47: Summary of AEs in study 1245.48

	Placebo (n=272)	Empagliflozin 10mg (n=276)	Empagliflozin 25mg (n=276)
One or more AE(s), n (%)	143 (52.6)	135 (48.9)	142 (51.4)
One or more drug-related AE(s), n (%)	21 (7.7)	55 (19.9)	54 (19.6)
AEs leading to discontinuation, n (%)	5 (1.8)	4 (1.4)	6 (2.2)
One or more serious AE(s), n (%)	7 (2.6)	3 (1.1)	4 (1.4)
Deaths, n (%)	0	1 (0.4)	0
AEs with frequency of ≥2% in any randomised group			
Nasopharyngitis, n (%)	26 (9.6)	15 (5.4)	20 (7.2)
UTI, n (%)	10 (3.7)	11 (4.0)	10 (3.6)
Hypoglycaemia, n (%)	14 (5.1)	10 (6.9)	19 (6.9)
Headache, n (%)	12 (4.4)	7 (2.5)	10 (3.6)
Dizziness, n (%)	2 (0.7)	7 (2.5)	8 (2.9)
Cough n (%)	9 (3.3)	2 (0.7)	5 (1.8)
Nausea, n (%)	2 (0.7)	2 (0.7)	6 (2.2)
Pollakiuria, n (%)	7 (2.6)	11 (4.0)	17 (6.2)
Polyuria, n (%)	1 (0.4)	8 (2.9)	4 (1.4)
Thirst, n (%)	1 (0.4)	2 (0.7)	15 (5.4)
Special interest categories			
Hypoglycaemia, n (%)	13 (4.8)	18 (6.5)	17 (6.2)
Events requiring assistance, n (%)	0	0	0
AEs belonging to BICMQ 'UTI', n (%)	10 (3.7)	11 (4.0)	13 (4.7)
AEs belonging to BICMQ 'genital infection', n (%)	1 (0.4)	14 (5.1)	15 (5.4)
AEs belonging to BICMQ 'volume depletion', n (%)	1 (0.4)	1 (0.4)	0

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; UTI = urinary tract infection

Empagliflozin add-on to multiple daily injections of insulin (1245.49 EMPA-REG MDI)

Overall, the frequency of on treatment AEs was balanced across all treatment groups (86.0%, 84.7% and 89.9% in the empagliflozin 10mg, empagliflozin 25mg and placebo groups, respectively). The highest frequency of AEs was reported for the MedDRA system-organ class 'metabolism and nutrition disorders': 59.1% for empagliflozin 10mg, 61.4% for empagliflozin 25mg and 65.4% for placebo.

A summary of AEs occurring in study 1245.49 can be seen in Table 48.

Table 48: Summary of AEs in study 1245.49

	Placebo (n=188)	Empagliflozin 10mg (n=186)	Empagliflozin 25mg (n=189)
One or more AE(s), n (%)	169 (89.9)	160 (86.0)	160 (84.7)
One or more drug-related AE(s), n (%)	64 (34.0)	56 (30.1)	76 (40.2)
AEs leading to discontinuation, n (%)	9 (4.8)	10 (5.4)	9 (4.8)
One or more serious AE(s), n (%)	22 (11.7)	20 (10.8)	22 (11.6)
Deaths, n (%)	0	0	1 (0.5)
AEs with frequency of ≥5% in any randomised group			
Hypoglycaemia, n (%)	111 (59.0)	97 (52.2)	110 (58.2)
Hyperglycaemia, n (%)	14 (7.4)	6 (3.2)	8 (4.2)
Nasopharyngitis, n (%)	40 (21.3)	34 (18.3)	27 (14.3)
UTI, n (%)	23 (12.2)	24 (12.9)	24 (12.7)
Influenza, n (%)	12 (6.4)	7 (3.8)	14 (7.4)
Bronchitis, n (%)	12 (6.4)	10 (5.4)	8 (4.2)
Gastroenteritis, n (%)	10 (5.3)	8 (4.3)	1 (0.5)
Arthralgia, n (%)	10 (5.3)	18 (9.7)	11 (5.8)
Back pain, n (%)	14 (7.4)	12 (6.5)	15 (7.9)
Diarrhoea, n (%)	17 (9.0)	12 (6.5)	18 (9.5)
Dizziness, n (%)	2 (1.1)	5 (2.7)	13 (6.9)
Headache, n (%)	9 (4.8)	8 (4.3)	11 (5.8)
Hypertension, n (%)	10 (5.3)	9 (4.8)	7 (3.7)
Special interest categories			
Hypoglycaemia, n (%)	109 (58)	95 (51.1)	109 (57.7)
Events requiring assistance, n (%)	3 (1.6)	3 (1.6)	1 (0.5)
AEs belonging to BICMQ 'UTI', n (%)	29 (15.4)	29 (15.6)	29 (15.3)
AEs belonging to BICMQ 'genital infection', n (%)	3 (1.6)	8 (4.3)	18 (9.5)

	Placebo (n=188)	Empagliflozin 10mg (n=186)	Empagliflozin 25mg (n=189)
AEs belonging to BICMQ 'volume depletion', n (%)	2 (1.1)	3 (1.6)	4 (2.1)

AEs = adverse events; BICMQ = BI-customised medical dictionary for drug regulatory activities (MedDRA) query; UTI = urinary tract infection

6.10 Interpretation of clinical evidence

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

Both doses of empagliflozin were associated with a statistically significant reduction in mean HbA_{1C} compared with placebo in treatment-naive patients and patients on different background therapies. Furthermore, these reductions in HbA_{1C} were maintained during the course of the study. Treatment with empagliflozin also resulted in statistically significant reductions in other measures of blood glucose, including FPG and MDG, compared with placebo. In addition to its effects on blood glucose, empagliflozin was shown to reduce blood pressure and body weight, both of which are important risk factors for cardiovascular events in patients with T2DM.

Both doses of empagliflozin had a favourable safety profile and were well tolerated over the course of the study. Overall, AEs and SAEs were similar between both empagliflozin groups and placebo. The incidence of hypoglycaemia was low across all treatment groups, although an increased frequency compared with placebo was observed when empagliflozin was administered in addition to SU or insulin as background therapy. Compared with placebo, there was an increased rate of genital infections observed with empagliflozin, although these were generally of mild or moderate intensity. The incidence of UTIs was similar across both empagliflozin groups and placebo, although empagliflozin was associated with a greater frequency of UTIs in females compared with placebo. In addition, both genital infections and UTIs were more common in females than males. The frequency of volume depletion was low across all clinical studies and comparable between all treatment groups. The highest incidences were observed in patients with moderate renal impairment in the dedicated renal impairment study (1245.36).

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

Reduction in HbA1c with empagliflozin is superior to placebo in treatment-naïve patients or in patients on different background therapies, including insulin. In addition to its effect on HbA_{1c}, empagliflozin reduces blood pressure and body weight, both important CV risk factors in patients with T2DM.

The majority of empagliflozin clinical trials demonstrate the efficacy and safety of empagliflozin versus placebo, as placebo-controlled data are the accepted standard for demonstrating glucose-lowering efficacy of new T2DM agents. However, no head-to-head trials have been conducted between empagliflozin and canagliflozin and/or dapagliflozin, which means that direct comparisons between the two products are not available

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

The empagliflozin comprehensive programme of clinical studies has been undertaken to demonstrate the efficacy and safety of empagliflozin in T2DM patients on a broad range of background therapies. The studies included in this submission involve T2DM patients who are inadequately controlled on their current therapy which reflects the decision problem of the submission. The outcomes of the studies are both relevant to clinical practice and address the unmet need for additional treatment options for patients inadequately controlled on their current therapy.

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

On most endpoints in the clinical trial programme, both doses of empagliflozin resulted in significant improvements compared with placebo. Both empagliflozin 10mg and 25mg consistently demonstrate sustained, clinically meaningful, and statistically significant efficacy in terms of HbA1c. Detailed recommendations for the use of empagliflozin will be described in the summary of product characteristics (SmPC), which will be made available after the marketing authorisation has been granted by the European Commission

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

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

No review of existing cost effectiveness models that included empagliflozin was conducted because no trial data has been published to allow a cost effectiveness analysis of empagliflozin to be conducted.

However, a review of existing diabetes cost effectiveness models and analyses were performed to identify values for utilities and costs and to inform the model structure. The identified analyses will also be used to conduct sensitivity analyses.

The review is an update of one conducted by Yi and co-workers (84) that identified models used in the assessment of OADs and their acceptability to HTA authorities. For this update the same search strategy was utilised.

The search was carried out on the computerised bibliographic databases MEDLINE, EMBASE, databases of the Centre for Reviews and Dissemination (CRD), and the Health Economic Evaluation Database (HEED).

The search strategy consisted of the combination of the following test words:

- ‘Economic$’ or ‘pharmaceutical’ or ‘cost$:’
- Combined with ‘model$’ or ‘analy$’ or ‘evaluation$’:
- Combined with ‘diabetes mellitus’ or ‘diabetes’ or ‘type II diabetes mellitus’ or ‘type 2 diabetes’ or type II diabetes$’ or ‘antidiabetic’ NOT ‘diabetes insipidus’.

The language was limited to English and a date limit was set to 1st September 2008 to 21st October 2013.

In addition, a search was conducted on 30/11/2013 of websites of HTA bodies in order to identify which models had been used in HTA evaluations for T2D drug treatments.

The websites for agencies listed as members of INAHTA (International Network of Agencies for HTA) were searched.

This includes:

- Scottish Medicines Consortium (SMC) (Scotland)
- The National Institute for Health and Clinical Excellence (NICE) (England and Wales)
- The Institute for Quality and Efficiency in Health Care (IQWIG) (Germany)
- Hau Autorite de Sante (HAS) (France)
- Agenazia Italiana del Farmco (AIFA) (Italian)
- Pharmaceutical Benefits Advisory Committee (PBAC) (Australia)
- College for Health Insurance (CVZ) (Netherlands)
- Tandvård-s och Läkemedelsförmånsverket (TLV) (Sweden)
- Canadian Agency for Drugs and Technologies in Health (CADTH) (Canada)

This review identified three new studies, which corresponded to NICE submissions for liraglutide and exenatide, both appraisals utilised the CORE model which is described in greater detail later in the submission.(85, 86)

In addition, a review of the input variables included in previous NICE technology appraisals of treatments within the scope was undertaken. This included dapagliflozin, liraglutide, exenatide, clinical guideline 87 and the appraisal consultation document (ACD) for canagliflozin. (41, 87, 88) Original references were identified following data extraction from manufacturer submissions and the assessment report (in CG87). The ACD and FADs were examined to identify any concerns the appraisal committee may have had with the values used in the economic modelling. These data extractions are reported in Sections 7.4 and 7.5 for utilities and costs respectively.

Section 9.8, Appendix 8 presents an overview of the main modelling techniques used across the assessment of diabetes. This review indicated that the two most

common models used in HTA submissions are the IMS CDM (IMS Diabetes CORE model) and the UKPDS outcomes equations.(26, 89)

Description of identified studies

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

Section 9.8, Appendix 8 presents an overview of the main modelling techniques used across the assessment of diabetes. This review indicated that the two most common models used in HTA submissions have been the CORE model and the UKPDS outcomes equations. (26, 89)

Both models are underpinned by the UKPDS risk equations.(90) The UKPDS health outcome risk equations were derived utilising data for a cohort of 3,642 diabetic patients aged 25-65 years in the UK. Weibull models were used for the estimation of the probabilities of diabetes-related complications, while panel models were used for the estimation of HbA1c, SBP and lipid ratio, logistic models for the estimation of the smoking status and event fatality, and gompertz models were sued for the estimation of diabetes mortality and other death.(90)

The UKPDS model is an integrated system of event risk equations and simulation algorithms that predict the occurrence and timing of seven diabetes-related complications and death. In addition, the equations are defined concerning HbA1c, systolic blood pressure (SBP), lipid ratio and smoking. The JADE model extends the UKPDS outcomes model by allowing an intervention comprising a series of treatment regimens to affect health outcomes, costs and quality of life over time through time-varying risk factors, risk of diabetes-related complications and AEs.(91)

The CORE model is composed of a series of interconnected Markov models which represent the patient characteristics, clinical parameters, risk factors, treatment effects, complications and economic parameters over time. The structure is subdivided into four separate elements: a user interface, the input databases, the data processor and the output database.

Both of these approaches have been used and accepted in submissions to NICE and in clinical guideline development.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Given the type of review undertaken, the suggested quality assessments are not appropriate. A considerable amount of work has gone into validating the models for diabetes, usually by comparing the predicted clinical results from the models with the results from long term clinical studies. The CORE and UKPDS outcomes models have been extensively internally and externally validated in peer reviewed publications and tested at the Mount Hood challenges, a conference organised regularly to assess and validate diabetes models in comparison to epidemiology studies (Palmer et al 2013).(26, 92, 93)

The original equations have been validated against recent CV studies including Leal and colleagues.(94) These studies have indicated that generally the UKPDS equations appear to overestimate the risk of certain CV events.

- A new system of risk equations based on the UKPDS data has been recently published, the UKPDS 82.(95) This new system of risk equations estimates first time and second time long term complications for the same complications initially included in the UKPDS 68. Furthermore, the new system of risk equations allows for the estimation regarding the incidence of ulcers. The authors have outlined several advantages of the new equations compared with the initial set of equations: The equations could be considered to be more representative of clinical practice. The dataset is larger and includes more recent data which was collected in a non-RCT setting.

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[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

- The system of risk equations captures more outcomes including:
    - first and second time events
    - ulcers
    - four types of mortality (previously only three types were included)
- The internal validation was conducted using a 25-year period, instead of a period of 12 years.
- The equations take into account new relevant risk factors (including eGFR), which result in more accurate predictions obtained over time.

However, the implementation of this new system of risk equations requires additional variables to populate the model, most of which have not been reported in clinical trials (i.e. white blood cell count and haemoglobin g/dL) (see clinical section 6). In addition, NICE appraisals Committees have indicated a preference for consistency in approach and the SGLT2is appraisals have both utilised the UKPDS 68 equations. Finally as the analysis is to be validated with the IMS CORE model which still utilises the UKPDS 68 equations it was decided to use the UKPDS equations in the model developed for NICE.

7.2 De novo analysis

Patients

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

Table 49 presents the patient characteristics included in the cost effectiveness analysis. The population considered in the model mainly reflected the T2DM population from the UKPDS study. Most of the values for the baseline characteristics were based on values from a subgroup of 3,642 individuals who were part of the 5,102 newly diagnosed T2DM patients included in the UKPDS. Baseline characteristics included the distribution of the population by sex, ethnicity (the percentage of individuals with Afro-Caribbean or with Asian background), smoking status (percentage of smokers) and the baseline biochemical measurements (HbA_{1C}, SBP and the lipid ratio).

These patients were selected as they corresponded to the population of interest in the UK. Patients in the UKPDS had no recent history of myocardial infarction (MI), ischemic heart disease (IHD) or coronary heart failure (CHF) and had never had more than one major vascular event or concurrent illness that would limit life expectancy and given that UKPDS patients were recently diagnosed and the model focused on second and third line therapies, the final values used to determine the percentage of patients that had experienced a CV or other type of complication at baseline were obtained from the T2DM clinical guidelines. These factors were reflected in the values of the parameters considered in the model. The age of patients initiating 2nd line therapy was obtained from 1245.28, in which patients were treated after failure with metformin. Therefore, representing initiation to second line therapy according to the UK clinical treatment pathway. Then the age of patients initiating third line therapy or insulin was reflected by the values used in the T2DM NICE clinical guidelines.

Age was the only parameter that was considered from this investigation as the majority of the study population was non-European (59%). Therefore, the overall patient population may not be representative of the UK T2DM population.

In the model developed for NICE clinical guideline 87, it was assumed that at the moment of diagnosis, T2DM patients did not have a history of atrial fibrillation or peripheral vascular disease. This was because the guideline developers could not identify any data that gave both baseline characteristics and CV history data. The empagliflozin model included these factors in the base case as evidence was identified for atrial fibrillation (Kothari et al 2002) and PVD (Walters et al 1992).

Table 49: Patient characteristics in the cost effectiveness analysis

	Patients initiating 2nd line				Patients initiating 3rd line			
	Mean	**Lower bound**	**Upper bound**	**SE**	**Mean**	**Lower bound**	**Upper bound**	**SE**
Age when initiating assessed treatment [years]	55.9‡			0.264	58†	48	68	
Female	45.15%**			0.017	39%†	31%	46.8%	
Afro-Caribbean	1.20%**			0.004	8%†	6.4%	9.6%	
Asian	1.50%**			0.004	10%†	8%	12%	
Smoking status	31%†			0.046	31%†	24.8%	37.2%	
Atrial fibrillation	0.62%†			0.001	0.62%†			0.001
Peripheral vascular disease	23.5%^	20.5%	26.5%		23.5%	20.5%	26.5%	
HbA1c when starting 2nd line (%)	7.5†	6	9					
HbA1c when starting 3rd line (%)					7.5†	6	9	
Systolic blood pressure when initiating assessed treatment (mm Hg)	135†			20	140†	130	150	
Total cholesterol:HDL when initiating assessed treatment	5.05**			1.13	4.4†	3.8	5	
BMI when initiating assessed treatment [kg/m2]	27.5†			5.2	30.42†	27.42	33.42	

HDL: High density lipoprotein
Source: UKPDS; NICE Clinical Guidelines†; Ridderstrale(2013)(11)‡, Walters (1992)(96)*; Clinical opinion** Kothari (2002)^

The parameters related to the disease history of patients are presented in Table 50. The same values were used for patients initiating second or third line therapy due to a lack of information for different lines of therapy.

Table 50: Disease history of patients in the cost effectiveness analysis

	Mean	Lower bound	Upper bound
% which have had ischaemic heart disease	3.2%	2.6%	3.8%
% for whom the first myocardial ischaemic event occurred during the past year	1.2%	1.0%	1.4%
% for whom the first myocardial ischemic event occurred more than 1 year ago	3.5%	2.8%	4.2%
% for whom first stroke event occurred during past year	0.2%	0.1%	0.2%
% for whom first stroke event occurred more than 1 year ago	1.2%	0.9%	1.4%
% who have experienced a CHF	0.7%	0.6%	0.8%
% with an amputation	0.4%	0.3%	0.4%
% who have experienced blindness on one eye	1.2%	1.0%	1.4%
% with renal failure	0.1%	0.0%	0.2%
Number of years after diagnosis of diabetes	5.0	0.0	10.0
% for whom it is the second year after diagnosis of diabetes	10.0%	10.0%	10.0%

Sources: All values from Clarke (2004)(26); NICE Clinical Guidelines CG66 (tables C1 and C4).

The average height and weight of women and men in the UK was considered to assess the impact of treatment efficacy on BMI by transforming height and weight into BMI (see Table 51).

Table 51: Average height for men and women to calculate BMI

	Average height
For men	1.77
For women	1.63

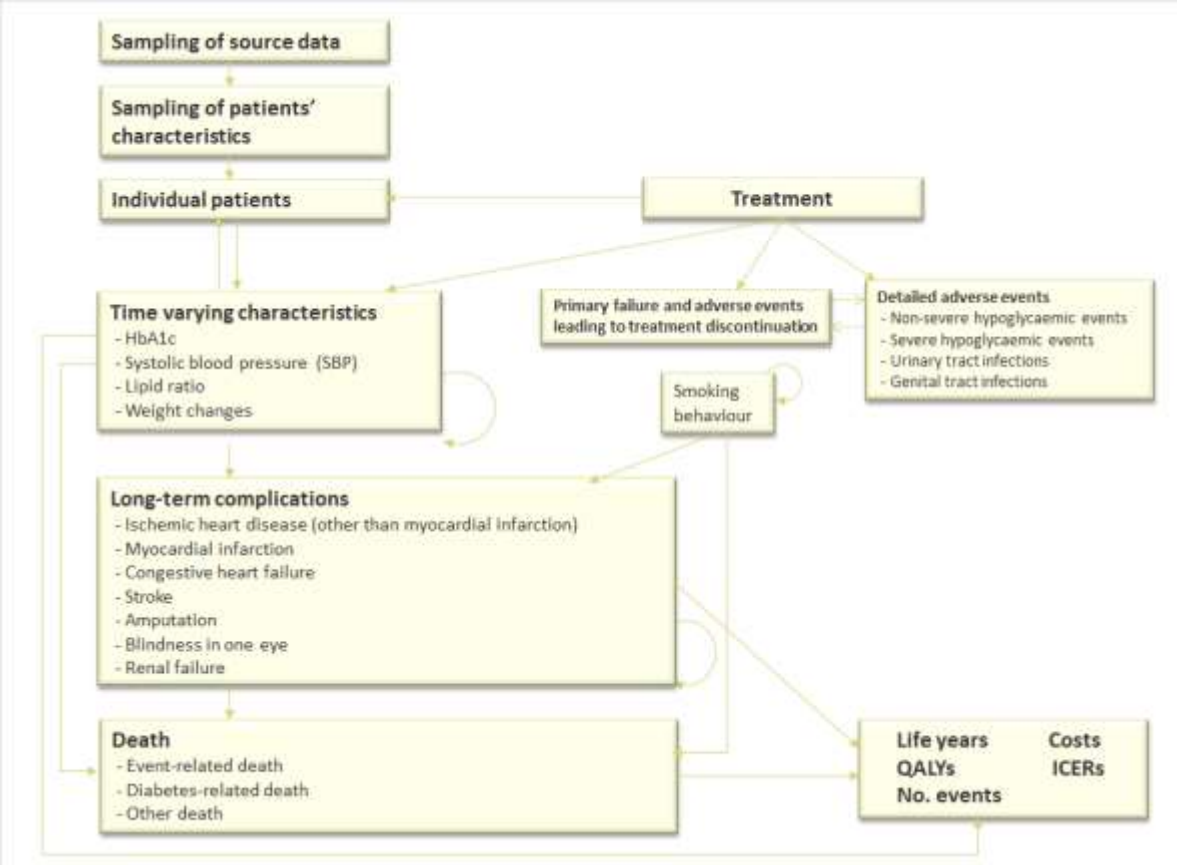
Source: Adult trend tables, Health Survey for England (2008)(97)

Model structure

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

Figure 33 presents a schematic of the model developed for this appraisal (hereafter referred to as ECCM).

Figure 33: Diagram of economic model



Model overview

The model was restricted to only comparing two treatments at a time. To enable the results of treatment combinations which were ran in different simulations to be replicated and compared, two random seeds (one for the random values used at the sample level and another one for the values used at the patient level) were implemented in the model and their values were fixed for the analyses. Patients progressed throughout the model in 6-month cycles (until death or until the end of the time horizon, for a maximum of 40 years). In total, 60,000 simulations were conducted, considering a sample of 30,000 patients per treatment arm (300 samples of 100 patients each). These values were chosen as this was the maximum number of simulations Excel can manage. To ensure that these were sufficient the model was run with fewer simulations to ensure that the cost effective estimates remained consistent.

Patient simulation

The ECEM started by sampling the efficacy, safety, discontinuation and costs associated with each of the treatment combinations, and the utility values to be applied per sample, with each of the samples in the model being allocated a different set of values. Then, the ECEM simulated a patient within a sample by assigning a baseline profile to that patient according to the corresponding risk factors that are drawn from the distributions of population characteristics of the UK adult population with T2DM (in terms of age, sex and ethnicity –determined by the proportion of individuals with a white, Afro-Caribbean or Asian background-, and the smoking status). These patient characteristics were mostly drawn according to the cohort within the UKPDS study, which was assumed to be representative of the target population for the UK. Additionally, individuals were assigned baseline risk factors (baseline BMI and HbA1c, SBP and lipid ratio levels) and a specific disease history (in terms of whether patients had experienced previous complications such as ischemic heart disease , myocardial infarction or stroke, and the number of years passed since the patient was diagnosed with diabetes). As patients progressed, their profiles were updated according to time, varying risk factors, AEs experienced and complications.

The ECEM simulated the standard pathway of pharmacological treatments used by an individual with T2DM. This pathway consisted on starting with either the intervention or the comparator of interest (at the point of initiating dual therapy or triple treatment, depending on the treatment strategies evaluated in the simulation).

Using the same approach as the JADE model, at the beginning of each cycle the ECCM checked whether a modification in the treatment was to be made.

The type of situations that could lead to treatment changes included:

- Primary failure
    - lack of efficacy during the first treatment cycle which resulted in the patient being administered the following line of treatment within the identified treatment pathway
- AEs leading to discontinuation
    - switch of the last treatment administered within the same treatment line due to experiencing an AE that necessitated discontinuation

- Uncontrolled HbA1c levels at any time after treatment initiation following glucose control with the administered treatment, when the HbA1c levels exceeded the threshold with the current treatment.
    - In this case insulin was to be added to the current treatments in line with NICE guidelines.

The ECEM checked for primary failures or AEs leading to discontinuation. If these cases arose the patient was to be administered the next treatment combination within the same treatment line. In case of discontinuation, the efficacy assumed for the first 6 months of treatment was that of the treatment initially administered rather than the treatment to which the patient was changed.

If no AE leading to discontinuation occurred, then the model evaluated whether the HbA1c levels exceeded the HbA1c threshold of 7.5% in line with current NICE guidance. If the threshold has been exceeded, insulin was to be prescribed which was the last treatment added.

In the ECEM, treatment efficacy was estimated as the impact of treatment on the HbA1c levels and on several other risk factors, including: systolic blood pressure (SBP) and body mass index (BMI). Each therapy was associated with an initial effect upon each of the risk factors (HbA1c, SPB and weight changes). Lipid ratio was assumed to remain constant over time given the lack of information identified through the systematic review of clinical evidence.

With each new administered treatment combination, HbA1c and SBP changes followed three stages:

- A drop in the levels of the risk factors occurred during the 1st cycle after treatment initiation.

- This effect was maintained during a period of time, which could be defined by the user. For the purposes of the base case analysis the maintenance period was set up to 1 year since based on the results of the empagliflozin phase III 1245.31 Extension Trial, the effect of treatment on risk factors such as HbA1c and SBP was observed during the first 6 months and these effects appeared to be maintained for 52 to 72 weeks after treatment initiation (see Section 6.5).

- Once the maintenance period was over, the levels of the risk factors increased based on the UKPDS system of risk equations.

It should be noted that the risk of an event was based on the UKPDS risk equations and was computed for each cycle. The UKPDS system of risk equations and the corresponding covariance matrices used in the ECEM are presented in Section 9.9, Appendix 9.

How efficacy was modelled

The estimation of the levels of HbA1c, SBP and lipid ratio from the UKPDS system of equations (presented in appendix 15) was based on annual measures of each risk factor, except for the smoking status of the patient, which was based on 3-year periods due to its less frequent ascertainment during the UKPDS study. Moreover, during each cycle, the BMI of the patient was updated based on weight changes experienced due to treatment. Probabilities were adjusted to reflect the 6-month cycle considered in the model.

To model the impact of T2DM treatments on weight five elements were taken into account:

- The baseline weight of the patient, before any treatment-related change or natural weight gain was applied.
- The treatment-related weight change experienced by the patient as a result of the treatment effect. Depending on the treatment and the simulated values, this treatment effect could result in a weight loss, weight increase or maintenance of weight (if the treatment did not have an effect on weight). Two alternative scenarios could be defined to determine the evolution of weight over time:
    - The first scenario assumed that every time a patient initiated a new treatment combination, the weight change associated with the new treatment would happen gradually during the cycles following the initiation of the new treatment and as long as the patient continued receiving the same treatment. The model allowed changing the duration of time during which the weight change would gradually happen. It was assumed that during this

period, the same weight change would happen during each cycle (i.e. weight change was distributed proportionally through time).

- The second scenario assumed that the change of weight was fixed and the full weight change would happen during the first cycle after initiating a new treatment. Therefore, the patient would experience a change of weight during the first cycle in which a new treatment was administered and would maintain that weight change as long as the patient continued receiving the same treatment.

As long as the patient continued to receive the same treatment, the weight change was assumed to be maintained over the time of weight loss maintenance after the full weight change had been achieved. This full weight change would take longer to achieve under scenario 1, and 6 months under scenario 2, as stated above. For the ECEM, whenever a patient switched to a different treatment, it was assumed that their weight at the beginning of the new treatment would be equal to their baseline weight plus the natural weight they would have experienced if no treatment would have influenced their weight since their initiation in the model (i.e. 0.1 kg multiplied by the number of years since treatment initiation) plus the impact on weight of the new treatment, independently of whether the previous treatment was a weight-loss or a weight-gain treatment.

Although this assumption may not be fully realistic for the treatments that result in weight gain (given that the expectation is for this weight gain to be maintained over time), it was considered to be very conservative, so that the weight change assumptions in this model could be in line with the assumptions made by the Decision Support Unit (DSU) consulted during the dapagliflozin NICE appraisal. In this case, when considering the impact of treatment changes on weight, the approach implemented by the DSU assumed that if an early treatment switch occurred, the starting weight of the new therapy would be set equal to the weight that should have been achieved after the weight regained period from the previous therapy was fully achieved. The idea behind this was to allow drugs associated with weight loss to converge over time. This was justified on the fact that considering that starting weight was based on weight at the time of switching from the previous treatment could be problematic since HbA1c levels may rise above

the switching threshold (7.5%) before treatment-related weight loss had had time to be regained.

For the base case analysis the first scenario was assumed as it was the most conservative. This was justified on the basis of the results of the empagliflozin Phase III 1245.31 Extension Trial. In this study, patients initially recruited in the clinical trials 1245.19, 1245.20 and 1245.23 continued to receive the same treatment as previous trials until the last patient entered had been treated for 76 weeks in total.

The study comprised 1,869 patients from a total population of 2,700 patients who were initially enrolled in the original trials. During the extension trial it was noted that patients receiving empagliflozin (52 weeks) either as monotherapy or as an add-on to pioglitazone or metformin experienced a gradual decrease in their weight. Furthermore, this reduction was maintained for the remaining treatment duration (up to 76 weeks) for patients receiving empagliflozin as monotherapy and in combination with metformin. Patients receiving 25 mg empagliflozin as an add-on to pioglitazone experienced a slight increase.). Patients treated with empagliflozin as an add-on to metformin plus SU reported full weight change 24 weeks following treatment initiation), which was maintained for the remaining duration of the trial (total treatment duration of 76 weeks).

Once the patient had achieved the full weight change, it was assumed that weight would be maintained for a half-a-year. During this period, the loss or gain of weight would be maintained, unless the patient experienced another treatment change.

Given the uncertainty around how long a patient losing weight due to a T2DM treatment would maintain that weight loss, the model allowed the conservative assumption of patients going back to their initial baseline weight.

Adverse events

The occurrence of medication-related side effects was estimated. The type of AEs that could be considered in the model included:

- Hypoglycaemias (both non-severe and severe)
- Urinary tract infections (UTIs)

- Genital infections

The estimation of diabetes-related events was conducted according to the first occurrence of the event and the time the diabetes-related complication occurs. Over time, simulated patients could develop multiple complications, although the model tracked the occurrence of only the first complication of each specific type. The types of diabetes-related complications simulated in the model included:

- IHD
- MI
- CHF
- Stroke
- Amputation
- Renal failure
- Blindness in one eye.

The frequency of events was based on the methods used in the UKPDS Outcomes Model. For the estimation of CV-related long term complications it was assumed that for patients who had experienced an MI, the patient could not subsequently develop IHD since IHD and CHF events in the study were only recorded prior to an MI event. Moreover, only the first occurrence of long term complications was measured.

A complication occurred whenever the computed risk of the event was greater than the random number drawn from a uniform distribution with values ranging between 0 and 1. The events were interdependent; the occurrence of an event could influence the likelihood of another event to happen, as stated by the system of risk equations. For example, the probability of an MI was greater when either an IHD or a CHF event had previously occurred. To capture the interdependency, risk equations were run in random order in each cycle. For this, in each cycle, random values were used to assess what risk equation should be first considered when estimating the outcomes per cycle, in order to avoid having always the same type of event estimated first and therefore increasing the likelihood of overestimating some of the events in detriment of some others.

For consistency with the UKPDS system of equations, according to which IHD and CHF events were recorded only if they had occurred prior to an MI event, the model assumed that IHD would not occur after a patient had experienced an MI.

The inclusion of UTIs and genital infections was based on evidence from Phase III trials.

Mortality

At the beginning of each cycle the model evaluated whether the patient was still alive. In each cycle a patient was at risk of dying due to diabetes or other causes.

The risk of event-related mortality and diabetes-related mortality followed the UKPDS system of equations and was dependent on if a patient had previously experienced an MI or stroke (first case) or an amputation or renal failure (second case). Death from other causes also followed the corresponding UKPDS risk equation although it was not influenced for the occurrence of complications.

Deaths were finally categorised in 2 groups: diabetes-related (which accounted for all deaths directly related to the occurrence of an event or due to diabetes) and due to other causes.

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

The ECEM development was based on a systematic review of economic models published by Li et al (2010) and NICE appraisals (see Section 2.5).

The ECEM allows the simulation of treatment pathways consistent with NICE clinical guidelines and incorporation of issues such as switching and discontinuations due to lack of efficacy or AEs. In addition, it includes the long term effects of diabetes so that the total burden can be estimated. The model was developed in Excel® 2010 using Visual Basic® for Applications (VBA).

The CORE model was not utilised as the primary analysis as with the ECEM reviewers can have access to the risk equations to assess their validity. It also allows for amendments to both inputs and structure. However, the CORE model was utilised in a validation exercise given its acceptance in previous HTAs and also due to the outcome of the dapagliflozin appraisal. (National Health Institute for Health and Clinical Excellence., 2013b)

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

As the model is a micro-simulation there are no health states as such. Patients are sampled and followed through the 6 month cycles until the end of the user-specified time horizon (in the base case 40 years), after which the majority of the cohort had died.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The main impact of diabetes on the health system is the impact of long term morbidity and increased mortality mainly due to macro-vascular complications, micro-vascular complications and other complications. The costs associated with the management of diabetes and its related complications are considerable such as amputations, and diabetic individuals experience substantially high productivity losses and other socioeconomic disadvantages regarding employment and income.(98) Within the UKPDS study it was noted that the risk of micro/macro-vascular events in patients with T2DM can be considerably reduced through long term glycaemic control.

The model captures this by linking biochemical variables (such as HbA_{1C} and SBP) to micro and macro-vascular events via the UKPDS equations and the JADE model which links them to long-term complications.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 52: Key features of analysis

Factor	Chosen values	Justification
Time horizon	Life time	NICE reference case
Cycle length	6 months	Average duration of the majority of clinical trials
Half-cycle correction	Yes	NICE reference case
Were health effects measured in QALYs; if not, what was used?	Yes	
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	NHS/PSS	

NHS = National Health Service; PSS = personal social services; QALYs = quality-adjusted life years

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Table 53 outlines the treatment sequences based on NICE clinical guidelines and advice from a clinical expert.(41) SU = sulphonylureas; TZD = thiazolidinedione

Table 54 displays the actual treatments considered under each heading. Table 55 presents the interventions and comparators considered under each line of therapy. Glimepiride and sitagliptin were chosen as they have the highest market share currently in the UK. (British National Formulary, 2011) Pioglitazone is currently the only licensed TZD in the UK. (Gelhorn et al., 2013) NPH insulin was chosen as it is recommended in NICE guidelines and glargine as it has the largest market share.(British National Formulary, 2011). In addition, glargine was chosen to represent rescue medication after insulin background comparisons.

Table 53: Treatment sequences

Treatment	Add-on treatment after loss of efficacy
Metformin + SGLT2i	Metformin + SGLT2i + insulin
Metformin + Sitagliptin	Metformin + sitagliptin + insulin
Metformin + SU + SGLT2i	Metformin + SU + SGLT2i + insulin
Metformin + SU + Sitagliptin	Metformin + SU + Sitagliptin +insulin
Metformin + TZD + SGLT2i	Metformin + TZD + SGLT2i + insulin
Metformin + TZD+ Sitagliptin	Metformin + TZD+ Sitagliptin + insulin
SGLT2i + insulin	None
Sitagliptin+ insulin	None
Treatment	**Add-on treatment after discontinuation**
Metformin + SGLT2i	Metformin + insulin
Metformin + Sitagliptin	Metformin + insulin
Metformin + SU + SGLT2i	Metformin + SU + insulin
Metformin + SU + Sitagliptin	Metformin + SU + insulin
Metformin + TZD + SGLT2i	Metformin + TZD + insulin
Metformin + TZD+ Sitagliptin	Metformin + TZD + insulin
SGLT2i + insulin	Insulin (glargine)
Sitagliptin+ insulin	Insulin (glargine)

SU = sulphonylureas; TZD = thiazolidinedione

Table 54: Treatments compared

Treatment line	Intervention	Comparators
Dual therapy	Met + Empagliflozin	Met + sitagliptin
		Met + dapagliflozin
		Met + canagliflozin
Triple therapy	Met + SU + Empagliflozin	Met + SU + sitagliptin
		Met + SU + canagliflozin
	Met + TZD + Empagliflozin	Met + TZD + sitagliptin
		Met + TZD + canagliflozin
Insulin combinations	Insulin + Empagliflozin	Insulin + sitagliptin
		Insulin + dapagliflozin
		Insulin + canagliflozin

Met = metformin; SU = sulphonylureas; TZD = thiazolidinedione

Table 55: Actual treatments considered in model

Class	Treatments
SU	Glimepiride
DPP-4i	Sitagliptin
SGLT2i	Empagliflozin

	Canagliflozin Dapagliflozin
TZD	Pioglitazone
Insulin	Neutral protamine Hagedorn (NPH) Glargine

DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SU = sulphonylureas; TZD = thiazolidinedione

The dual combination of sulphonylurea and empagliflozin was not included as there was no direct trial evidence to inform the estimates of effectiveness or safety. In addition, dapagliflozin and canagliflozin excluded dual therapy with sulphonylureas from their NICE submissions.

Where possible, interventions were included in the model as per their marketing authorisation. However, dose titration was not included in the model because there is no clinical evidence relating to the efficacy or safety of a dose titration regimen. This was addressed by including all individual doses stated in the marketing authorisation. Therefore, presenting the cost effectiveness of all doses compared with each other.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- *The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).*
- *The robustness and plausibility of the endpoint on which the rule is based.*
- *Whether the 'response' criteria defined in the rule can be reasonably achieved.*
- *The appropriateness and robustness of the time at which response is measured.*
- *Whether the rule can be incorporated into routine clinical practice.*

- *Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.*
- *Issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

Treatment is continued until HbA_{1C} rises above the target value of 7.5%. As outlined in CG66 & 87 this should be part of standard NHS practice. Once this threshold was reached for the treatments under review patients were initiated on insulin. For metformin, metformin plus SU and metformin plus TZD the switch will be add-on to NPH insulin. For insulin background patients will switch to rescue insulin with glargine. This is in line with NICE clinical guidelines where after the failure of dual or triple therapy patients can be moved to insulin. The same holds true if the patient suffers from a treatment related AE. Patients are assumed to remain on rescue insulin until the time horizon is reached or the patient has died.

When insulin is added the efficacy estimates from insulin combinations was used assuming that the impact of adding insulin on the efficacy on HbA1c and SBP as determined by a study by Khunti and colleagues.(99) This was a 24-week, multi-centre, open-label, non-randomised, observational study investigating the initiation of once-daily insulin detemir in people with type 2 diabetes. Only UK patients were considered. The intervention assessed in this study represents insulin initiation on T2DM patients not achieving glucose control despite diet, exercise and one or more oral antidiabetics (insulin-naïve patients). In the case of rescue insulin with glargine, the efficacy has been assumed similar to that estimated from the NMA for insulin alone. For adverse events estimates from the NMA were utilised as these were unlikely to be affected by the order the medications are administered.

Using these two different estimates was justified because in one case (add-on insulin) patients were insulin-naïve and an estimate that would reflect the effect of insulin on treatment-naïve patients was needed. Moving to insulin alone within the insulin background is a different situation, where patients had already received insulin and in this case we are assuming that patients moving to insulin rescue medication would get the effect of insulin alone observed from the NMA.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

It was decided that the data from the mixed treatment comparisons should be used wherever possible to populate the model (see Section 6.7). If the data was unavailable then data was obtained from the clinical trials and NICE submissions for those interventions. For any clinical inputs where data was not available it was assumed that there was no treatment effect for example for the lipid ratio (i.e. total cholesterol/HDL ratio); this was confirmed with a clinical expert.

For continuous outcomes the estimates for empagliflozin 10 mg and 25 mg was implemented into the model as absolute changes from the pooled baseline from the network meta-analysis then the relative differences between the other treatments and empagliflozin were inputted. Events in the model were implemented as relative risks applied to the baseline rate from the NMA whenever available or clinical trials if needed. In addition, for events an estimate was assigned to the number of events experienced. These were derived from the empagliflozin clinical trials as it was assumed that the number of events experienced did not vary between treatments, although there was variation between doses. When there was no data, the lowest value was used.

If data for treatments was not available then a number of sources were consulted, For example, if network meta-analysis estimates were not available then estimates from the NICE STA submissions were used for the SGLT2is and where possible sitagliptin. The rationale for this was that these estimates have been presented to Appraisal Committee's and generally accepted. If no evidence was available from these sources then estimates from the SGLT2i trial programs for specific background treatments were used as these were consistent with the majority of the

clinical data. Finally if no other data source was available SmPCs were consulted for safety outcomes for remaining estimates.

For severe hypoglycaemia an alternative method was used as there were a high number of zero data points that resulted in results that could not be considered robust. Therefore, it was decided to use the placebo rates from the trials as there was no evidence from the data extraction that there was any difference with placebo (please see Section 9.7, Appendix 7). In addition, it was assumed that people on average only experienced one severe hypoglycaemic event as it was considered clinically reasonable

Even though the model assumed that treatment effects lasted for one year it was decided to utilise the networks populated with 24 week data. This was because there was far more data available for all the treatments at 24 weeks such was the case of the triple therapy network for metformin plus TZD. Therefore, the estimates should be more robust. Data from patients who received treatment for 52 week was utilised in a sensitivity analysis in order to explore the effect on the cost-effectiveness results.

Table 56: Dual therapy

	Value	CI/SD	Source
		HbA1C	
Baseline	-0.05	-0.1 to -0.01	NMA
Met + Sitagliptin	-0.79	-0.96 to -0.62	
Met + Empagliflozin 10mg	-0.60	-0.92 to -0.28	
Met + Empagliflozin 25mg	-0.70	-0.95 to -0.45	
Met + Canagliflozin 100mg	-0.66	-0.91 to -0.41	
Met + Canagliflozin 300mg	-0.78	-1.04 to -0.53	
Met + Dapagliflozin	-0.56	-0.74 to -0.37	
		SBP	
Baseline	-2.19	-3.09 to -1.271	NMA
Met + Sitagliptin	-2.13	-5.09 to 0.97	
Met + Empagliflozin 10mg	-4.31	-6.98 to -1.57	
Met + Empagliflozin 25mg	-5.11	-7.21 to -2.94	
Met + Canagliflozin 100mg	-4.11	-6.39 to -2.00	
Met + Canagliflozin 300mg	-5.37	-7.75 to -3.31	
Met + Dapagliflozin	-3.77	-5.51 to -1.97	
		BMI/weight loss	
Baseline	-0.87	-1.11—0.662	NMA
Met + Sitagliptin	0.34	-0.23 to 0.85	

	Value	CI/SD	Source
Met + Empagliflozin 10mg	-1.76	-2.50 to -1.04	
Met + Empagliflozin 25mg	-2.26	-2.83 to -1.71	
Met + Canagliflozin 100mg	-2.02	-2.67 to -1.43	
Met + Canagliflozin 300mg	-2.72	-3.37 to -2.12	
Met + Dapagliflozin	-2.03	-2.47 to -1.59	
Discontinuation (% AE's leading to discontinuation)			
Met + Sitagliptin	0.008	0.002	Sitagliptin (Januvia) SmPC
Met + Empagliflozin 10mg	0.028	0.012	1245.31
Met + Empagliflozin 25mg	0.033	0.015	1245.31
Met + Canagliflozin 100mg	0.041	0.004	NICE 2013. Single technology appraisal for Canagliflozin for the treatment of type 2 diabetes mellitus, manufacturer's submission Page: 143 out of 310
Met + Canagliflozin 300mg	0.051	0.004	
Met + Dapagliflozin	0.059	0.012	Nauck, M. A. et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 34, 2015–2022 (2011) in NICE. 2012. Single technology appraisal for Dapagliflozin for the treatment of type 2 diabetes: Table 58
Hypoglycaemia – non severe (prob.)			
Baseline risk	0.018	0.0129-0.0261	NMA canagliflozin 100mg and 30mg assumed to be equivalent to dapagliflozin 5mg and 10mg
Met + Sitagliptin	0.5	0.11-1.85	
Met + Empagliflozin 10mg	4.17	0.42-32.8	
Met + Empagliflozin 25mg	2.87	0.26-25.5	
Met + Canagliflozin 100mg	2.27	0.67-8.49	
Met + Canagliflozin 300mg	1.38	0.49-3.88	
Met + Dapagliflozin	1.38	0.49-3.88	
Hypoglycaemia – non severe (number)			
Met + Sitagliptin	1.5	Not varied	Clinical study report 1245-0023 Met ; page 1160 – for empa 25mg (1.5) and for empa 10 (3.33)
Met + Empagliflozin 10mg	3.33		
Met + Empagliflozin 25mg	1.5		
Met + Canagliflozin 100mg	1.5		
Met + Canagliflozin 300mg	1.5		
Met + Dapagliflozin	1.5		
Hypoglycaemia – severe			
Baseline risk	0		Zero events recorded in trials
Met + Sitagliptin			
Met + Empagliflozin 10mg			
Met + Empagliflozin 25mg			
Met + Canagliflozin 100mg			
Met + Canagliflozin 300mg			
Met + Dapagliflozin			
UTIs (RR)			
Baseline risk	0.03	0.022-0.042	NMA

	Value	CI/SD	Source
Met + Sitagliptin 100mg	0.87	0.02-24.32	
Met + Empagliflozin 10mg	1.15	0.06-16.5	
Met + Empagliflozin 25mg	1.09	0.06-15.5	
Met + Canagliflozin 100mg	1.15	0.06-16.5	
Met + Canagliflozin 300mg	1.09	0.06-15.5	
Met + Dapagliflozin 10mg	2.21	0.26-19.9	
UTIs (number)			
Met + Sitagliptin 100mg	1	Not varied	Calculated from study 1245.23, sitagliptin assumed equivalent to placebo. Canagliflozin and dapagliflozin assume to be 1 due to lack of data.
Met + Empagliflozin 10mg	1.41		
Met + Empagliflozin 25mg	1		
Met + Canagliflozin 100mg	1		
Met + Canagliflozin 300mg	1		
Met + Dapagliflozin 10mg	1		
GTIs (prob.)			
Met + Sitagliptin 100mg	0		Assumption
Met + Empagliflozin 10mg	0.036866	0.01279	Clinical study report 1245-023 (met only)
Met + Empagliflozin 25mg	0.046729	0.01443	Clinical study report 1245-023 (met only)
Met + Canagliflozin 100mg	0.06339	0.00438	NICE 2013. Single technology appraisal for Canagliflozin for the treatment of type 2 diabetes mellitus, manufacturer's submission Page: 145 out of 310 (Table 23)
Met + Canagliflozin 300mg	0.06288	0.00437	
Met + Dapagliflozin	0.123	0.0163	Nauck, M. A. et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 34, 2015–2022 (2011) in NICE. 2012. Single technology appraisal for Dapagliflozin for the treatment of type 2 diabetes: Table 58
GTIs (number)			
Met + Sitagliptin	0	Not varied	Calculated from study 1245.23, sitagliptin assumed equivalent to placebo. Canagliflozin and dapagliflozin assumed to be 1 due to lack of data.
Met + Empagliflozin 10mg	1.25		
Met + Empagliflozin 25mg	1		
Met + Canagliflozin 100mg	1		
Met + Canagliflozin 300mg	1		
Met + Dapagliflozin	1		

AEs = adverse events; BMI = body mass index; CI/SD = confidence interval/standard deviation; empa = empagliflozin; HbA1C =glycated haemoglobin; NMA = network meta analysis; met =metformin; SBPsystolic blood pressure

Table 57: Triple therapy

	Value	CI/SD	Source
HbA1c (change from baseline)			
Baseline (Met + SU)	-0.135	-0.238 to -0.029	NMA
Met + SU + Sitagliptin	-0.81	-0.98 to 0.65	
Met + SU + Empagliflozin 10mg	-0.65	-0.79 to -0.51	
Met + SU + Empagliflozin 25mg	-0.60	-0.74 to -0.46	
Met + SU + Canagliflozin 100mg	-0.76	-0.97 to -0.55	
Met + SU + Canagliflozin 300mg	-1.01	-1.18 to -0.85	
Baseline (Met + TZD)	-0.262	-0.354 to -0.173	
Met + Pioglitazone + Sitagliptin	-0.7	-0.84 to -0.56	
Met + Pioglitazone + Empagliflozin 10mg	-0.44	-0.66 to -0.22	
Met + Pioglitazone + Empagliflozin 25mg	-0.59	-0.80 to -0.38	
Met + Pioglitazone + Canagliflozin 100mg	-0.63	-0.82 to -0.44	
Met + Pioglitazone + Canagliflozin 300mg	-0.77	-0.93 to -0.61	
SBP (change from baseline) mm			
Baseline (Met + SU)	-0.54	-1.49 to 0.41	NMA
Met + SU + Sitagliptin	4.21	1.09 to 7.33	
Met + SU + Empagliflozin 10mg	-2.72	-4.66 to -0.79	
Met + SU + Empagliflozin 25mg	-2.10	-4.05 to -0.19	
Met + SU + Canagliflozin 100mg	-2.35	-4.99 to 0.27	
Met + SU + Canagliflozin 300mg	-1.77	-4.36 to 0.86	
Baseline (Met + TZD)	-0.94	-1.14 to 2.97	
Met + Pioglitazone + Sitagliptin	NR	NR	
Met + Pioglitazone + Empagliflozin 10mg	-4.24	-6.91 to -1.54	
Met + Pioglitazone + Empagliflozin 25mg	-4.06	-6.72 to -1.36	
Met + Pioglitazone + Canagliflozin 100mg	-4.11	-6.98 to -1.22	
Met + Pioglitazone + Canagliflozin 300mg	-3.54	-6.46 to -0.54	
BMI/weight change (change from baseline) kg			
Baseline (Met + SU)	-0.49	-0.797 to -0.171	NMA
Met + SU + Sitagliptin	0.97	0.41 to 1.53	
Met + SU + Empagliflozin 10mg	-1.77	-2.18 to -1.35	
Met + SU + Empagliflozin 25mg	-2.00	-2.43 to -1.57	
Met + SU + Canagliflozin 100mg	-1.26	-1.88 to -0.62	
Met + SU + Canagliflozin 300mg	-1.69	-2.23 to -1.16	
Baseline (Met + TZD)	0.907	0.527 to 1.287	
Met + Pioglitazone + Sitagliptin	0.20	-0.40 to 0.80	
Met + Pioglitazone + Empagliflozin 10mg	-2.14	-2.82 to -1.45	
Met + Pioglitazone + Empagliflozin 25mg	-1.98	-2.68 to -1.28	
Met + Pioglitazone + Canagliflozin 100mg	-2.55	-3.36 to -1.74	
Met + Pioglitazone + Canagliflozin 300mg	-3.49	-4.29 to -2.69	
Discontinuation (% AE's leading to discontinuation)			
Met + SU + Sitagliptin	0.008		Sitagliptin SmPC

	Value	CI/SD	Source
HbA1c (change from baseline)			
Met + SU + Empagliflozin 10mg	0.027	0.011	1245.23 assume equivalency between doses
Met + SU + Empagliflozin 25mg	0.032	0.012	
Met + SU + Canagliflozin 100mg	0.027	0.011	
Met + SU + Canagliflozin 300mg	0.032	0.011	
Met + Pioglitazone + Sitagliptin	0.008		Sitagliptin SmPC
Met + Pioglitazone + Empagliflozin 10mg	0.012	0.009	1245.19
Met + Pioglitazone + Empagliflozin 25mg	0.030	0.013	
Met + Pioglitazone + Canagliflozin 100mg	0.041	0.004	Canagliflozin STA
Met + Pioglitazone + Canagliflozin 300mg	0.051	0.004	
Hypoglycaemia – non severe (prob.)			
Baseline risk (Met +SU)	0.083	0.057 to 0.114	NMA Estimate for sitagliptin assumed to the same as that for alogliptin 25 mg in NMA
Met + SU + Sitagliptin	1.62	0.71 to 3.6	
Met + SU + Empagliflozin 10mg	1.68	1.02 to 2.73	
Met + SU + Empagliflozin 25mg	1.29	0.75 to 2.18	
Met + SU + Canagliflozin 100mg	2.27	1.41 to 3.61	
Met + SU + Canagliflozin 300mg	2.76	1.81 to 4.23	
Baseline risk (Met + Pio)	0.01	0.005 to 0.027	
Met + Pioglitazone + Sitagliptin	2.29	1.21 to 5.53	
Met + Pioglitazone + Empagliflozin 10mg	0.62	0.11 to 2.62	
Met + Pioglitazone + Empagliflozin 25mg	1.49	0.53 to 5.42	
Met + Pioglitazone + Canagliflozin 100mg	0.1	0 to 29.8	
Met + Pioglitazone + Canagliflozin 300mg	0.11	0 to 30.94	
Hypoglycaemia – non severe (Number)			
Met + SU + Sitagliptin	2.25	Not varied	1245.23 assume 10mg Empa equivalent to 100mg canagliflozin and sitagliptin 100mg
Met + SU + Empagliflozin 10mg	2.25		
Met + SU + Empagliflozin 25mg	2.62		
Met + SU + Canagliflozin 100mg	2.25		
Met + SU + Canagliflozin 300mg	2.62		
Met + Pioglitazone + Sitagliptin	1		1245.9 placebo rate
Met + Pioglitazone + Empagliflozin 10mg	0.75		1245.19 assume 10mg empagliflozin equivalent to canagliflozin 100mg and empagliflozin 25mg equivalent to canagliflozin 300mg
Met + Pioglitazone + Empagliflozin 25mg	1.125		
Met + Pioglitazone + Canagliflozin 100mg	0.75		
Met + Pioglitazone + Canagliflozin 300mg	1.125		
Hypoglycaemia – severe			
Met + SU + Sitagliptin	0	0	Assumed that treatment did
Met + SU + Empagliflozin 10mg			

	Value	CI/SD	Source
HbA1c (change from baseline)			
Met + SU + Empagliflozin 25mg			not increase in severe hypoglycaemia
Met + SU + Canagliflozin 100mg			
Met + SU + Canagliflozin 300mg			
Met + Pioglitazone + Sitagliptin			
Met + Pioglitazone + Empagliflozin 10mg			
Met + Pioglitazone + Empagliflozin 25mg			
Met + Pioglitazone + Canagliflozin 100mg			
Met + Pioglitazone + Canagliflozin 300mg			
UTIs			
Baseline (Met + SU)	0.062	0.043 to 0.083	NMA
Met + SU + Sitagliptin	0.48	0.12 to 1.51	
Met + SU + Empagliflozin 10mg	1.3	0.71 to 2.35	
Met + SU + Empagliflozin 25mg	1.04	0.54 to 1.99	
Met + SU + Canagliflozin 100mg	0.063	0.004	Data from Cana submission
Met + SU + Canagliflozin 300mg	0.063	0.004	
Baseline (Met + TZD)	0.021	0.007 to 0.049	NMA, Sita 100 assumed similar to alogliptin 25 mg, which was the only DPP4 identified and included in the NMA for this background tx
Met + Pioglitazone + Sitagliptin	1.46	0.89 to 2.63	
Met + Pioglitazone + Empagliflozin 10mg	1.1	0.62 to 2	
Met + Pioglitazone + Empagliflozin 25mg	0.65	0.31 to 1.25	
Met + Pioglitazone + Canagliflozin 100mg	0.063	0.004	Data from Cana submission
Met + Pioglitazone + Canagliflozin 300mg	0.063	0.004	
UTIs (number)			
Met + SU + Sitagliptin	1	Not varied	Placebo rate from 1245.23
Met + SU + Empagliflozin 10mg	1.09		1245.23 canagliflozin 100mg equivalent to empagliflozin 10mg
Met + SU + Empagliflozin 25mg	1.11		
Met + SU + Canagliflozin 100mg	1.09		
Met + SU + Canagliflozin 300mg	1.11		
Met + Pioglitazone + Sitagliptin	1.11		Placebo rate from 1245.19
Met + Pioglitazone + Empagliflozin 10mg	1.14		1245.19 canagliflozin assumed equivalent to empagliflozin according to dose level
Met + Pioglitazone + Empagliflozin 25mg	1.2		
Met + Pioglitazone + Canagliflozin 100mg	1.14		
Met + Pioglitazone + Canagliflozin 300mg	1.2		
GTIs			
Met + SU + Sitagliptin	0		Assumption
Met + SU + Empagliflozin 10mg	0.027	0.011	1245.23
Met + SU + Empagliflozin 25mg	0.023	0.01	

	Value	CI/SD	Source
HbA1c (change from baseline)			
Met + SU + Canagliflozin 100mg	0.06339	0.00438	Data from Cana submission
Met + SU + Canagliflozin 300mg	0.06288	0.00437	
Met + Pioglitazone + Sitagliptin	0		Assumption
Met + Pioglitazone + Empagliflozin 10mg	0.085	0.022	1245.19
Met + Pioglitazone + Empagliflozin 25mg	0.036	0.014	
Met + Pioglitazone + Canagliflozin 100mg	0.06339	0.00438	Data from Cana submission
Met + Pioglitazone + Canagliflozin 300mg	0.06288	0.00437	
GTIs (number)			
Met + SU + Sitagliptin	0	Not varied	Assumption
Met + SU + Empagliflozin 10mg	1		1245.23 assume empagliflozin equivalent to canagliflozin
Met + SU + Empagliflozin 25mg	1		
Met + SU + Canagliflozin 100mg	1		
Met + SU + Canagliflozin 300mg	1		
Met + Pioglitazone + Sitagliptin	0		Assumption
Met + Pioglitazone + Empagliflozin 10mg	1.18		1245.19 assume empagliflozin equivalent to canagliflozin
Met + Pioglitazone + Empagliflozin 25mg	1.17		
Met + Pioglitazone + Canagliflozin 100mg	1.18		
Met + Pioglitazone + Canagliflozin 300mg	1.17		

AEs = adverse events; BMI = body mass index; CI/SD = confidence interval/standard deviation; GTIs = genital tract infections; HbA1C =glycated haemoglobin; NMA = network meta analysis; met =metformin; SBP = systolic blood pressure; SU = sulphonylureas; TZD = thiazolidinedione; UTIs = urinary tract infections

Table 58: Insulin combinations

	Value	CI/SD	Source
HbA1c			
Baseline risk (insulin)	-0.191	-0.255 to -0.133	NMA
Insulin + Sitagliptin 100mg	-0.41	-0.58 to -0.24	
Insulin + Empagliflozin 10mg	-0.50	-0.61 to -0.39	
Insulin + Empagliflozin 25mg	-0.57	-0.69 to -0.46	
Insulin + Canagliflozin 100mg	-0.64	-0.8 to -0.47	
Insulin + Canagliflozin 300mg	-0.73	-0.9 to -0.56	
Insulin + Dapagliflozin 10mg	-0.50	-0.66 to -0.35	
Insulin add-on	-1.30	Not varied	Khunti K et al 2013 (99)
SBP			
Baseline risk (insulin)	-1.901	-2.83 to -0.982	NMA
Insulin + Sitagliptin 100mg	0	0	
Insulin + Empagliflozin 10mg	-2.85	-4.51 to -1.18	
Insulin + Empagliflozin 25mg	-2.24	-3.94 to -0.59	
Insulin + Canagliflozin 100mg	-2.61	-5.6 to 0.34	
Insulin + Canagliflozin 300mg	-4.39	-7.43 to -1.38	
Insulin + Dapagliflozin 10mg	-3.12	-5.76 to -0.42	

	Value	CI/SD	Source
Insulin add-on	4.00	Not varied	Khunti K et al 2013 (99)
BMI/weight change			
Baseline risk (insulin)	0.323	0.121 to 0.514	NMA
Insulin + Sitagliptin 100mg	0.21	-0.29 to 0.71	
Insulin + Empagliflozin 10mg	-1.36	-1.81 to -0.91	
Insulin + Empagliflozin 25mg	-1.78	-2.28 to -1.29	
Insulin + Canagliflozin 100mg	-1.85	-2.44 to -1.26	
Insulin + Canagliflozin 300mg	-2.33	-2.91 to -1.74	
Insulin + Dapagliflozin 10mg	-1.43	-1.97 to -0.89	
Insulin add-on	0.5	Not varied	Khunti K et al 2013 (99)
Discontinuation (% AE's leading to discontinuation)			
Insulin + Sitagliptin 100mg	0.048	0.016	Assumed similar to the insulin arm from the clinical report 1245-49
Insulin + Empagliflozin 10mg	0.054	0.017	Clinical study 1245-49
Insulin + Empagliflozin 25mg	0.048	0.015	
Insulin + Canagliflozin 100mg	0.071	0.017	Equivalency between dapagliflozin and canagliflozin according to dose level, obtained from dapagliflozin studies
Insulin + Canagliflozin 300mg	0.051	0.016	
Insulin + Dapagliflozin 10mg	0.051	0.015	
Hypoglycaemia – non severe			
Baseline risk (Insulin)	0.241	0.206 to 279	NMA
Insulin + Sitagliptin 100mg	0.97	0 to 4.5	
Insulin + Empagliflozin 10mg	1.06	0.84 to 1.32	
Insulin + Empagliflozin 25mg	1.07	0.85 to 1.33	
Insulin + Canagliflozin 100mg	1.44	1.22 to 1.68	
Insulin + Canagliflozin 300mg	1.4	1.19 to 1.63	
Insulin + Dapagliflozin 10mg	1.02	0.74 to 1.35	
Hypoglycaemia – non severe (number)			
Insulin	4.82	Not varied	1245.49 placebo rate
Insulin + Sitagliptin 100mg	4.68		Assumed similar to empa 10
Insulin + Empagliflozin 10mg	4.68		1245.49 equivalency between doses
Insulin + Empagliflozin 25mg	5.42		
Insulin + Canagliflozin 100mg	4.68		
Insulin + Canagliflozin 300mg	5.42		
Insulin + Dapagliflozin 10mg	5.42		

	Value	CI/SD	Source
Hypoglycaemia – severe			
Insulin	0.0096	0.0051- 0.0169	Pooled insulin rates from NMA
Insulin + Sitagliptin 100mg			
Insulin + Empagliflozin 10mg			
Insulin + Empagliflozin 25mg			
Insulin + Canagliflozin 100mg			
Insulin + Canagliflozin 300mg			
Insulin + Dapagliflozin 10mg			
UTIs			
Insulin	0.15	0.03	1245.49
Insulin + Sitagliptin 100mg	0.063	0.004	NICE STA Dapagliflozin
Insulin + Empagliflozin 10mg	0.16	0.03	1245-49
Insulin + Empagliflozin 25mg	0.15	0.03	
Insulin + Canagliflozin 100mg	0.06	0.004	NICE STA canagliflozin
Insulin + Canagliflozin 300mg	0.06	0.004	
Insulin + Dapagliflozin 10mg	0.056	0.004	NICE STA Dapagliflozin
UTIs (number)			
Insulin	1.71	Not varied	1245.49 placebo rate assumed
Insulin + Sitagliptin 100mg	1.71		
Insulin + Empagliflozin 10mg	1.31		1245.49 equivalence between doses assumed
Insulin + Empagliflozin 25mg	1.19		
Insulin + Canagliflozin 100mg	1.31		
Insulin + Canagliflozin 300mg	1.19		
Insulin + Dapagliflozin 10mg	1.19		
GTIs			
Insulin	0.016	0.009	1245.49 placebo rate
Insulin + Sitagliptin 100mg	0.003	0.004	NICE STA dapagliflozin TA288
Insulin + Empagliflozin 10mg	0.043	0.015	1245-49
Insulin + Empagliflozin 25mg	0.095	0.021	
Insulin + Canagliflozin 100mg	0.063	0.004	NICE STA for canagliflozin
Insulin + Canagliflozin 300mg	0.063	0.004	
Insulin + Dapagliflozin 10mg	0.063	0.004	Same as Cana 300
GTIs (Number)			
Insulin	1	Not varied	1245.49 assumed to be placebo rate
Insulin + Sitagliptin 100mg	1		
Insulin + Empagliflozin 10mg	1.125		1245.49 equivalence assumed between
Insulin + Empagliflozin 25mg	1.416		
Insulin + Canagliflozin 100mg	1.125		

	Value	CI/SD	Source
Insulin + Canagliflozin 300mg	1.416		respective doses
Insulin + Dapagliflozin 10mg	1.125		

AEs = adverse events; BMI = body mass index; CI/SD = confidence interval/standard deviation; GTIs = genital tract infections; HbA1C =glycated haemoglobin; NMA = network meta analysis; met =metformin; SBP = systolic blood pressure; SU = sulphonylureas; TZD = thiazolidinedione; UTIs = urinary tract infections

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Efficacy was estimated in terms of the effect of the alternative treatments on HbA1c levels (calculated as the percentage decrease from baseline levels; Tables 40 to 42). In addition, the impact of treatments on SBP levels and weight was also considered as part of the efficacy assessment. There was insufficient data reported in the clinical trials included in the NMA on the changes from baseline in the lipid ratio due to the effect of the different treatments. Therefore, it was assumed that there was no treatment effect on the lipid ratio. Therefore, lipid ratio was assumed to be maintained at baseline levels. This assumption was validated by the clinical expert who considered that lipid ratio was an increasingly obsolete marker and that LDl-C is more relevant.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Of the variables included in the model, the risk of macro and micro vascular events differ by time and this has been captured within the UKPDS 68 equations.

Evidence from the standard treatment sequences show that treatment effects are also likely to deteriorate over time. For the treatment of interest this has been modelled by assuming the treatment effects last for 1 year and then afterwards treatment related variables return to follow the UKPDS 68 equations.

Hypoglycaemias can occur as long as patients are on treatment. For UTIs and genital infections it’s been assumed that they will occur within the first 6 months upon advice of clinical experts who stated that they were unlikely that will occur after a longer time period.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

UKPDS 68 risk equations were used to link changes in HbA1c, SBP, BMI and cholesterol to the occurrence of micro and macrovascular complications. These equations are described in more detail in Section 7.2.2.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- *the criteria for selecting the experts*
- *the number of experts approached*
- *the number of experts who participated*
- *declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
- *the method used to collect the opinions*
- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *the questions asked*
- *whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

The choice of whether to use the estimates from the NMA or directly from the trials was discussed with the UK clinical expert and also their implementation in the model with the UK health economist who advised on the methodology of implementation.

To ensure face validity, expert meetings with a UK clinical diabetologists were conducted by Boehringer Ingelheim to validate the disease process and the evolution of the levels of risk factors and the probabilities on long term complications over time. Moreover, during the development of the model, a clinical expert and a health economics expert with expertise in the UK were consulted at different stages to validate the modelling approach and the formulation of assumptions in the model in preparation for a NICE submission. These experts

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

were approached throughout the development of the model and also when selecting the inputs used in the model.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 59: Summary of variables applied in the economic model

Variable	Mean	Reference
Baseline characteristics Dual therapy		
Age when initiating assessed treatment [years]	55.9	Ridderstrale(2013)
Female	45.15%	Clinical opinion
Afro-Caribbean	1.20%	Clinical opinion
Asian	1.50%	Clinical opinion
Smoking status	31%	UKPDS
Atrial fibrillation	0.62%	UKPDS
Peripheral vascular disease	0.235	Walters (1992)
HbA1c when starting 2nd line (%)	7.5	NICE clinical guideline no.87
Systolic blood pressure when initiating assessed treatment (mm Hg)	135	NICE clinical guideline no.87
Total cholesterol:HDL when initiating assessed treatment	5.05	Clinical opinion
BMI when initiating assessed treatment [kg/m2]	27.5	NICE clinical guideline no.87
Baseline characteristics Triple therapy		
Age when initiating assessed treatment [years]	58†	UKPDS
Female	39%	
Afro-Caribbean	8%	
Asian	10%	
Smoking status	31%	
Atrial fibrillation	0.62%	
Peripheral vascular disease	0.235	
HbA1c when starting 2nd line (%)	7.5	
Systolic blood pressure when initiating assessed treatment (mm Hg)	140	
Total cholesterol:HDL when initiating assessed treatment	4.4	
BMI when initiating assessed treatment [kg/m2]	30.42	
Clinical efficacy estimates		

Variable	Mean	Reference
HbA1C		
Baseline	-0.05	NMA
Met + Sitagliptin	-0.79	
Met + Empagliflozin 10mg	-0.60	
Met + Empagliflozin 25mg	-0.70	
Met + Canagliflozin 100mg	-0.66	
Met + Canagliflozin 300mg	-0.78	
Met + Dapagliflozin	-0.56	
SBP		
Baseline	-2.19	NMA
Met + Sitagliptin	-2.13	
Met + Empagliflozin 10mg	-4.31	
Met + Empagliflozin 25mg	-5.11	
Met + Canagliflozin 100mg	-4.11	
Met + Canagliflozin 300mg	-5.37	
Met + Dapagliflozin	-3.77	
BMI/weight loss		
Baseline	-0.87	NMA
Met + Sitagliptin	0.34	
Met + Empagliflozin 10mg	-1.76	
Met + Empagliflozin 25mg	-2.26	
Met + Canagliflozin 100mg	-2.02	
Met + Canagliflozin 300mg	-2.72	
Met + Dapagliflozin	-2.03	
Discontinuation (% AE's leading to discontinuation)		
Met + Sitagliptin	0.008	Sitagliptin (Januvia) SmPC:
Met + Empagliflozin 10mg	0.028	1245.31
Met + Empagliflozin 25mg	0.033	1245.31
Met + Canagliflozin 100mg	0.041	NICE 2013. Single technology appraisal for Canagliflozin for the treatment of type 2 diabetes mellitus, manufacturer's submission Page: 143 out of 310
Met + Canagliflozin 300mg	0.051	
Met + Dapagliflozin	0.059	Nauck, M. A. et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 34, 2015–2022 (2011) in NICE. 2012. Single technology appraisal for Dapagliflozin for the treatment of type 2 diabetes: Table 58
Hypoglycaemia – non severe (prob.)		
Baseline risk	0.018	NMA canagliflozin 100mg and 30mg assumed to be equivalent to dapagliflozin 5mg and 10mg
Met + Sitagliptin	0.5	

Variable	Mean	Reference
Met + Empagliflozin 10mg	4.17	
Met + Empagliflozin 25mg	2.87	
Met + Canagliflozin 100mg	2.27	
Met + Canagliflozin 300mg	1.38	
Met + Dapagliflozin	1.38	
Hypoglycaemia – non severe (number)		
Met + Sitagliptin	1.5	Clinical study report 1245-0023 Met ; page 1160 – for empa 25mg (1.5) and for empa 10 (3.33)
Met + Empagliflozin 10mg	3.33	
Met + Empagliflozin 25mg	1.5	
Met + Canagliflozin 100mg	1.5	
Met + Canagliflozin 300mg	1.5	
Met + Dapagliflozin	1.5	
Hypoglycaemia – severe		
Baseline risk	0	Zero events recorded in trials
Met + Sitagliptin		
Met + Empagliflozin 10mg		
Met + Empagliflozin 25mg		
Met + Canagliflozin 100mg		
Met + Canagliflozin 300mg		
Met + Dapagliflozin		
UTIs (RR)		
Baseline risk	0.03	NMA
Met + Sitagliptin 100mg	0.87	
Met + Empagliflozin 10mg	1.15	
Met + Empagliflozin 25mg	1.09	
Met + Canagliflozin 100mg	1.15	
Met + Canagliflozin 300mg	1.09	
Met + Dapagliflozin 10mg	2.21	
UTIs (number)		
Met + Sitagliptin 100mg	1	Calculated from study 1245.23, sitagliptin assumed equivalent to placebo. Canagliflozin and dapagliflozin assume to be 1 due to lack of data.
Met + Empagliflozin 10mg	1.41	
Met + Empagliflozin 25mg	1	
Met + Canagliflozin 100mg	1	
Met + Canagliflozin 300mg	1	
Met + Dapagliflozin 10mg	1	
GTIs (prob.)		
Met + Sitagliptin 100mg	0	Assumption
Met + Empagliflozin 10mg	0.036866	Clinical study report 1245-023 (met only)
Met + Empagliflozin 25mg	0.046729	Clinical study report 1245-023 (met only)
Met + Canagliflozin 100mg	0.06339	NICE 2013. Single technology appraisal for Canagliflozin for the treatment of type 2 diabetes mellitus,

Variable	Mean	Reference
		manufacturer's submission Page: 145 out of 310 (Table 23)
Met + Canagliflozin 300mg	0.06288	
Met + Dapagliflozin	0.123	Nauck, M. A. et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 34, 2015–2022 (2011) in NICE. 2012. Single technology appraisal for Dapagliflozin for the treatment of type 2 diabetes: Table 58
GTIs (number)		
Met + Sitagliptin	0	Calculated from study 1245.23, sitagliptin assumed equivalent to placebo. Canagliflozin and dapagliflozin assumed to be 1 due to lack of data.
Met + Empagliflozin 10mg	1.25	
Met + Empagliflozin 25mg	1	
Met + Canagliflozin 100mg	1	
Met + Canagliflozin 300mg	1	
Met + Dapagliflozin	1	
Triple therapy		
HbA1c (change from baseline)		
Baseline (Met + SU)	-0.135	NMA
Met + SU + Sitagliptin	-0.81	
Met + SU + Empagliflozin 10mg	-0.65	
Met + SU + Empagliflozin 25mg	-0.60	
Met + SU + Canagliflozin 100mg	-0.76	
Met + SU + Canagliflozin 300mg	-1.01	
Baseline (Met + TZD)	-0.262	
Met + Pioglitazone + Sitagliptin	-0.7	
Met + Pioglitazone + Empagliflozin 10mg	-0.44	
Met + Pioglitazone + Empagliflozin 25mg	-0.59	
Met + Pioglitazone + Canagliflozin 100mg	-0.63	
Met + Pioglitazone + Canagliflozin 300mg	-0.77	
SBP (change from baseline) mm		
Baseline (Met + SU)	-0.54	NMA
Met + SU + Sitagliptin	4.21	
Met + SU + Empagliflozin 10mg	-2.72	

Variable	Mean	Reference
Met + SU + Empagliflozin 25mg	-2.10	
Met + SU + Canagliflozin 100mg	-2.35	
Met + SU + Canagliflozin 300mg	-1.77	
Baseline (Met + TZD)	-0.94	
Met + Pioglitazone + Sitagliptin	NR	
Met + Pioglitazone + Empagliflozin 10mg	-4.24	
Met + Pioglitazone + Empagliflozin 25mg	-4.06	
Met + Pioglitazone + Canagliflozin 100mg	-4.11	
Met + Pioglitazone + Canagliflozin 300mg	-3.54	
BMI/weight change (change from baseline) kg		
Baseline (Met + SU)	-0.49	NMA
Met + SU + Sitagliptin	0.97	
Met + SU + Empagliflozin 10mg	-1.77	
Met + SU + Empagliflozin 25mg	-2.00	
Met + SU + Canagliflozin 100mg	-1.26	
Met + SU + Canagliflozin 300mg	-1.69	
Baseline (Met + TZD)	0.907	
Met + Pioglitazone + Sitagliptin	0.20	
Met + Pioglitazone + Empagliflozin 10mg	-2.14	
Met + Pioglitazone + Empagliflozin 25mg	-1.98	
Met + Pioglitazone + Canagliflozin 100mg	-2.55	
Met + Pioglitazone + Canagliflozin 300mg	-3.49	
Discontinuation (% AE's leading to discontinuation)		
Met + SU + Sitagliptin	0.008	Sitagliptin SmPC
Met + SU + Empagliflozin 10mg	0.027	1245.23 assume equivalency between doses
Met + SU + Empagliflozin 25mg	0.032	
Met + SU + Canagliflozin	0.027	

Variable	Mean	Reference
100mg		
Met + SU + Canagliflozin 300mg	0.032	
Met + Pioglitazone + Sitagliptin	0.008	Sitagliptin SmPC
Met + Pioglitazone + Empagliflozin 10mg	0.012	1245.19
Met + Pioglitazone + Empagliflozin 25mg	0.030	
Met + Pioglitazone + Canagliflozin 100mg	0.041	Canagliflozin STA
Met + Pioglitazone + Canagliflozin 300mg	0.051	
Hypoglycaemia – non severe (prob.)		
Baseline risk (Met +SU)	0.083	NMA
Met + SU + Sitagliptin	1.62	NMA
Met + SU + Empagliflozin 10mg	1.68	Estimate for sitagliptin assumed to the same as that for alogliptin 25 mg in NMA
Met + SU + Empagliflozin 25mg	1.29	
Met + SU + Canagliflozin 100mg	2.27	
Met + SU + Canagliflozin 300mg	2.76	
Baseline risk (Met + Pio)	0.01	
Met + Pioglitazone + Sitagliptin	2.29	
Met + Pioglitazone + Empagliflozin 10mg	0.62	
Met + Pioglitazone + Empagliflozin 25mg	1.49	
Met + Pioglitazone + Canagliflozin 100mg	0.1	
Met + Pioglitazone + Canagliflozin 300mg	0.11	
Hypoglycaemia – non severe (Number)		
Met + SU + Sitagliptin	2.25	1245.23 assume 10mg Empa equivalent to 100mg canagliflozin and sitagliptin 100mg
Met + SU + Empagliflozin 10mg	2.25	
Met + SU + Empagliflozin 25mg	2.62	
Met + SU + Canagliflozin 100mg	2.25	
Met + SU + Canagliflozin 300mg	2.62	
Met + Pioglitazone +	1	1245.9 placebo rate

Variable	Mean	Reference
Sitagliptin		
Met + Pioglitazone + Empagliflozin 10mg	0.75	1245.19 assume 10mg empagliflozin equivalent to canagliflozin 100mg and empagliflozin 25mg equivalent to canagliflozin 300mg
Met + Pioglitazone + Empagliflozin 25mg	1.125	
Met + Pioglitazone + Canagliflozin 100mg	0.75	
Met + Pioglitazone + Canagliflozin 300mg	1.125	
Hypoglycaemia – severe		
Met + SU + Sitagliptin	0	Assumed that treatment did not increase in severe hypoglycaemia
Met + SU + Empagliflozin 10mg		
Met + SU + Empagliflozin 25mg		
Met + SU + Canagliflozin 100mg		
Met + SU + Canagliflozin 300mg		
Met + Pioglitazone + Sitagliptin		
Met + Pioglitazone + Empagliflozin 10mg		
Met + Pioglitazone + Empagliflozin 25mg		
Met + Pioglitazone + Canagliflozin 100mg		
Met + Pioglitazone + Canagliflozin 300mg		
UTIs		
Baseline (Met + SU)	0.062	NMA
Met + SU + Sitagliptin	0.48	
Met + SU + Empagliflozin 10mg	1.3	
Met + SU + Empagliflozin 25mg	1.04	
Met + SU + Canagliflozin 100mg	0.063	Data from Cana submission
Met + SU + Canagliflozin 300mg	0.063	
Baseline (Met + TZD)	0.021	NMA; Sita 100 assumed similar to alogliptin 25 mg, which was the only DPP4 identified and included in the NMA for this background treatment
Met + Pioglitazone + Sitagliptin	1.46	
Met + Pioglitazone + Empagliflozin 10mg	1.1	
Met + Pioglitazone +	0.65	

Variable	Mean	Reference
Empagliflozin 25mg		
Met + Pioglitazone + Canagliflozin 100mg	0.063	Data from Cana submission
Met + Pioglitazone + Canagliflozin 300mg	0.063	
UTIs (number)		
Met + SU + Sitagliptin	1	Placebo rate from 1245.23
Met + SU + Empagliflozin 10mg	1.09	1245.23 canagliflozin 100mg equivalent to empagliflozin 10mg
Met + SU + Empagliflozin 25mg	1.11	
Met + SU + Canagliflozin 100mg	1.09	
Met + SU + Canagliflozin 300mg	1.11	
Met + Pioglitazone + Sitagliptin	1.11	Placebo rate from 1245.19
Met + Pioglitazone + Empagliflozin 10mg	1.14	1245.19 canagliflozin assumed equivalent to empagliflozin according to dose level
Met + Pioglitazone + Empagliflozin 25mg	1.2	
Met + Pioglitazone + Canagliflozin 100mg	1.14	
Met + Pioglitazone + Canagliflozin 300mg	1.2	
GTIs		
Met + SU + Sitagliptin	0	Assumption
Met + SU + Empagliflozin 10mg	0.027	1245.23
Met + SU + Empagliflozin 25mg	0.023	
Met + SU + Canagliflozin 100mg	0.06339	Data from Canagliflozin submission
Met + SU + Canagliflozin 300mg	0.06288	
Met + Pioglitazone + Sitagliptin	0	Assumption
Met + Pioglitazone + Empagliflozin 10mg	0.085	1245.19
Met + Pioglitazone + Empagliflozin 25mg	0.036	
Met + Pioglitazone + Canagliflozin 100mg	0.06339	Data from Canagliflozin submission
Met + Pioglitazone + Canagliflozin 300mg	0.06288	
GTIs (number)		

Variable	Mean	Reference
Met + SU + Sitagliptin	0	Assumption
Met + SU + Empagliflozin 10mg	1	1245.23 assume empagliflozin equivalent to canagliflozin
Met + SU + Empagliflozin 25mg	1	
Met + SU + Canagliflozin 100mg	1	
Met + SU + Canagliflozin 300mg	1	
Met + Pioglitazone + Sitagliptin	0	Assumption
Met + Pioglitazone + Empagliflozin 10mg	1.18	1245.19 assume empagliflozin equivalent to canagliflozin
Met + Pioglitazone + Empagliflozin 25mg	1.17	
Met + Pioglitazone + Canagliflozin 100mg	1.18	
Met + Pioglitazone + Canagliflozin 300mg	1.17	
Insulin combinations		
HbA1c		
Baseline risk (insulin)	-0.191	NMA
Insulin + Sitagliptin 100mg	-0.41	
Insulin + Empagliflozin 10mg	-0.50	
Insulin + Empagliflozin 25mg	-0.57	
Insulin + Canagliflozin 100mg	-0.64	
Insulin + Canagliflozin 300mg	-0.73	
Insulin + Dapagliflozin 10mg	-0.50	
Insulin add-on	-1.3	Khunti K et al 2013 (99)
SBP		
Baseline risk (insulin)	-1.901	NMA
Insulin + Sitagliptin 100mg	0	
Insulin + Empagliflozin 10mg	-2.85	
Insulin + Empagliflozin 25mg	-2.24	
Insulin + Canagliflozin 100mg	-2.61	
Insulin + Canagliflozin 300mg	-4.39	
Insulin + Dapagliflozin 10mg	-3.12	
Insulin add-on	4	Khunti K et al 2013 (99)
BMI/weight change		
Baseline risk (insulin)	0.323	NMA
Insulin + Sitagliptin 100mg	0.21	
Insulin + Empagliflozin 10mg	-1.36	
Insulin + Empagliflozin 25mg	-1.78	

Variable	Mean	Reference
Insulin + Canagliflozin 100mg	-1.85	
Insulin + Canagliflozin 300mg	-2.33	
Insulin + Dapagliflozin 10mg	-1.43	
Insulin add-on	0.5	Khunti K et al 2013 (99)
Discontinuation (% AE's leading to discontinuation)		
Insulin + Sitagliptin 100mg	0.048	Assumed similar to the insulin arm from the clinical report 1245-49
Insulin + Empagliflozin 10mg	0.054	Clinical study 1245-49
Insulin + Empagliflozin 25mg	0.048	
Insulin + Canagliflozin 100mg	0.071	Equivalency between dapagliflozin and canagliflozin according to dose level, obtained from dapagliflozin studies
Insulin + Canagliflozin 300mg	0.051	
Insulin + Dapagliflozin 10mg	0.051	
Hypoglycaemia – non severe		
Baseline risk (Insulin)	0.241	NMA
Insulin + Sitagliptin 100mg	0.97	
Insulin + Empagliflozin 10mg	1.06	
Insulin + Empagliflozin 25mg	1.07	
Insulin + Canagliflozin 100mg	1.44	
Insulin + Canagliflozin 300mg	1.4	
Insulin + Dapagliflozin 10mg	1.02	
Hypoglycaemia – non severe (number)		
Insulin	4.82	1245.49 placebo rate
Insulin + Sitagliptin 100mg	4.68	Assumed similar to empa 10
Insulin + Empagliflozin 10mg	4.68	1245.49 equivalency between doses
Insulin + Empagliflozin 25mg	5.42	
Insulin + Canagliflozin 100mg	4.68	
Insulin + Canagliflozin 300mg	5.42	
Insulin + Dapagliflozin 10mg	5.42	
Hypoglycaemia – severe		
Insulin	0.0096	Pooled insulin rates from NMA
Insulin + Sitagliptin 100mg		
Insulin + Empagliflozin 10mg		
Insulin + Empagliflozin 25mg		
Insulin + Canagliflozin 100mg		
Insulin + Canagliflozin 300mg		
Insulin + Dapagliflozin 10mg		
UTIs		
Insulin	0.15	1245.49
Insulin + Sitagliptin 100mg	0.063	NICE STA Dapagliflozin
Insulin + Empagliflozin 10mg	0.16	1245-49
Insulin + Empagliflozin 25mg	0.15	

Variable	Mean	Reference
Insulin + Canagliflozin 100mg	0.06	NICE STA canagliflozin
Insulin + Canagliflozin 300mg	0.06	
Insulin + Dapagliflozin 10mg	0.056	NICE STA Dapagliflozin
UTIs (number)		
Insulin	1.71	1245.49 placebo rate assumed
Insulin + Sitagliptin 100mg	1.71	
Insulin + Empagliflozin 10mg	1.31	1245.49 equivalence between doses assumed
Insulin + Empagliflozin 25mg	1.19	
Insulin + Canagliflozin 100mg	1.31	
Insulin + Canagliflozin 300mg	1.19	
Insulin + Dapagliflozin 10mg	1.19	
GTIs		
Insulin	0.016	1245.49 placebo rate
Insulin + Sitagliptin 100mg	0.003	NICE STA dapagliflozin TA288
Insulin + Empagliflozin 10mg	0.043	1245-49
Insulin + Empagliflozin 25mg	0.095	
Insulin + Canagliflozin 100mg	0.063	NICE STA for canagliflozin
Insulin + Canagliflozin 300mg	0.063	
Insulin + Dapagliflozin 10mg	0.063	Same as Cana 300
GTIs (Number)		
Insulin	1	1245.49 assumed to be placebo rate
Insulin + Sitagliptin 100mg	1	
Insulin + Empagliflozin 10mg	1.125	1245.49 equivalence assumed between respective doses
Insulin + Empagliflozin 25mg	1.416	
Insulin + Canagliflozin 100mg	1.125	
Insulin + Canagliflozin 300mg	1.416	
Insulin + Dapagliflozin 10mg	1.125	
	Utility	
Diabetes without complications	0.77	(100)
IHD	-0.09	(114)
MI	-0.055	(114)
CHF	-0.108	(114)
Stroke	-0.164	(114)
Amputation	-0.28	(114)
Blindness in one eye	-0.074	(114)
Renal failure	-0.0963	(101)
Hypoglycaemic event (non-severe)	-0.0035	(41)
Hypoglycaemic event	-0.01	(41)

Variable	Mean	Reference
(severe)		
UTIs	-0.00283	(101)
GTIs	-0.00283	Assumed to be same as UTI
Transient ischemic attacks	-0.03214	(101)
Non-fatal strokes (Stroke)	-0.05083	(101)
Non-fatal myocardial infarctions (MI)	-0.0557	(101)
Other myocardial ischemias (IHD, including angina)	-0.0468	(101)
Weight gain (per kg)	-0.0159	(102)
IHD	-0.09	(114)
MI	-0.0557	(114)
CHF	-0.108	(114)
Stroke	-0.164	(114)
Amputation	-0.28	(114)
Blindness in one eye	-0.074	(114)
Renal failure	-0.0963027	(101)
Transient ischemic attacks	-0.0321367	(101)
Non-fatal strokes (Stroke)	-0.164	(101)
Non-fatal myocardial infarctions (MI)	-0.055	(101)
Other myocardial ischemias (IHD, including angina)	-0.09	(101)

Variable	Mean	Reference
IHD	£7,628.14	(103)
MI	£8,179.41	(103)
CHF	£6,773.98	(103)
Stroke	£10,932.6	(103)
Amputation (one leg)	£13,556.0	(103)
Blindness (one eye)	£7,003.14	(103)
Renal failure	£34,488.31	(104)
Fatal MI	£2,511.20	(103)
Fatal CHF	£2,511.20	Assumption based on (103)
Fatal stroke	£6,773.98	(103)
Fatal amputation	£6,280.48	Assumption based on (103)
Fatal renal failure	£34,488.31	Assumption based on (41)
Other mortality related to diabetes	£2,511.20	Assumption based on (103)
Diabetes without complications	£483.00	Dapagliflozin ERG(105)
Costs for subsequent years		
IHD	£6,112.13	Clarke 2003
MI	£5,773.99	Clarke 2003
CHF	£6,565.65	Clarke 2003
Stroke	£4,759.57	Clarke 2003
Amputation (one leg)	£5,831.68	Clarke 2003
Blindness (one eye)	£4,719.51	Clarke 2003
Renal failure	£34,488	NICE CKD costing report
Hypoglycaemic event – non-severe	0	Assumption
Hypoglycaemic event - severe	£90	Dapagliflozin ERG
Urinary tract infections	£36	Dapagliflozin ERG
Genital infections	£36	Dapagliflozin ERG
Metformin	£8.94	MIMs 2014 and BNF 66
SU	£19.60	
Empagliflozin 10mg	£477.30	
Empagliflozin 25mg	£477.30	
Dapagliflozin 10mg	£477.30	
Canagliflozin 100mg	£477.30	
Canagliflozin 300mg	£608.63	
Sitagliptin 100mg	£433.86	
Insulin NPH	£396.21	Burslem et al 2011

Variable	Mean	Reference
Insulin glargine	£557.55	

AEs = adverse events; BMI = body mass index; CHF = congestive heart failure; GTIs = genital tract infections; HbA1C =glycated haemoglobin; HDL: = high density lipoprotein; IHD = ischaemic heart disease; met =metformin; MI = myocardial infarction; Pio = Pioglitazone; SBP = systolic blood pressure; SU = sulphonylureas; TIA = transient ischemic attack; TZD = thiazolidinedione; UKPDS = UK prospective diabetes study; UTIs = urinary tract infections

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

The treatment effectiveness was assumed to last only 1 year before patients resumed their natural history according to the UKPDS equations. So it was not extrapolated beyond the trial period.

However, while the treatment effect was constrained to one year, the impact of that treatment effect also needs to be managed. For example, the reduction in body weight while only lasting for a year will delay the progression of weight by a year going forward. It is unlikely that this effect will endure significantly into the future. Therefore, in the model the residual effect of the treatments were assumed to follow the pathway of the ERGs modifications implemented in the dapagliflozin technology appraisal where the patient's weight converged after the initiation of insulin.

Costs were not assumed to change over time, so potential price changes due to loss of exclusivity have not been modelled. The same assumption was also modelled for utilities. These were not implemented to be in keeping with previous assessments. However, these were explored in a sensitivity analysis utilising the values from the Sullivan et al 2011 utilities.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The key assumptions in the model are as follows along with justifications.

- UKPDS 68 (2004) equations used instead of UKPDS 82 please see Section 7.1.3 for details.
- The UKPDS 68 equations can be used for patients receiving second and third line therapy. This was accepted in CG 87.
- When insulin is added on to existing treatments the efficacy estimates from an observation study to model the impact of adding insulin.
- Data from the 24 week network is the most appropriate to use in the base case: please see Section 7.3.1. However, 52 week data was utilised in sensitivity analysis.
- When there was missing efficacy values from the NMA assumptions were made around similarity of SGLT2is and use of additional sources, please see Sections 7.3.1 and 7.3.2
- Due to the structure of the model and the absence of data on the evolution of weight over time in patients receiving empagliflozin it was assumed that, whenever a patient switches to a different treatment, the weight they'll start in the new treatment would be their baseline weight plus the natural weight they would have experienced if no treatment would have influenced their weight (i.e. 0.1 multiplied by the number of years since treatment initiation) and the impact on weight of the new treatment, independently of whether the previous treatment was a weight-loss or a weight-gain treatment. Please see Section 7.2.2
- Participants in the clinical trial program that informed efficacy estimates are representative of patients receiving dual, triple and insulin combination therapy in the UK.

- Given the absence of long term data on the effectiveness of empagliflozin it was assumed that the treatment effect only lasted one year before natural history was implemented.

- No age adjusted utilities or costs. While this is a potential weakness with the modelling this was addressed by utilising the utilities from Sullivan et al 2011 which included an adjustment factor for age.(101)

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

A conjoint analysis, Gelhorn and co-workers (2013)(106) identified the factors most likely to influence patients' preferences around treatment options for OADs in a sample of patients with early and advanced diabetes. This type of analysis establishes the relative importance of various attributes in determining the overall value of a product. .

In order to perform the analysis a literature review and pilot study was undertaken in addition to seeking clinical expert opinion. These identified the various attributes to explore and how they should be described to the participants. The inclusion criteria included people aged over 18 years, a self-diagnosis of type 2 diabetes and individuals who had taken an OAD for at least 6 months. Exclusion criteria included individuals receiving insulin, patients with type 1 diabetes mellitus (T1DM), renal disease or gestational diabetes.

Invitations were sent to 735 potential participants. A total of 354 individuals responded and 342 patients completed the screening. Of these 342 patients 150 were eligible for inclusion; 138 consented and initiated the survey. A total of 100 individuals were included in the final analysis. A sample size of 100 evaluable patients was targeted for the survey; this allowed for a sufficient number of participants for the planned subgroup analyses. Of these 100 patients, 50 individuals received one medication and the remainder received two or more medications. The overall results are presented in Table 60.

Table 60: Overall results of the aspects of the condition that most affect patients' quality of life

Attributes and Levels	Overall Utility Value	Relative Importance	Rank
Hypoglycaemic events	1.98	24.73	1
Weight Change	1.65	20.62	2
Gastrointestinal (GI)/Nausea Side Effects	1.49	18.59	3
Efficacy	1.44	17.97	4
UTI and GTI Side Effects	0.79	9.91	5
Cardiovascular risk	0.34	4.28	6
Blood Pressure	0.31	3.90	7

GTI = genital tract infection; UTI = urinary tract infection

The four most important attributes were hypoglycaemic events, weight change, GI/nausea side effects and efficacy. Patients considered UTI/GTI, CV risk and blood pressure side effects to be of lesser importance.

The results by number of medications are presented in Table 61.

Table 61: Factors most likely to influence preferences for OAD therapy in patients receiving 1 or ≥2 medications (Gelhorn et al., 2013)

Attributes and Levels	1 Medication			2 or more Medications			P-value[1,2]
	Overall Utility Value	Relative Importance	Rank	Overall Utility Value	Relative Importance	Rank	
Hypoglycaemic events	2.45	27.05	1	1.65	22.34	2	**0.0045**
Weight Change	1.58	17.41	4	1.80	24.42	1	**<0.0001**
Gastrointestinal (GI)/Nausea Side Effects	1.59	17.58	3	1.43	19.44	3	0.1946
Efficacy	1.82	20.07	2	1.15	15.62	4	**0.0016**
UTI and GTI Side Effects	0.82	9.06	5	0.79	10.74	5	0.1092
Cardiovascular risk	0.52	5.71	6	0.20	2.66	7	**<0.0001**
Blood Pressure	0.28	3.12	7	0.35	4.78	6	0.0122

GTI = genital tract infection; UTI = urinary tract infection

These results indicate that for patients receiving one medication the top four attributes were hypoglycaemic events, efficacy, GI/nausea and weight change. For those receiving 2 or more medications, weight change was the most important attribute, followed by hypoglycaemic events, GI/nausea effects and then efficacy. For both groups UTI/GTI, CV risk and blood pressure were of less importance.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As diabetes progresses the main factor that has the most impact on a patient's quality of life is CV events rather than diabetes itself. These have been incorporated into the model as separate quality of life estimates.(107, 108)

There has been a demonstrable effect of improved glycaemic control, reduced incidence of hypoglycaemia, and weight loss with an improvement in health-related quality of life (HRQL).(Davies and Speight, 2012) The conjoint analysis suggests that patients prefer treatments with reduced AEs which may in turn lead to greater adherence.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- *Method of elicitation.*
- *Method of valuation.*
- *Point when measurements were made.*
- *Consistency with reference case.*
- *Appropriateness for cost-effectiveness analysis.*
- *Results with confidence intervals.*

The data from the clinical trials is presented in Section 6.5. This data demonstrates that at all time points and for the majority of the subgroup analyses there was no difference between the treatment arms or the placebo/ comparator treatment. This finding reinforces the lack impact of HbA1c on quality of life. The baseline quality of life in the trials according to EQ-5D was ranged from 0.8 to 1.0. The lower score of 0.77 is consistent with the age adjusted EQ-5D score for the baseline population at age 62. This figure suggests that over the relatively short time horizon the score remains stable and there are no significant treatment related impacts on quality of

life. Unfortunately, these scores are inappropriate for inclusion into the model as the scores cannot be linked to a specific HbA1c score or clinical event. .

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- *Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.*
- *Details of the methodology used.*
- *Details of validation of the mapping technique.*

Not applicable as no mapping was conducted.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

As stated previously a review of previous NICE technology appraisals was conducted to identify relevant utility values.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- *Population in which health effects were measured.*
- *Information on recruitment.*
- *Interventions and comparators.*
- *Sample size.*
- *Response rates.*
- *Description of health states.*
- *Adverse events.*
- *Appropriateness of health states given condition and treatment pathway.*
- *Method of elicitation.*
- *Method of valuation.*
- *Mapping.*
- *Uncertainty around values.*
- *Consistency with reference case.*
- *Appropriateness for cost-effectiveness analysis.*
- *Results with confidence intervals.*
- *Appropriateness of the study for cost-effectiveness analysis.*

Table 62 reviews the utility values and sources from previous NICE Technology Appraisals or treatments included in the original scope.

Table 62: Utilities used in previous technology appraisals and CG87

Utilities			
Baseline utility	**Utility**	**Technology appraisal**	**Original reference**
Diabetes without complications	0.814	Liraglutide	(100)
	0.814	Exenatide	(100)
	0.785	CG87	(100)
Baseline	1.027	Canagliflozin	(102, 109)
Age per 10 years	-0.0235	Canagliflozin	(102)
Female	-0.093	Canagliflozin	(102)
Disease duration per 10 years	-0.163	Canagliflozin	(102)
Utility decrements			
IHD	-0.090	Dapagliflozin	(100)
	-0.280	Canagliflozin	(102)
	-0.090	CG87	(100)
Angina	0.682	Liraglutide	(100)
	0.682	Exenatide	(100)
Peripheral vascular disease	0.570	Liraglutide	(110)
	0.562	Exenatide	(111),
MI	-0.055	Dapagliflozin	(100)
	-0.074	Canagliflozin	(102)
	-0.055	CG87	(100)
MI year 1	-0.129	Liraglutide	(100)
	-0.129	Exenatide	(100)
MI year 1+	0.736	Liraglutide	(100)
	0.736	Exenatide	(100)
CHF	-0.108	Dapagliflozin	(100)
	-0.028	Canagliflozin	(102)
	-0.108	CG87	(100)
	0.633	Liraglutide	(100)
	0.633	Exenatide	(100)
Stroke	-0.164	Dapagliflozin	(100)
	-0.115	Canagliflozin	(102)
	-0.164	CG87	(100)
Stroke year 1	-0.181	Liraglutide	(100)
	-0.181	Exenatide	(100)
Stroke year 1+	0.545	Liraglutide	(100)
	0.545	Exenatide	(100)
One lower extremity amputation	-0.272	Canagliflozin	(102)
Two lower extremity amputation	-0.272	Canagliflozin	(102)

Utilities			
Baseline utility	**Utility**	**Technology appraisal**	**Original reference**
Amputation	-0.280	Dapagliflozin	(100)
	-0.280	CG87	(100)
Amputation year 1	-0.109	Liraglutide	(100)
	-0.109	Exenatide	(100)
Amputation year 1+	0.680	Liraglutide	
	0.680	Exenatide	
Blindness in one eye	-0.074	Dapagliflozin:	
	-0.057	Canagliflozin	(102)
	-0.074	CG87:	(100)
Severe vision loss/blindness	0.814	Liraglutide	(100)
	0.790	Exenatide	(100, 112)
Peripheral vascular disease (PVD)	-0.061	Canagliflozin	(102)
Symptomatic neuropathy & PVD	-0.085	Canagliflozin	(102)
Background diabetic Retinopathy	0.814	Liraglutide	(100)
	0.790	Exenatide	; (100, 112)
Proliferative diabetic retinopathy	0.794	Liraglutide	(100)
	0.79	Exenatide	(100, 112)
Cataract	0.794	Liraglutide	(100)
	0.814	Exenatide	(100, 112)
Macular oedema	0.794	Liraglutide	(100)
	0.790	Exenatide	(100, 112)
Gross proteinuria	-0.048	Canagliflozin	(102)
ESRD	-0.175	Canagliflozin	(102)
Renal failure	-0.263	Dapagliflozin	(113),
	-0.263	CG87	(100)
Haemodialysis	0.490	Liraglutide	(110)
	0.621	Exenatide	(114) (115),
Peritoneal dialysis	0.560	Liraglutide	(110)
	0.581	Exenatide	(114) (115),
Renal transplant	0.762	Liraglutide	(110)
	0.762	Exenatide	(114) (115)
Hypoglycaemic event (non-severe)	-0.042	Dapagliflozin	(116)
	-0.0036	Canagliflozin	(116)
	-0.0035	Liraglutide	(116)
	-0.004	Exenatide	(116)
Hypoglycaemic event (severe)	-0.047	Dapagliflozin	(116)
	-0.0118	Canagliflozin	(116)
	-0.0118	Liraglutide	(116)
	-0.012	Exenatide	(116)
Diabetic Ulcer	-0.17	Canagliflozin:	(102)
GI event (healed ulcer)	0.814	Exenatide	(100, 117)

Utilities			
Baseline utility	**Utility**	**Technology appraisal**	**Original reference**
GI event (active ulcer)	0.727	Exenatide	(100) (117)
UTIs	-0.00283	Dapagliflozin	(118)
Lower UTIs	-0.0012	Canagliflozin	(63)
Upper UTIs	-0.0073	Canagliflozin	(63)
GenIs	-0.00283	Dapagliflozin	Assumed same as UTIs
Balanoposthitis	-0.0046	Canagliflozin	(63)
Candidal vulvovaginitis	-0.0046	Canagliflozin	(63)
Nausea	-0.012	CG87	
Weight for each 1 kg/m^2 above 25 kg/m^2	-0.0061	Canagliflozin	(41)
Weight gain (per BMI unit increase)	-0.0472	Dapagliflozin	ISPOR poster (119)
	-0.0061	CG87	(102)
	-0.01	Liraglutide	(120)
Weight loss (per BMI unit decrease)	+0.0171	Dapagliflozin	ISPOR poster (119)

CHF = congestive heart failure; ESRD = end-stage renal stages; GI = gastrointestinal; MI = myocardial infarction; PVD = peripheral vascular disease; UTIs = urinary tract infections

Within the appraisals the values associated with CV events were generally accepted by the Appraisal Committees. Therefore, the estimates from Clarke and co-workers (2002), which were the most commonly reference for utilities, appear appropriate. These EQ-5D values were derived from the UKPDS study and from a UK population.

For treatment related AEs there were several issues with estimates chosen. In particular the disutility's chosen for hypoglycaemia and BMI changes. The most popular source for the quality of life decrement associated with hypoglycaemia was developed by Currie and colleagues (2006). However, the general consensus from NICE appraisals is that the fear of hypoglycaemia should not be used (CG87).

There have been significant issues over the choice of utility for BMI changes from previous NICE appraisals. The most accepted value has been the estimate from Bagust and Beale (2005). This was demonstrated in NICE TA288 dapagliflozin where it was recommended in the ACD as part of a minded not to recommend for the analysis to be conducted. (National Health Institute for Health and Clinical Excellence. 2013b)

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

From the clinical trials, the only comparable figure is the baseline quality of life and as stated previously this value lacks face validity since it is considerably higher than the age adjusted utilities often quoted in studies.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Treatment-related AEs can have a number of different effects on patients. Serious AEs, such as hypoglycaemic events may necessitate a change in therapy. Other more mild AEs, such as nausea, could result in compliance issues and short term reduction in a patient's quality of life. The AEs considered in the model were:

- Hypoglycaemia (severe and non-severe)
- UTIs
- Genital tract infections

Hypoglycaemia is assumed to potentially occur in all cycles as long the patient continues to receive the treatment that is causing this event.

UTIs and genital infections are assumed to occur only in the first cycle after the patient initiates the treatment associated with the AE.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Based on the review of previous models the most common utilities used to inform health states are those developed by Clarke and colleagues (2002). These EQ-5D values were derived from the UKPDS study and are therefore relevant in a UK context.

However, alternative values were available from a sponsored study. The UK catalogue of utilities comprised of EQ-5D scores for a number of different conditions including diabetes and also comorbidities.(Sullivan et al., 2011) An average value per patient with diabetes with or without complications was provided

as part of this catalogue,. Additionally, values were estimated that represented the marginal decrement in EQ-5D index scores for each condition after controlling for age, comorbidity, gender, race, ethnicity, income and education. These values could be used as disutilities to apply whenever a patient had experienced a complication on the top of their main condition (in this case, on the top of being a patient with T2DM). The limitation with these utilities was that, although community-based UK preferences were applied to EQ-5D descriptive questionnaire responses, the population responding the questionnaire was from the US-based Medical Expenditure Panel Survey (MEPS).

Therefore, following recommendations from a UK clinical expert, this additional set of utilities was used as sensitivity analysis. Although these values were considered not to be wholly representative of the UK population compared with the utility values considered in the base case, they did allow disutilities associated to complications and an age-related disutility to be taken into account. Table 63 and Table 64 summarise the methodologies and the values from both studies.(Clarke et al., 2002(100); Sullivan et al., 2011(101))

Table 63: UKPDS vs UK Catalogue of utilities

	UKPDS (Clarke et al 2002)	**UK Catalogue (Sullivan et al 2011)**
Diabetic patients	All (n = 3,192)	Over 79,522 individuals: 5,914 without complications 180 with complications
Baseline characteristics	Age: 62.3 (SD = 9.0) Duration of diabetes: 10.6 years	Age: 42.8 (entire sample) 60.2 (diabetes without complications) 60.0 (diabetes with complications) Duration of diabetes: NR
UK-specific?	Yes	No, US patients with UK preference weights
Disutilities for complications specific to diabetic patients?	Yes	No
Allows age-adjustment?	No	Yes

SD =standard deviation; UKPDS = UK prospective diabetes study

Table 64: Diabetes-related utilities and disutility values for long term complications from the UKPDS vs UK Catalogue of utilities

	UK Catalogue of utilities (101)		**UKPDS 62(100)**					
			Tariff from Tobit model			VAS from Tobit model		
	Mean	SE	Mean	95% CI		Mean	95% CI	
Diabetes w/o complications	0.664	0.005	-	-	-	-	-	-

Diabetes w/ complications	0.57	0.033	-	-	-	-	-	-
Diabetes mellitus	0.661	0.006	0.77	SD = 0.27		0.74	SD = 0.19	
Age-related disutility	-0.0003	0.0002	-	-	-	-	-	-
Disutility IHD	-0.0468	0.007616	–0.090	–0.126	–0.054	–0.044	–0.071	–0.018
Disutility MI	-0.0557	0.0112	–0.055	–0.067	–0.042	–0.041	–0.043	–0.038
Disutility CHF	-0.10338	0.016188	–0.108	–0.169	–0.048	–0.065	–0.109	–0.021
Disutility Stroke	-0.05083	0.012626	–0.164	–0.222	–0.105	–0.069	–0.112	–0.026
Disutility Amputation	-	-	–0.280	–0.389	–0.170	–0.120	–0.201	–0.038
Disutility Blindness in one eye	-0.0642	0.012118	–0.074	–0.252	–0.124	–0.043	–0.078	–0.008
Disutility Renal failure	-0.0963	0.011515	-	-	-	-	-	-

CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction

Unfortunately the UKPDS study by Clarke and colleagues (2002) does not include values for treatment related adverse events. Therefore, values were obtained from the dapagliflozin NICE appraisal. (National Health Institute for Health and Clinical Excellence. 2013b) Values for BMI changes were taken from Bagust and Beale (2005) the value used for UTIs/GTIs in the dapagliflozin NICE appraisal was considered appropriate as they had been accepted previously

For weight gain, an additional adjustment had to be conducted as the recommended disutility reflected disutility per increased unit of BMI, while the model took into account weight-related disutilities. For this, the average baseline height and weight of patients entering the model was considered and the disutility was proportionally allocated per kilogram of weight increased independently of the initial BMI or the amount of BMI increased.

The final values chosen are summarised in Table 65.

Table 65: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval/ Standard error		Reference in submission	Notes
Diabetes without complications	0.77	0.0048		(100)	
IHD	-0.09	-0.126	-0.054	(114)	
MI	-0.055	-0.067	-0.042	(114)	

CHF	-0.108	-0.169	-0.048	(114)	
Stroke	-0.164	-0.222	-0.105	(114)	
Amputation	-0.28	-0.389	-0.17	(114)	
Blindness in one eye	-0.074	-0.252	-0.124	(114)	
Renal failure	-0.0963	0.011515		(101)	
Hypoglycaemic event (non-severe)	-0.0035			(41)	
Hypoglycaemic event (severe)	-0.01			(41)	
UTIs	-0.00282	0.008044		(101)	
GTIs	-0.00282	0.008044		(101)	
Weight gain (per kg)	-0.0159	0.0076159		(102)	converted to Kg rather than BMI (-0.0061*mean height squared)
Subsequent years (lower and upper limits or SE)					
IHD	-0.09	-0.126	-0.054	(114)	
MI	-0.0557	-0.067	-0.042	(114)	
CHF	-0.108	-0.169	-0.048	(114)	
Stroke	-0.164	-0.222	-0.105	(114)	
Amputation	-0.28	-0.389	-0.17	(114)}	
Blindness in one eye	-0.074	-0.252	-0.124	(114)	
Renal failure	-0.0963027	0.0115147		(101)	
Transient ischemic attacks	-0.0321367	0.0241837		(101)	
Non-fatal strokes (Stroke)	-0.164	-0.222	-0.105	(101)	
Non-fatal myocardial infarctions (MI)	-0.055	-0.067	-0.042	(101)	
Other myocardial ischemias (IHD, including angina)	-0.09	-0.126	-0.054	(101)	

CHF = congestive heart failure; GTIs = genital tract infections; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infections

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- *the criteria for selecting the experts*
- *the number of experts approached*
- *the number of experts who participated*
- *declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- *the method used to collect the opinions*
- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *the questions asked*
- *Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

The UK clinical and health economic experts were consulted over the use of UKPDS or Sullivan utilities and advised that as the UKPDS estimates were from a UK specific population they should be favoured.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Not applicable as the model does not contain health states. However, the following outlines how the utilities were combined.

The model differentiated between disutilities to be applied per event, such as those related to adverse events (e.g. disutilities related to hypoglycaemias or UTIs and genital infections), from those that were applied per year for patients that had experienced a complication, either in the same year or in a previous year. For a patient who experienced multiple complications, it was assumed that multiple complications had an additive effect on utility. Moreover, it was assumed the same decrements were to be applied to patients with comparable complications regardless of their type of treatment. Given lack of specific disutilities related to long term complications in subsequent years after the event happened, the same value as for the year in which the event happened were used.

When considering the QALY-adjustments related to weight changes, it was assumed that weight loss did not have an impact on utilities while weight gain would result in a decrease of utility. This disutility was applied whenever the weight gain was higher than the baseline weight of the patient as a result of a treatment-related weight gain. The reason for this adjustment was to avoid considering disutilities related to medications associated with a weight loss for whom patients later on regained the lost weight through time. Moreover, weight-related disutilities were applied only to treatment-related weight increases, not to natural increase of weight.

Based on the recommendation from the dapagliflozin ERG, it was assumed that each 3% increase in the patient's BMI would result in a disutility of -0.004. Given that the model considered disutilities related to each kilogram of weight increased, the disutility per kilogram was estimated considering the baseline values in terms of BMI, average height for men and women, and proportion of females when initiating second and third treatment line. For this estimation, both second and third line treatments were considered and given the same weight.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The following health effects were excluded from the analysis due to a lack of data within the clinical trials and their exclusion from previous NICE appraisals.

- Peripheral oedema
- Fracture – this has been associated with pioglitazone, however, pioglitazone has been included as a background medication rather than a comparator, so the exclusion of this effect is unlikely to be significant.(121)
- Fear of hypoglycaemia as stated before has been excluded since this was considered unreliable in NICE CG 87.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life was based on the utility from the UKPDS population. All events were considered as disutilites versus this baseline.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility values were not assumed to change over time. However, to incorporate changes to the baseline utility estimates from Sullivan et al 2011 were utilised in sensitivity analysis.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No adjustments were made to the values before implementation into the model other than to account for discounting when summing the QALYs over time.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Diabetes is mainly managed in primary care and involves appointments with GPs and nurses depending on the local service arrangement. However, it is anticipated that there will be no differences in the number of appointments between the various oral anti-diabetic drugs other than managing adverse events.

The main elements of diabetes care that are covered by HRGs and PbR codes are related to the management of long-term conditions and hypoglycaemic events. The relevant codes from the 2011/2012 NHS reference costs are shown in Table 66 (NHS reference costs 2011/2012.)

Table 66: NHS reference costs

Code	Description	Unit Cost (£)
KB01A	Diabetes with Hypoglycaemic Disorders, 70 years and over	1,274
KB01B	Diabetes with Hypoglycaemic Disorders, 69 years and under	912
KB02A	Diabetes with Hyperglycaemic Disorders, 70 years and over with Major CC	2,087
KB02B	Diabetes with Hyperglycaemic Disorders, 70 years and over with Intermediate CC	1,223
KB02C	Diabetes with Hyperglycaemic Disorders, 70 years and over without CC	983
KB02D	Diabetes with Hyperglycaemic Disorders, 69 years and under with Major CC	1,645
KB02E	Diabetes with Hyperglycaemic Disorders, 69 years and under with Intermediate CC	789
KB02F	Diabetes with Hyperglycaemic Disorders, 69 years and under without CC	605
KB03A	Diabetes with Lower Limb Complications, with Major CC	3,090
KB03B	Diabetes with Lower Limb Complications, without Major CC	1,569
KB04Z	Continuous Subcutaneous Insulin Infusion	635
PA38C	Renal Disease with Renal Failure, with length of stay 0 days	535

PA38D	Renal Disease with Renal Failure, with length of stay 1 day or more	3,301
PA67Z	Diabetes Mellitus, with Ketoacidosis or Coma	1,065
PA68Z	Diabetes Mellitus, without Ketoacidosis or Coma	1,255
QZ12Z	Foot Procedures for Diabetes or Arterial Disease, or Procedures to Amputation Stumps	4,801
AA04A	Major Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC	12,652
AA04B	Major Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy, without CC	9,817
EB03H	Heart Failure or Shock, with CC	2,232
EB03I	Heart Failure or Shock, without CC	1,387
EB10Z	Actual or Suspected Myocardial Infarction	1,582
VC38Z	Rehabilitation for Acute Myocardial Infarction and Other Cardiac Disorders	286

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The costs from the PbR tariff and HRG are likely to be inappropriate since a number of the costs are likely to cover a number of different and potentially irrelevant conditions. In addition, there are concerns that the reference costs include too many different procedures and may not be representative of the true cost of diabetes. Within previous assessments by NICE NHS reference costs have not been commonly utilised. Estimates derived from published studies have been preferred and are referred to in Section 7.5.3.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- *country of study*
- *date of study*
- *applicability to UK clinical practice*
- *cost valuations used in study*
- *costs for use in economic analysis*
- *Technology costs.*

As stated in Section 0 review of the inputs used in previous NICE appraisals was conducted. A summary of the costs included are presented in Table 67, IU =

international units; NPH = neutral protamine Hagedorn; SU = sulphonylureas

Table 68 and UTIs = urinary tract infections

Table 69.

Table 67: Medication costs in previous NICE appraisals

Medication	Cost per day (£)	Cost per year (£)	Reference
Metformin	0.02	23.46	(122)
	0.07	24.16	(85)
	NR	26.07	(41)
SU	0.04	27.90	(122)
	0.17	62.17	(85)
	NR	20.56	(41)
Glimepiride	1.39	30.44	(88)
Gliclazide	1.16	19.60	(88)
Pioglitazone	1.13	414.07	(122)
	1.41	515.00	(86)
	NR	437.22	(41)
	0.099	36.13	(88)
Sitagliptin	1.19	433.57	(122)
	1.19	433.57	(85)
	1.19	434.65	(86)
	1.19	433.57	(41)
	NR	433.86	(88)
Exenatide 5mg	2.27	830.25	(85)
	2.27	829.12	(86)
	2.27	830.25	(41)
Exenatide 10mg	2.27	830.25	(85)
	NR	830.82	(88)
	2.27	829.12	(86)
	2.27	830.25	(41)(+31.10 for snap on needle costs)
Exenatide 1 weekly	2.62	959.96	(86)
Liraglutide 1.2mg	2x3 mL refill pens = 78.48 (30 days @1.2 mg dose)		(85)
		955.49	(88)
	1.2mg = £2.62 per day	954.84	(86)
Liraglutide 1.8mg	3x3 mL refill pens = 117.72 (30 days @1.8 mg dose)		(85)
	3.92	1,432.26	(86)
Dapagliflozin	1.31	476.92	(122)
	NR	477.30	(88)
Insulin			
Intensified insulin (NPH)-add on to metformin	0.0080 per kg/day	272.00 estimate	(122)
Insulin (insuman	0.0096 per kg/day	NR	(122)

Medication	Cost per day (£)	Cost per year (£)	Reference
basal) (NPH)-add on to insulin			
Intensified insulin (NPH)-add on to insulin	0.0120per kg/day	NR	(122)
Insulin (NPH)	0.51 per day;	185.71	(85)
		4.26	(88)
Insulin (Glargine)	Optiset = 1.01	379.60	(85)
	Solostar = 1.08	392.84	(85)
	10-60 IU/day	10.11	(88)
	31.1 IU/day = 0.42 per day	314.12	(86)
	40IU = 1.11 per day	405.43	(86)
Insulin (aspart)	5-200 IU/day	6.89	(88)

IU = international units; NPH = neutral protamine Hagedorn; SU = sulphonylureas

Table 68: Treatment related adverse events in previous NICE appraisals

Treatment related AE	Cost (£)	Technology Appraisal	Original reference
Hypoglycaemic event (non-severe)	0	Dapagliflozin	Assumption
	0	Canagliflozin	Assumption
Hypoglycaemic event (severe)	390.00	Dapagliflozin	(123)
	621.41	Canagliflozin	(124) calculated
	335.00	CG87	
Healed ulcer	20.81 per year	Exenatide	(125)
Infected ulcer	1,891.93 per month	Exenatide	(125)
Standard uninfected ulcer	1,854.83 per month	Exenatide	(125)
Annual follow-up cost for diabetic foot ulcer	244.59	Canagliflozin	(125)
UTIs	36.00	Dapagliflozin:	by assumption of cost of one GP visit (126)
Lower UTIs (male)	86.82	Canagliflozin	assume 2 GP visits and treatment (63)
Lower UTIs (female)	43.35	Canagliflozin	assume 1 GP visit and treatment (63)
Upper UTIs (male)	87.64	Canagliflozin	assume 2 GP visits and treatment (63)
Upper UTIs (female)	87.64	Canagliflozin	assume 2 GP visits and treatment (63)
GenIs	36.00	Dapagliflozin	by assumption of cost of one GP visit (126)
Balanoposthitis	53.60	Canagliflozin	assume 1 GP visit and treatment (63)
Vulvovaginitis	45.00	Canagliflozin	assume 1 GP visit and treatment (63)

UTIs = urinary tract infections

Table 69: CV (macro and micro) adverse events in previous NICE appraisals

Treatment related adverse event	Cost (£)	Technology appraisal	Original Reference
No complications	419.00	CG87:	**(103)**
IHD (non-fatal)	3,479.00	Dapagliflozin	**(103)**
	3,020.00	CG87:	**(103)**
IHD (Maintenance)	1,149.00	Dapagliflozin	**(103)**
	998.00	CG87:	**(103)**
Angina (1st year)	2,548.00	Liraglutide	**(103)**
	3,422.34	Exenatide	**(103) (127)**
	3601.34	Canagliflozin	**(103)**
Angina (2nd year)	842.00	Liraglutide	**(103)**
	1,130.25	Exenatide	**(103) (127)**
	1189.36	Canagliflozin	**(103)**
Peripheral vascular disease (1st year)	2,618.00	Liraglutide	**(103)**
	4,193.58	Exenatide	**(103) (127)**
	4,412.91	Canagliflozin	**Bradbury et al, 2010**
Peripheral vascular disease (2nd year)	2,618.00	Liraglutide	**(103)**
	863.68	Exenatide	**(103) (127)**
	908.85	Canagliflozin	**Bradbury, 2010**
MI (Fatal)	2,244.00	Dapagliflozin	**(103)**
	1,530.00	CG87	**(103)**
MI (Non-Fatal)	6,709.00	Dapagliflozin	**(103)**
	5,823.00	CG87	**(103)**
MI (Maintenance)	1,105.00	Dapagliflozin	**(103)**
	959.00	CG87	**(103)**
MI (1st year)	4,914.00	Liraglutide:	**(103)**
	3,816.65	Exenatide	**(103)**
	6354.87	Canagliflozin	**(103)**
MI (2nd year)	809.00	Liraglutide	**(103)**
	1,086.60	Exenatide	**(103)**
	1143.43	Canagliflozin	**(103)**
CHF (Fatal)	3,880.00	Dapagliflozin	**(103)**
	3,368.00	CG87	**(103)**
CHF (Non-fatal)	3,880.00	Dapagliflozin	**(103)**
	3,368.00	CG87	**(103)**
CHF (Maintenance)	1,360.00	Dapagliflozin	**(103)**
	1,180.00	CG87	**(103)**
CHF (1st year)	2,842.00	Liraglutide	**(103)**
	3,816.65	Exenatide	**(103)**
	4016.27	Canagliflozin	**(103)**
CHF (2nd year)	996.00	Liraglutide	**(103)**
	1,337.94	Exenatide	**(103)**
Stroke (Fatal)	5,658.00	Dapagliflozin	**(103)**

Treatment related adverse event	Cost (£)	Technology appraisal	Original Reference
	4,492.00	CG87	**(103)**
	3,791.00	Liraglutide	**(103)**
	5,091.38	Exenatide	**(103)**
Stroke (Non-fatal)	4,103.00	Dapagliflozin	**(103)**
	3,562.00	CG87	**(103)**
Stroke (Maintenance)	776.00	Dapagliflozin	**(103)**
	673.00	CG87	**(103)**
Stroke (1st year)	3,006.00	Liraglutide	**(103)**
	4,036.38	Exenatide	**(103)**
	5,505.92	Canagliflozin	**(103)**
Stroke (2nd year)	568.00	Liraglutide	**(103)**
	763.03	Exenatide	**(103)**
	802.94	Canagliflozin	**(103)**
Amputation (one leg) (Fatal)	13,359.00	Dapagliflozin	**(103)**
	11,596.00	CG87	**(103)**
Amputation (one leg) (Non-fatal)	13,359.00	Dapagliflozin	**(103)**
	11,596.00	CG87	**(103)**
Amputation (one leg) (surgery)	9,832.00	Liraglutide	**(103)**
Amputation (one leg) (Prosthesis)	625.00	Liraglutide	**(103)**
	839.78	Exenatide	**(103, 125);**
Amputation (lower extremity)	13,204.77	Exenatide	**(103, 125),**
	13,828.89	Canagliflozin	**(103)**
Neuropathy:	361.60	Exenatide	**(103, 125)**
Gangrene treatment: per month	3,299.79	Exenatide	**(103, 125)**
Amputation (one leg) (Maintenance)	771.00	Dapagliflozin	**(103)**
	798.19	Canagliflozin	**(103)**
	670.00	CG87	**(103)**
Blindness (one eye) (Non-fatal)	1,752.00	Dapagliflozin	**(103)**
	1,521.00	CG87	**(103)**
Blindness (one eye) (Maintenance)	742.00	Dapagliflozin	**(103)**
	644.00	CG87:	**(103)**
Blindness (one eye) (1st Year)	977.00	Liraglutide	**(103)**
	2402.67	Canagliflozin:	**(103, 128)**
Blindness (one eye) (Following years)	315.00	Liraglutide	**(103)**
	768.10	Canagliflozin	**(103)**
Cataract extraction (1st Year)	2,337.25	Exenatide	**(103, 128)**
Cataract extraction (subsequent years)	158.02	Exenatide	**(103, 128)**
Blindness (one eye) Laser treatment	160.00	Exenatide	**(103, 128)**
Blindness (one eye)	1,312.35	Exenatide	**(103, 128)**

Treatment related adverse event	Cost (£)	Technology appraisal	Original Reference
Severe vision loss/blindness (1st year)			
Blindness (one eye) Severe vision loss/blindness (subsequent years)	422.90	Exenatide	**(103, 128)**
Laser treatment	160.00	Exenatide	**(103, 128)**
Renal failure (Fatal)	33,600.00	CG87	**(103)**
Renal failure (Non-fatal)	34,806.00	Dapagliflozin	**(129)**
	33,600.00	CG87	**(103)**
Renal failure (maintenance)	34,806.00	Dapagliflozin	**(129)**
	24,917.38	Canagliflozin	**(130)**
	33,600.00	CG87	**(103)**
Renal failure (HD 1st year)	27,863.00	Liraglutide	**(131)**
	38,144.12	Exenatide	**(129); NHS tariff**
Renal failure (HD 2+ year)	27,863	Liraglutide	**(131)**
	38,144.12	Exenatide	**(129); NHS tariff**
Renal failure (PD 1st year)	20,920.00	Liraglutide	**(131)**
	20,977.29	Exenatide	**(129); NHS tariff**
Renal failure (PD 2+ year)	20,920.00	Liraglutide	**(131)**
	20,977.29	Exenatide	**(129); NHS tariff**
Renal failure (RRT 1st year)	22,191.00	Liraglutide	**(131)**
	30,246.57	Exenatide	**(129); NHS tariff**
Renal failure (RRT 2+ year)	7,212.00	Liraglutide	**(131)**
	2,761.80	Exenatide	**(129); NHS tariff**

CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; RRT = renal replacement therapy

In all cases, costs have been inflated to the relevant submission date using the HCHS index published by Curtis as part of the PSSRU.(Curtis)

As can been seen most of the costs for the majority of long term adverse events are taken from Clarke and colleagues (2003). These costs are derived from the UKPDS study and have been used in most of the previous NICE TAs, NICE CG87 that have generally been accepted. The main exceptions were costs associated with renal failure and ocular management; these costs were taken from a study of dialysis costs in the UK by Baboolal and co-workers (2008) which utilised the NHS tariff.

Treatment-related AE costs that are of most relevance to empagliflozin are hypoglycaemia and UTIs/GTIs. Cost data taken from dapagliflozin and CG 87

associated with hypoglycaemia were similar; this was also the case for those associated with UTIs/GTIs taken from canagliflozin and dapagliflozin.

The source of medication costs was the British National Formulary (BNF) and NHS drug tariff and these are consistent with NICE guidance to manufacturers. The cost of insulin was calculated in different ways depending on the appraisal. On the whole, the cost was based on the average IU incorporating costs of blood sugar test strips and other activities. These costs were then averaged per day.

In addition, health care resource use was measured within the empagliflozin clinical trial program. Table 70 notes the data collection point from each of the trials.

Table 70: Timing of data collection in addition to baseline, weeks after baseline

Trial	HCRU
1245.19	6, 12, 24
1245.20	6, 12, 24
1245.23a	6, 12, 24
1245.23b	6, 12, 24
1245.28	4, 8, 12, 16, 28, 40, 52, 65, 78, 91, 104
1245.36[a]	6, 12, 24, 52
1245.49	4, 18, 24, 40, 52

HCRU = Health care resource utilisation

Health care resource utilisation (HCRU) data included:

- Hospitalizations: intensive care and emergency department overnight stays
- Emergency department visits
- Outpatient visits: the type specialty of physician seen during the visit
- Home visits
- The number of days the patient was unable to perform paid work due to diabetes.

For each type of resource use, data were collected to indicate whether or not the resource used was related to diabetes. At baseline, current employment status and occurrence of diabetes-related hospitalization (yes/no) in the preceding year were captured. The analysis population for HCRU consisted of all patients in the full analysis set in each trial. HCRU variables were summarized only during the first 24 weeks of the treatment period using pooled trial data. HCRU data were summarized during the treatment period rather than the study period to avoid

counting resources used after treatment was discontinued. Data from 1 day after last intake was also used in the HCRU data set.

The proportion of patients who used any type of health care resource (i.e., diabetes- or non–diabetes-related) during the treatment period was relatively low and was similar among empagliflozin and placebo treatment arms (Table 71).

Table 71: Summary of Resource Use during the Treatment Period (Pooled Data, Full Analysis Set)

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
Emergency Room Visit	n (%)	47 (3.5%)	28 (2.5%)	75 (3.1%)	47 (3.5%)
	Average visits (SD)	1.2 (0.5)	1.1 (0.3)	1.1 (0.4)	1.1 (0.5)
	Median	1	1	1	1
	Q1, Q3	1, 1	1, 1	1, 1	1, 1
	Min,max	1, 4	1, 2	1, 4	1, 3
Hospitalizations					
General Ward[b]	n (%)	31 (2.3%)	29 (2.6%)	60 (2.5%)	39 (2.9%)
	Average days (SD)	8.7 (11.1)	7.4 (6.8)	8.1 (9.2)	9.4 (9.6)
	Median	3	5	4	6
	Q1, Q3	2, 10	3, 11	3, 11	3, 10
	Min,max	1, 49	1, 32	1, 49	1, 40
Intensive Care	n (%)	3 (0.2%)	5 (0.4%)	8 (0.3%)	3 (0.2%)
	Average days (SD)	2.0 (1.7)	5.8 (7.0)	4.4 (5.7)	3.0 (0.0)
	Median	1	3	3	3
	Q1, Q3	1, 4	2, 5	1, 5	3, 3
	Min,max	1, 4	1, 18	1, 18	3, 3
Overnight Emergency Room Visit	n (%)	4 (0.3%)	3 (0.3%)	7 (0.3%)	7 (0.5%)
	Average days (SD)	7.8 (8.5)	1.0 (0.0)	4.9 (7.0)	2.9 (3.7)
	Median	5	1	1	1
	Q1, Q3	2, 14	1, 1	1, 7	1, 3
	Min,max	1, 20	1, 1	1, 20	1, 11
Outpatient Visits					
General Physician	n (%)	200 (15.0%)	198 (17.8%)	398 (16.3%)	205 (15.4%)
	Average visits (SD)	1.8 (1.5)	2.0 (2.0)	1.9 (1.7)	1.9 (1.3)
	Median	1	2	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 14	1, 17	1, 17	1, 10
Specialist	n (%)	137 (10.3%)	125 (11.2%)	262 (10.7%)	141 (10.6%)
	Average visits (SD)	2.0 (1.4)	2.1 (1.9)	2.0 (1.6)	2.0 (1.6)
	Median	2	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 8	1, 11	1, 11	1, 11
Nurse	n (%)	16 (1.2%)	7 (0.6%)	23 (0.9%)	13 (1.0%)
	Average visits (SD)	5.0 (11.6)	2.4 (1.0)	4.2 (9.7)	1.3 (0.6)
	Median	1	3	1	1
	Q1, Q3	1, 4	1, 3	1, 3	1, 1
	Min,max	1, 48	1, 3	1, 48	1, 3
Dietician	n (%)	2 (0.2%)	3 (0.3%)	5 (0.2%)	4 (0.3%)
	Average visits (SD)	1.0 (0.0)	1.7 (0.6)	1.4 (0.5)	1.3 (0.5)
	Median	1	2	1	1

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
	Q1, Q3	1, 1	1, 2	1, 2	1, 2
	Min,max	1, 1	1, 2	1, 2	1, 2
Chiropodist	n (%)	1 (0.1%)	0	1 (<0.1%)	0
	Average visits (SD)	1.0		1.0	
	Median	1		1	
	Q1, Q3	1, 1		1, 1	
	Min,max	1, 1		1, 1	
Other	n (%)	35 (2.6%)	37 (3.3%)	72 (2.9%)	39 (2.9%)
	Average visits (SD)	2.4 (4.3)	1.9 (1.6)	2.1 (3.2)	1.8 (1.5)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 26	1, 9	1, 26	1, 8
Home Visits	n (%)	8 (0.6%)	9 (0.8%)	17 (0.7%)	17 (1.3%)
	Average visits (SD)	4.4 (4.4)	2.2 (2.3)	3.2 (3.5)	4.2 (5.3)
	Median	2	1	1	1
	Q1, Q3	1, 9	1, 3	1, 3	1, 8
	Min,max	1, 11	1, 8	1, 11	1, 18

SD = standard deviation

Table 72: Summary of Diabetes-Related Resource Use during the Treatment Period (Pooled Data, Full Analysis Set)

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
Emergency Room Visit	n (%)	8 (0.6%)	2 (0.2%)	10 (0.4%)	3 (0.2%)
	Average visits (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.3 (0.6)
	Median	1	1	1	1
	Q1, Q3	1, 1	1, 1	1, 1	1, 2
	Min,max	1, 1	1, 1	1, 1	1, 2
Hospitalizations					
General Ward[b]	n (%)	8 (0.6%)	2 (0.2%)	10 (0.4%)	9 (0.7%)
	Average days (SD)	11.3 (15.0)	22.0 (14.1)	13.4 (14.7)	11.7 (8.9)
	Median	6	22	9	8
	Q1, Q3	1, 17	12, 32	1, 24	6, 17
	Min,max	1, 43	12, 32	1, 43	2, 29
Intensive Care	n (%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
	Average days (SD)	4.0	18.0	11.0 (9.9)	3.0
	Median	4	18	11	3
	Q1, Q3	4, 4	18, 18	4, 18	3, 3
	Min,max	4, 4	18, 18	4, 18	3, 3
Overnight Emergency Room Visit	n (%)	2 (0.2%)	0	2 (0.1%)	0
	Average days (SD)	4.0 (4.2)		4.0 (4.2)	
	Median	4		4	
	Q1, Q3	1, 7		1, 7	
	Min,max	1, 7		1, 7	
Outpatient Visits					
General Physician	n (%)	22 (1.7%)	28 (2.5%)	50 (2.0%)	28 (2.1%)
	Average visits (SD)	1.6 (0.8)	1.6 (0.9)	1.6 (0.9)	1.8 (1.1)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 3	1, 2	1, 3
	Min,max	1, 3	1, 3	1, 3	1, 5
Specialist	n (%)	28 (2.1%)	23 (2.1%)	51 (2.1%)	38 (2.9%)
	Average visits (SD)	1.7 (1.4)	1.7 (2.1)	1.7 (1.7)	1.6 (1.3)

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 8	1, 11	1, 11	1, 7
Nurse	n (%)	6 (0.5%)	2 (0.2%)	8 (0.3%)	6 (0.5%)
	Average visits (SD)	9.3 (16.1)	3.0 (0.0)	7.8 (13.9)	1.2 (0.4)
	Median	3	3	3	1
	Q1, Q3	1, 6	3, 3	2, 5	1, 1
	Min,max	1, 42	3, 3	1, 42	1, 2
Dietician	n (%)	2 (0.2%)	3 (0.3%)	5 (0.2%)	3 (0.2%)
	Average visits (SD)	1.0 (0.0)	1.3 (0.6)	1.2 (0.4)	1.3 (0.6)
	Median	1	1	1	1
	Q1, Q3	1, 1	1, 2	1, 1	1, 2
	Min,max	1, 1	1, 2	1, 2	1, 2
Chiropodist	n (%)	0	0	0	0
	Average visits (SD)				
	Median				
	Q1, Q3				
	Min,max				
Other	n (%)	4 (0.3%)	7 (0.6%)	11 (0.4%)	9 (0.7%)
	Average visits (SD)	1.3 (0.5)	1.1 (0.4)	1.2 (0.4)	1.6 (1.0)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 1	1, 1	1, 2
	Min,max	1, 2	1, 2	1, 2	1, 4
Home Visits	n (%)	1 (0.1%)	0	1 (<0.1%)	3 (0.2%)
	Average visits (SD)	11.0		11.0	3.3 (4.0)
	Median	11		11	1
	Q1, Q3	11, 11		11, 11	1, 8
	Min,max	11, 11		11, 11	1, 8

SD = standard deviation

Table 73: Summary of Non-Diabetes-Related Resource Use during the Treatment Period (Pooled Data, Full Analysis Set)

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
Emergency Room Visit	n (%)	39 (2.9%)	26 (2.3%)	65 (2.7%)	45 (3.4%)
	Average visits (SD)	1.2 (0.6)	1.1 (0.3)	1.2 (0.5)	1.1 (0.4)
	Median	1	1	1	1
	Q1, Q3	1, 1	1, 1	1, 1	1, 1
	Min,max	1, 4	1, 2	1, 4	1, 3
Hospitalizations					
General Ward[b]	n (%)	25 (1.9%)	27 (2.4%)	52 (2.1%)	31 (2.3%)
	Average days (SD)	7.2 (7.0)	6.3 (5.0)	6.7 (6.0)	8.4 (9.8)
	Median	4	4	4	5
	Q1, Q3	3, 10	2, 10	3, 10	3, 9
	Min,max	1, 27	1, 16	1, 27	1, 40
Intensive Care	n (%)	2 (0.2%)	4 (0.4%)	6 (0.2%)	2 (0.2%)
	Average days (SD)	1.0 (0.0)	2.8 (1.7)	2.2 (1.6)	3.0 (0.0)
	Median	1	3	2	3
	Q1, Q3	1, 1	2, 4	1, 3	3, 3
	Min,max	1, 1	1, 5	1, 5	3, 3

Resource Type	Statistic[a]	E 25 mg (N = 1332)	E 10 mg (N = 1114)	E 25 mg + 10 mg (N = 2446)	Placebo (N = 1332)
Overnight Emergency Room Visit	n (%)	2 (0.2%)	3 (0.3%)	5 (0.2%)	7 (0.5%)
	Average days (SD)	11.5 (12.0)	1.0 (0.0)	5.2 (8.3)	2.9 (3.7)
	Median	12	1	1	1
	Q1, Q3	3, 20	1, 1	1, 3	1, 3
	Min,max	3, 20	1, 1	1, 20	1, 11
Outpatient Visits					
General Physician	n (%)	182 (13.7%)	179 (16.1%)	361 (14.8%)	189 (14.2%)
	Average visits (SD)	1.8 (1.5)	2.0 (2.0)	1.9 (1.8)	1.8 (1.3)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 14	1, 17	1, 17	1, 10
Specialist	n (%)	118 (8.9%)	106 (9.5%)	224 (9.2%)	113 (8.5%)
	Average visits (SD)	1.9 (1.3)	2.1 (1.8)	2.0 (1.6)	2.0 (1.7)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 7	1, 11	1, 11	1, 11
Nurse	n (%)	12 (0.9%)	5 (0.4%)	17 (0.7%)	7 (0.5%)
	Average visits (SD)	2.0 (1.8)	2.2 (1.1)	2.1 (1.6)	1.4 (0.8)
	Median	1	3	1	1
	Q1, Q3	1, 3	1, 3	1, 3	1, 2
	Min,max	1, 6	1, 3	1, 6	1, 3
Dietician	n (%)	0	1 (0.1%)	1 (<0.1%)	1 (0.1%)
	Average visits (SD)		1.0	1.0	1.0
	Median		1	1	1
	Q1, Q3		1, 1	1, 1	1, 1
	Min,max		1, 1	1, 1	1, 1
Chiropodist	n (%)	1 (0.1%)	0	1 (<0.1%)	0
	Average visits (SD)	1.0		1.0	
	Median	1		1	
	Q1, Q3	1, 1		1, 1	
	Min,max	1, 1		1, 1	
Other	n (%)	32 (2.4%)	33 (3.0%)	65 (2.7%)	31 (2.3%)
	Average visits (SD)	2.4 (4.5)	1.9 (1.7)	2.2 (3.4)	1.8 (1.6)
	Median	1	1	1	1
	Q1, Q3	1, 2	1, 2	1, 2	1, 2
	Min,max	1, 26	1, 9	1, 26	1, 8
Home Visits	n (%)	7 (0.5%)	9 (0.8%)	16 (0.7%)	14 (1.1%)
	Average visits (SD)	3.4 (3.8)	2.2 (2.3)	2.8 (3.0)	4.4 (5.6)
	Median	2	1	1	2
	Q1, Q3	1, 6	1, 3	1, 3	1, 8
	Min,max	1, 11	1, 8	1, 11	1, 18

SD = standard deviation

The proportion of patients who were admitted to a general ward was low and varied only slightly (2.3% to 2.9%) across treatment arms. The average number of days in the general ward was similar for empagliflozin 25 mg (8.7 days) and empagliflozin 10 mg (7.4 days) and a slightly longer for placebo (9.4 days). The mean (SD) number of days in intensive care was higher for empagliflozin 10 mg

treatment, 5.8 (7.0) days (likely due to a patient in study 1245.19 who had 18 days in intensive care) than for empagliflozin 25 mg, 2.0 (1.7) days, or placebo, 3.0 (0) days. The median number of days was 3 for both empagliflozin 10 mg and placebo, indicating that the difference in mean values is due to the possible outlier mentioned previously. The mean (SD) number of days for overnight emergency room stays was higher for empagliflozin 25 mg, 7.8 (8.5) days, than for empagliflozin 10 mg, 1.0 (0) day, or placebo, 2.9 (3.7) days. However, these differences are likely not to be statistically significant due to large standard deviations.

Emergency room visits were also relatively rare, with 3.5% of patients receiving empagliflozin 25 mg and placebo, and 2.5% of patients receiving empagliflozin 10mg.

The average number of emergency room visits was about 1.1 in all treatment arms. A similar average number of visits to general practitioners and specialists were observed in all treatment arms, but not for visits to a nurse. A higher mean (SD) number of nurse visits was observed for patients receiving empagliflozin 25 mg, 5.0 (11.6) visits, than for patients receiving empagliflozin 10 mg, 2.4 (1.0) visits, or placebo, 1.3 (0.6) visits. This finding is possibly due to a patient in trial 1245.23 who had 48 visits. The median number of nurse visits for patients receiving empagliflozin 25 mg and placebo was 1, which confirms the impact of the mentioned outlier.

At baseline, those patients who reported that they were employed at least part time, the mean (SD) number of days of work missed due to diabetes was 71.5 (69.0) days for patients receiving empagliflozin 25 mg. This finding was due to 2/4 patients who reported large numbers of days absence (126 days for a patient in trial 1245.36 and 136 days for a patient in trial 1245.23a), whereas 3 patients receiving placebo reported 1, 4, and 17 days of work missed.

The proportion of patients who used health care resources during the treatment period was relatively low and similar among empagliflozin (both doses) and placebo treatment arms. The health care resources with the highest percentage of

use by patients were general physician visits and specialist visits. The majority of these resources used were non–diabetes-related.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- *the criteria for selecting the experts*
- *the number of experts approached*
- *the number of experts who participated*
- *declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
- *the method used to collect the opinions*
- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *the questions asked*
- *Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

The estimates were validated with the clinical and health economic experts who both confirmed that these values were appropriate for inclusion.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Table 70 outlines the costs of medications used in the model.

Table 74: Medication costs

Drug	Strength (mg) or average daily IU	Pills per pack	Price per pack (£)	Daily dose (mg)	Pills per day	Net cost per day (£)	Net cost per year (£)
Metformin	500 mg	84	£0.81	1270 mg	1	£0.02	£8.95
SU	80 mg	60	£1.61	160 mg	2	£0.05	£19.60
Pioglitazone	30mg	28	£2.77	30mg	1	0.10	£36.13
Empagliflozin	10mg	28	£36.59	10mg	1	£1.31	£477.30

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Empagliflozin	25mg	28	£36.59	25mg	1	£1.31	£477.30
Dapagliflozin	10mg	28	£36.59	10mg	1	£1.31	£477.30
Canagliflozin	100mg	30	£39.20	100mg	1	£1.31	£477.30
Canagliflozin	300mg	30	£49.99	300mg	1	£1.66	£608.63
Sitagliptin	100mg	28	£33.26	100mg	1	£1.19	£433.85
Insulin NPH	31.7 IU	N/A	N/A	N/A	N/A	£0.44	£396.20
Insulin glargine	31.7 IU	N/A	N/A	N/A	N/A	£0.86	£557.55

IU: International units.
All drug unit costs per year were obtained from the British National Formulary September 2013 No 66

All drug unit costs per year were obtained from the BNF No 66.

Treatment costs included the acquisition costs of the different drugs administered as part of the combination therapies assessed in the analyses. The assumed dosage form, packaging information and the per pack unit costs for each of the therapies included in the analysis were obtained from the BNF. The BNF September 2013 was consulted to identify the relevant strength, number of pills per pack and price per pack across treatments available in the UK market.

In the case of metformin, the daily dose was taken from one study used in the NICE Clinical Guidelines where the average dose of metformin was reported. Based on the feedback from a UK clinical expert, the most important SUs in the UK are glimepiride, glibenclamide and gliclazide. The dosing and price used in the base case reflected that of gliclazide 80mg, 60-tab pack, since this was the least expensive SU available. A dose of 160mg daily was assumed, based on the recommendations of the BNF of administering up to 160 mg as a single dose; max. 320 mg daily. In the case of insulin, due to the diversity of agents available and the different doses prescribed, expert opinion was sought. The two types of insulin included in the model represented those used in the clinical practice for the treatment of T2DM patients in the UK: NPH (with an annual net cost equal to £159.50, and representing clinical practice in the UK) and glargine (with an annual net cost equal to £312.40). Based on the recommendation from NICE the cost of insulin (either for NPH or glargine) reflected the daily cost of insulin per patient in the UK, plus the daily cost of insulin pens, needles and test strips. The annual cost of different components of insulin treatment in the UK was:(Burslem et al., 2011)

- Insulin pen costs: £31 per year
- Needle costs: £5 per year

- Test strip costs: £180 per year

Costs were for 2010 prices and have been updated to 2012 prices using the HCHS index.(Curtis; Curtis; Curtis; Curtis; Frier; National Institute for Health and Clinical Excellence.; Palmer et al., 2004; Burslem et al., 2011; Frier, 2011)

The direct annual per patient medical cost of following up patients was an estimated £483. This cost was applied to all patients, independently of whether they had experienced a complication.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

There are no health state costs as such; costs are associated with treatments and complications and adverse events.

Adverse-event costs

7.5.7 *Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2*.

The unit costs per type of complication are presented in Table 57. The majority of the costs were derived from Clarke and co-workers (2003) and adjusted for inflation to the 2013 costs using the HCHS index. No cost was allocated to weight gain since no reliable data was identified; therefore, it was assumed that weight gain impacted utilities but not costs.

The cost for diabetes without complications was accepted by the appraisal committee for dapagliflozin and it was originally included in the UKPDS study. Therefore, it was applied without further adjustment.

Different unit costs related to the management of long term complications were considered, where available, to reflect the expenses incurred on the year in which the event occurred versus on subsequent years (Table 56and Table 57). The costs

of renal failure were derived from NICE costing report for CKD and the NICE T2DM CG. (National Institute for Health and Clinical Excellence).

The cost of renal failure represented the annual cost of haemodialysis, which has been reported to be the main mode of renal replacement therapy in the UK. The cost of fatal renal failure was assumed to be the same as the annual cost of renal failure, as it was assumed in the economic model developed in the NICE clinical guidelines for diabetes.

The cost of fatal CHF was assumed to be the same as that of fatal MI. The cost of fatal amputation was assumed to be 46.33% of that of non-fatal amputation and non-fatal renal failure, respectively. This proportion was estimated as the average between the proportion of the fatal cost over the non-fatal cost for MIs (30.70%) and strokes (61.96%). The cost of other mortality related to diabetes was assumed to be similar to the cheapest mortality cost identified from Clarke et al., (2003) (i.e. that of MI).

Table 75: Adverse event costs in first year

Event	Costs in British Pounds (£)	Lower bound	Upper bound	Reference
IHD	£7,628.14	£5,987.13	£9,717.86	(103)
MI	£8,179.41	£7,189.04	£9,304.40	(103)
CHF	£6,773.98	£5,498.35	£8,346.08	(103)
Stroke	£10,932.6	£8,421.40	£14,195.39	(103)
Amputation (one leg)	£13,556.0	£8,365.31	£21,964.55	(103)
Blindness (one eye)	£7,003.14	£5,158.61	£9,507.93	(103)
Renal failure	£34,488.31			(104)
Fatal MI	£2,511.20	£2,049.66	£3,075.29	(103)
Fatal CHF	£2,511.20	£2,049.66	£3,075.29	Assumption based on (103)
Fatal stroke	£6,774	£3,932.66	£11,666.56	(103)
Fatal amputation	£6,28	£3,875.65	£10,176.18	Assumption based on (103)
Fatal renal failure	£34,488			Assumption based on (41)
Other mortality related to diabetes	£2,511	£2,049.66	£3,075.29	Assumption based on (103)

The cost of renal failure represented the annual cost of haemodialysis, which has been reported to be the main mode of renal replacement therapy in the UK. The cost of fatal renal failure was assumed to be the same as the annual cost of renal failure, as it was assumed in the economic model developed in the NICE clinical guidelines for diabetes.

The cost of fatal CHF was assumed to be the same as that of fatal MI. The cost of fatal amputation was assumed to be 46.33% of that of non-fatal amputation and non-fatal renal failure, respectively. This proportion was estimated as the average between the proportion of the fatal cost over the non-fatal cost for MIs (30.70%) and strokes (61.96%). The cost of other mortality related to diabetes was assumed to be similar to the cheapest mortality cost identified from Clarke 2003 (i.e. that of MI).
CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction

Table 76: Event costs in subsequent years

Event	Costs in British Pounds	Lower bound	Upper bound	References
Diabetes without complications	£483.00			Dapagliflozin ERG(105)
For long term complications:				
IHD	£6,112.13	£5,273.99	£7,083.27	Clarke 2003
MI	£5,773.99	£5,022.39	£6,637.76	Clarke 2003
CHF	£6,565.65	£5,044.83	£8,543.19	Clarke 2003
Stroke	£4,759.57	£3,650.61	£6,205.07	Clarke 2003
Amputation (one leg)	£5,831.68	£3,918.23	£8,679.41	Clarke 2003
Blindness (one eye)	£4,719.51	£3,764.39	£5,916.61	Clarke 2003
Renal failure	£34,488			NICE CKD costing report

The cost of TIAs was approximated by the cost of carotid endarterectomy (i.e. £3,434 for 2006/07 prices) and it was inflated to 2011 prices. The cost of other myocardial infarctions was approximated to that of IHD.
AE= adverse events; CHF = congestive heart failure; CV= cardiovascular; IHD = ischaemic heart disease; MI = myocardial infarction; TIA = transient ischemic attack

Adverse event costs were derived from a number of sources. The values from the Dapagliflozin appraisal were utilised as they were broadly accepted by the Appraisal Committee. For non-severe hypoglycaemic events it was assumed that there was no cost associated with non-severe hypoglycaemic events. (Table 77)

The NICE ERG based the cost of severe hypoglycaemias on CG87, which relied upon the study by Leese and co-workers (2003) of medically managed severe hypoglycaemic events. The study included both patients with T2DM and T1DM, and the authors reported that the balance between events among patients with T2DM and patients with T1DM was roughly equal. CG87 calculated an average cost of £335 per event which, updated to 2011 prices using the HCSPPI, resulted in £360 per event. Applying the CG87, 25% would result in an average cost per event of only £90. This is the conservative estimate that the dapagliflozin NICE ERG recommended for the cost of severe hypoglycaemias.

UTIs and GTIs are assumed to require one GP consultation at a cost of £36 as drawn from the PSSRU 2011 Unit Costs of Health and Social Care, following the dapagliflozin submission.

Table 77: Costs of treatment-related AE per cycle

Event	Costs in British Pounds (£)	Lower bound	Upper bound	References
Hypoglycaemic event – non-severe	£0	£0	£0	Assumption
Hypoglycaemic event - severe	£90			Dapagliflozin ERG
Urinary tract infections	£36	£32.40	£39.60	Dapagliflozin ERG
Genital infections	£36	£32.40	£39.60	Dapagliflozin ERG

The ERG based this estimation on CG87, which relied upon the study by Leese (2003) of medically managed severe hypoglycaemic events. The study included both patients with T2DM and patients with T1DM, and the authors reported that the balance between events among patients with T2DM and patients with T1DM was roughly equal. CG87 calculated an average cost of £335 per event which, updated to 2011 prices using the HCSPPI, resulted in £360 per event. Applying the CG87 25% would result in an average cost per event of only £90. This is the conservative estimate that the dapagliflozin ERG recommended for the cost of severe hypoglycaemias.

UTIs and GIs are assumed to require one GP consultation at a cost of £36 as drawn from the PSSRU 2011 Unit Costs of Health and Social Care, following the dapagliflozin submission.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

- 52 week data analysis

24 week data was used in the base case as there was more data available for the treatments in the decision space. However, data from longer time points is obviously preferable if available. Therefore an analysis was run with 52 week data from the NMAs. Unfortunately there was not enough information to inform 52 week networks for metformin and TZD networks therefore this analysis was not included. No other data was changed in the model.

- IMS model validation

The IMS model was used to validate the analysis by conducting a series of cost effectiveness analyses using where possible the same input parameters. The analysis included the metformin, metformin and SU and insulin background therapies. The treatments chosen were empagliflozin, canagliflozin and dapagliflozin to compare the SGLT2is to explore if there are any significant differences within the class.

A full report detailing the analysis is detailed in Section 9.12, Appendix 12. The results are presented in Section 7.8.

The main structural differences between the models is that the CORE model includes separate Markov models for a number of long-term conditions such as ulcers which enables it to include specific factors around the costs and outcomes not contained within the ECEM. The treatment pathway modelled in the CORE model also differed to the ECEM. In the ECEM after the failure of initial treatment insulin was added to the current treatment and then only in the insulin background treatment analysis did patients switch onto rescue insulin (glargine). In the CORE model patients remained on the initial treatment for three years and were then switched to rescue insulin (NPH). Thereafter patients remained on the rescue insulin. In addition, for weight loss and corresponding weight regain, patients benefited from the weight loss for three years (period on treatment) and then rebounded to their starting weight which they stayed at for the remainder of the model.

Given the different structure of the model certain inputs had to differ and also their implementation differed. These key differences are:

- 52 week data – the CORE model has a 12 month cycle and therefore utilised the 12 month clinical data from the network meta-analysis.
- Baseline utility – given the number of additional health states within the CORE model, if the baseline utility used in the ECEM was used it could result in negative utility values and therefore produce counter intuitive results. Therefore, the standard baseline utility value from the CORE model was used.

- Calculation of adverse events, the CORE model uses rates of adverse events to calculate the accumulation of adverse events over a life time, therefore, rates of hypoglycaemia, UTIs and GTIs were used.
- A number of sub-events such as the progression of ulcers and retinopathy are included in the CORE model and are not captured in the ECEM and therefore as no input parameters were identified for the ECEM, standard inputs for the CORE model were used

A full list of inputs are presented in Section 9.12, Appendix 12. The results of this analysis will be compared to the results of the ECEM and any differences will be explored.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Given the structure of the model the following variables were explored in sensitivity analysis. These values were considered the most relevant for review as the majority of the values had been accepted by previous NICE appraisals.

- A different set of utility values was taken into account to consider utilities, complication-related disutilities and age-related disutilities from the UK catalogue of utilities, whenever available, (instead of using UKPDS utilities). Two analyses were conducted on utility values, one taking into account disutilities from the UK catalogue of utilities, without applying the age-related disutility, while a second analysis took into account age-related disutlities as well. The main difference in this case was the consideration of age-related disutilities and a much lower disutility value for strokes.

- Discontinuation rates: the discontinuation rates of all treatments were assumed to be similar to those of empagliflozin 10 mg (since this presented the lowest rates).

- The number of adverse events happening per patient experiencing an adverse event. For this, the lowest number of adverse events observed across treatments (for non-severe hypoglycaemias, severe hypoglycaemias, UTIs and genital infections) was applied to each of the treatments.

- In the base case analysis it was assumed that BMI could directly affect the incidence of CHF, which was expected to decrease the incidence of CHF and other long-term complications as a result of this, and therefore, increase life years and QALYs and decrease the costs associated to long-term complications across treatments resulting in a reduction of the patients' BMI. As part of the sensitivity analysis, this assumption was modified so that BMI changes did not impact the incidence of CHF or the disutility of patients due to weight changes.

- Assumptions related to weight changes, by considering a less conservative scenario. In this case, the base case conservative assumptions around weight change were relaxed by assuming that weight change would initially occur over the first cycle and this weight change would be maintained over one year. Then over the next two years, weight would return to the base case value. After this point, the annual weight increase was assumed to be 0.1 kg.

- Assumption related to the duration of the treatment effect, by considering that the maintenance of benefit would last for two years instead of one.

- Time horizon for the analysis, by considering a 10-year time horizon instead of 40 years.

- The assessment of the impact of different discount rates on costs and effects (with discount rates set to 0% and 6% across different analyses).

The sensitivity analyses focused on considering the comparisons provided in the table below. The reason to focus on dapagliflozin 10 mg and sitagliptin 100 mg in the sensitivity analyses was that these were the treatments for which NICE had issued recommendations at the time of the preparation of the empagliflozin submission for NICE and it was felt that it was informative to present comparisons against canagliflozin doses in the base case analysis, but it would help in the interpretation of the results to focus the sensitivity analyses on those relevant, recommended treatments at the time of the submission

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Beta distributions were considered when simulating probabilities of events happening, utility and disutility values, and allocation of baseline characteristics such as sex and ethnicity, and disease history. Given that when drawing simulations from beta distributions in Excel with some extreme values may result in an error, uniform distributions were used alternatively in case errors occurred.

Gamma distributions were used for the estimation of the unit costs of events, and some of the baseline characteristics of patients (including age, number of years from diagnosis, SBP, lipid ratio and BMI).

Normal distributions were used for efficacy estimates (so that the change from baseline in HbA1c levels, SBP levels, lipid ratio and weight could be estimated probabilistically), and for hazard ratios (whenever these were used; in the UK analyses.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The graphs presenting the evolution over time for the three main clinical variables (HbA1c, SBP and body weight) for the comparison with dapagliflozin and sitagliptin in the four lines of therapy (in combination with metformin, metformin and sulphonylurea, metformin and thiazolidinediones and insulin) are in Section 9.10, Appendix 10.

All the graphs demonstrate that the initial decrease occurs over the first couple of cycles before gradually increasing back to the baseline level. Thereafter there is a convergence in outcomes across all the treatments usually within 8 years. The one exception is the weight progression associated with metformin plus TZD. In these scenarios the weight convergence is over a greater time period. This is due to the considerable weight gain associated with this combination and therefore, the time to convergence takes significantly longer.

All the graphs comparing empagliflozin and the other SGLT2is indicate that there is a degree of variation within the 95% intervals that there is very little difference in the mean estimates over time. This suggests that there should be very little difference in the incremental QALYs. This is in line with the clinical inputs which demonstrate a lack of clinically significant differences between the SGLT2is.

For the comparisons with sitagliptin, there are differences for SBP and weight in the first year which is to be expected based on the results of the NMA. However, over time these differences do not continue. The most significant difference is with metformin plus TZD combination where the weight gain associated with the background treatment affects the weight profile for sitagliptin the most. However, there does seem to be a slow convergence between the various treatments.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

As the model is not a Markov model this is not applicable.

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

The following are graph is for the average QALY and costs per surviving patient per year and how much they contribute to the final QALY and cost estimates. The analysis chosen was empagliflozin 25mg compared to sitagliptin 100mg in combination with metformin as this was considered representative of the majority of the analyses. This demonstrate that as time progresses in the model, the number of patients in the cohort contributing to the cost effectiveness estimates decreases until it is near zero. Therefore, suggesting that the cohort is being assessed by the model appropriately. For costs the increase in the 95% limit for costs around 5 years is probably associated with the occurrence of LTC in people at this point in time

Figure 34: Average discounted QALYs per surviving patient per cycle for empagliflozin 25mg compared to sitagliptin 100mg

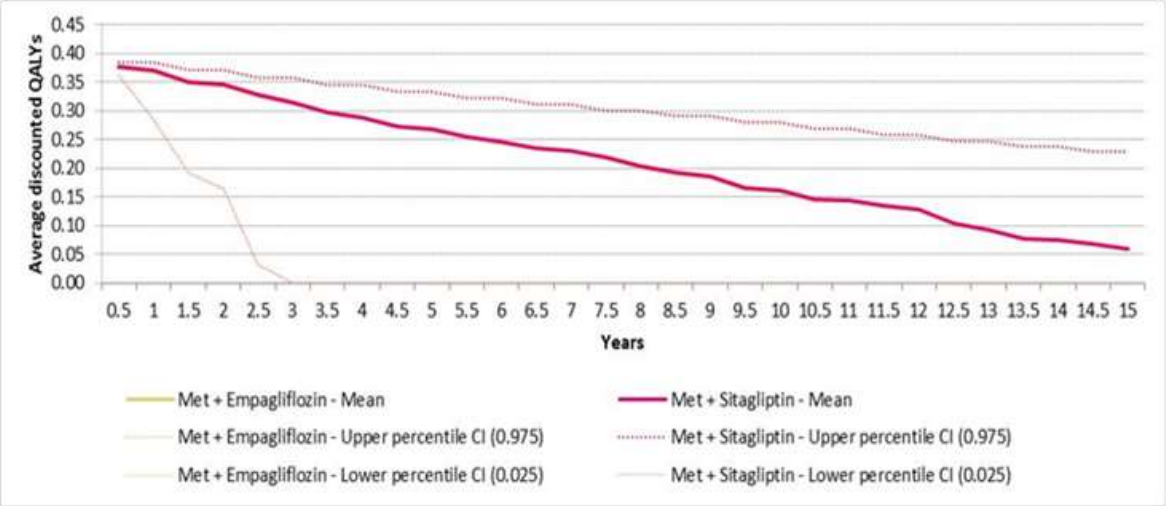
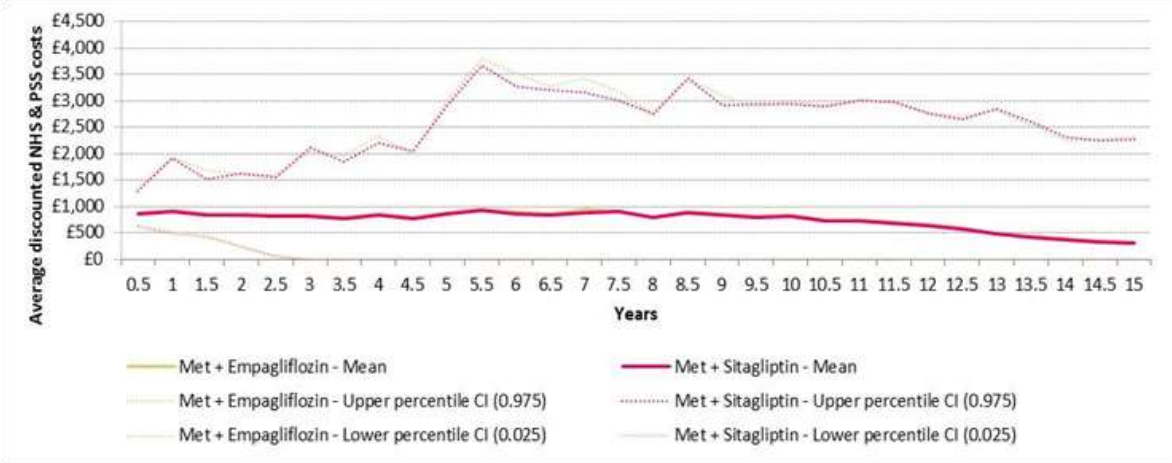


Figure 35: Average discounted NHS costs per surviving patient per cycle for empagliflozin 25mg compared to sitagliptin 100mg



7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.*

Table 78 to Table 81 presents the disaggregated number of events for each treatment considered and for each of the four background treatments. For the majority of analyses there does not appear to be any clinically significant differences between the SGLT2is in terms of the number of events. Generally sitagliptin is associated with more LTCs but fewer treatment related adverse events.

For LTCs there are no significant differences with all the estimates being around 0.7. For treatment related adverse events there are generally larger differences in terms of hypoglycaemia and also in some analyses infection rates.

The relative importance of these differences in terms of the incremental QALYs will be explored in the next section when exploring the contributions to the incremental QALYS

Table 78: Breakdown of clinical events for analysis of dual therapy

	Dual therapy - Metformin					
	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Sitagliptin 100mg	Dapagliflozin 10mg
QALY	7.424	7.433	7.415	7.418	7.425	7.404
Life Years	9.952	9.958	9.937	9.941	9.942	9.919

LTCs: Total number of events	0.704	0.702	0.710	0.705	0.706	0.713
IHDs	0.090	0.089	0.090	0.090	0.091	0.090
MIs	0.222	0.220	0.223	0.221	0.224	0.225
CHFs	0.076	0.075	0.076	0.075	0.077	0.076
Strokes	0.174	0.177	0.178	0.179	0.174	0.179
Amputations	0.082	0.081	0.082	0.081	0.081	0.083
Blindness in one eye	0.041	0.041	0.040	0.040	0.040	0.041
Renal failures	0.019	0.019	0.019	0.019	0.019	0.019
Years free of complication	7.484	7.507	7.480	7.510	7.497	7.457
AEs: Total number of events	28.91	27.77	29.72	31.25	27.95	26.47
Hypoglycaemic events (non-severe)	28.20	27.10	29.25	30.76	27.42	25.74
Hypoglycaemic events (severe)	0.178	0.176	0.175	0.178	0.160	0.184
UTIs	0.448	0.348	0.179	0.189	0.361	0.365
GTIs	0.084	0.141	0.112	0.117	0.005	0.179
Total deaths	1.000	1.000	1.000	1.000	1.000	1.000
Diabetes-related deaths	0.270	0.270	0.273	0.272	0.272	0.275
Other deaths	0.730	0.730	0.727	0.728	0.728	0.725

QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = Urinary tract infection; GTIs = Genital infection

Table 79: Breakdown of clinical events for analysis of triple therapy - metformin plus SU

	Triple therapy - Metformin plus Sulphonylureas				
	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Sitagliptin 100mg
QALY	6.991	6.978	6.980	6.976	6.959
Life Years	9.369	9.360	9.362	9.364	9.343
LTCs: Total number of events	0.722	0.728	0.721	0.725	0.732
IHDs	0.093	0.094	0.094	0.094	0.096
MIs	0.211	0.212	0.211	0.211	0.216
CHFs	0.094	0.094	0.094	0.094	0.097
Strokes	0.179	0.183	0.178	0.183	0.180
Amputations	0.080	0.080	0.078	0.078	0.080
Blindness in one eye	0.046	0.047	0.046	0.045	0.046
Renal failures	0.019	0.019	0.019	0.019	0.019
Years free of complication	6.978	6.957	6.982	6.983	6.926

AEs: Total number of events	23.030	25.748	28.719	31.738	27.233
Hypoglycaemic events (non-severe)	22.532	25.217	28.2823	31.294	26.941
Hypoglycaemic events (severe)	0.163	0.167	0.155	0.152	0.147
UTIs	0.272	0.248	0.169	0.172	0.132
GTIs	0.063	0.117	0.112	0.120	0.013
Total deaths	1.000	1.000	1.000	1.000	1.000
Diabetes-related deaths	0.268	0.269	0.269	0.267	0.271
Other deaths	0.732	0.731	0.731	0.733	0.729

QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

Table 80: Breakdown of clinical events for analysis of triple therapy - metformin plus TZD

	Triple therapy - Metformin plus TZDs				
	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Sitagliptin 100mg
QALY	6.995	6.999	6.983	6.978	6.967
Life Years	9.368	9.376	9.363	9.359	9.352
LTCs: Total number of events	0.725	0.721	0.727	0.726	0.728
IHDs	0.095	0.094	0.095	0.095	0.095
MIs	0.213	0.211	0.211	0.210	0.214
CHFs	0.094	0.094	0.094	0.093	0.097
Strokes	0.178	0.179	0.183	0.186	0.178
Amputations	0.080	0.079	0.079	0.078	0.079
Blindness in one eye	0.047	0.046	0.046	0.046	0.045
Renal failures	0.019	0.019	0.019	0.019	0.019
Years free of complication	6.966	6.981	6.975	6.978	6.958
AEs: Total number of events	19.826	22.685	26.685	28.788	25.520
Hypoglycaemic events (non-severe)	19.346	22.242	26.269	28.370	25.231
Hypoglycaemic events (severe)	0.139	0.122	0.110	0.094	0.133
UTIs	0.206	0.189	0.186	0.199	0.143
GTIs	0.136	0.131	0.121	0.125	0.013
Total deaths	1.000	1.000	1.000	1.000	1.000
Diabetes-related deaths	0.269	0.267	0.268	0.269	0.270
Other deaths	0.731	0.733	0.732	0.731	0.730

QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

Table 81: Breakdown of clinical events for analysis of insulin combinations

	Insulin combinations					
	Empagliflozin 10mg	Empagliflozin 25mg	Canagliflozin 100mg	Canagliflozin 300mg	Sitagliptin 100mg	Dapagliflozin 10mg
QALY	6.947	6.948	6.944	6.957	6.912	6.953
Life Years	9.325	9.329	9.325	9.344	9.301	9.335
LTCs: Total number of events	0.749	0.748	0.749	0.743	0.759	0.748
IHDs	0.098	0.098	0.098	0.098	0.099	0.098
MIs	0.219	0.218	0.218	0.217	0.222	0.218
CHFs	0.095	0.095	0.094	0.094	0.098	0.094
Strokes	0.189	0.189	0.191	0.189	0.192	0.190
Amputations	0.081	0.081	0.080	0.080	0.082	0.081
Blindness in one eye	0.049	0.049	0.049	0.048	0.048	0.049
Renal failures	0.019	0.019	0.019	0.019	0.019	0.019
Years free of complication	6.876	6.881	6.890	6.919	6.836	6.892
AEs: Total number of events	28.914	30.278	31.583	33.419	32.101	29.924
Hypoglycaemic events (non-severe)	28.189	29.491	30.950	32.784	31.519	29.296
Hypoglycaemic events (severe)	0.231	0.231	0.232	0.231	0.229	0.231
UTIs	0.430	0.406	0.315	0.300	0.333	0.294
GTIs	0.064	0.150	0.086	0.103	0.020	0.104
Total deaths	1.000	1.000	1.000	1.000	1.000	1.000
Diabetes-related deaths	0.278	0.278	0.278	0.275	0.282	0.277
Other deaths	0.722	0.722	0.722	0.725	0.718	0.723

QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 82 to Table 85 presents the disaggregated QALYs and costs between empagliflozin and the various comparators.

Table 82: Disaggregated QALYs and costs – metformin background

		Empagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 100 mg	Canagliflozin 300 mg	Dapagliflozin 10 mg	Sitagliptin 100 mg
Deaths	**Diabetes-related deaths**	0.27	0.27	0.27	0.27	0.28	0.27
	Other deaths	0.73	0.73	0.73	0.73	0.73	0.73
Life Years	**Total LYs**	9.95	9.96	9.94	9.94	9.92	9.94
QALYs	**Lost due to LTCs**						
	IHD	-0.07	-0.06	-0.06	-0.06	-0.06	-0.07
	MI	-0.05	-0.05	-0.05	-0.05	-0.05	-0.05
	CHF	-0.03	-0.03	-0.03	-0.03	-0.03	-0.03
	Strokes	-0.13	-0.13	-0.13	-0.13	-0.13	-0.12
	Amputation	-0.10	-0.10	-0.10	-0.09	-0.10	-0.10
	Blindness in one eye	-0.02	-0.02	-0.02	-0.02	-0.02	-0.02
	Renal failure	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01
	Subtotal	-0.40	-0.40	-0.40	-0.39	-0.40	-0.39
	Lost due to AEs						
	Hypoglycaemic events (non-severe)	-0.08	-0.07	-0.08	-0.08	-0.07	-0.07
	Hypoglycaemic events (severe)	0.00	0.00	0.00	0.00	0.00	0.00
	UTIs	0.00	0.00	0.00	0.00	0.00	0.00
	GenIs	0.00	0.00	0.00	0.00	0.00	0.00
	Weight gain	-0.01	-0.01	-0.01	-0.01	-0.02	-0.01
	Subtotal	-0.09	-0.09	-0.09	-0.10	-0.08	-0.09
	Lost QALYs due to deaths						
	Diabetes-related deaths	0.00	0.00	0.00	0.00	0.00	0.00
	Other deaths	0.00	0.00	0.00	0.00	0.00	0.00
	Subtotal	0.00	0.00	0.00	0.00	0.00	0.00
	Total QALYs	7.42	7.43	7.41	7.42	7.40	7.42
Costs							
	Diabetes w/o complications	£4,725.00	£4,728.00	£4,718.00	£4,720.00	£4,709.00	£4,720.00
	LTCs						
	IHD	£4,177.00	£4,145.00	£4,160.00	£4,136.00	£4,159.00	£4,173.00
	MI	£4,691.00	£4,669.00	£4,670.00	£4,619.00	£4,685.00	£4,722.00
	CHF	£1,877.00	£1,846.00	£1,874.00	£1,829.00	£1,867.00	£1,874.00
	Strokes	£3,934.00	£3,948.00	£3,938.00	£3,913.00	£3,942.00	£3,739.00
	Amputation	£2,289.00	£2,254.00	£2,226.00	£2,165.00	£2,262.00	£2,226.00
	Blindness in one eye	£1,462.00	£1,458.00	£1,471.00	£1,462.00	£1,471.00	£1,438.00

Renal failure	£2,248.00	£2,204.00	£2,277.00	£2,239.00	£2,267.00	£2,205.00
Subtotal	£20,677.00	£20,524.00	£20,616.00	£20,363.00	£20,652.00	£20,376.00
AEs						
Hypoglycaemic events (non-severe)	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Hypoglycaemic events (severe)	£11.00	£11.00	£11.00	£11.00	£12.00	£10.00
UTIs	£15.00	£12.00	£6.00	£6.00	£13.00	£12.00
GenIs	£3.00	£5.00	£4.00	£4.00	£6.00	£0.00
Subtotal	£29.00	£27.00	£21.00	£21.00	£30.00	£23.00
Treatment costs						
First treatment	£1,592.00	£1,605.00	£1,510.00	£1,909.00	£1,329.00	£1,712.00
Subsequent treatments	£5,203.00	£5,044.00	£5,010.00	£5,296.00	£5,021.00	£4,789.00
Subtotal	£6,796.00	£6,649.00	£6,520.00	£7,205.00	£6,350.00	£6,501.00
Deaths	£427.00	£424.00	£426.00	£428.00	£437.00	£426.00
Total NHS and PSS costs	£32,654.00	£32,353.00	£32,300.00	£32,737.00	£32,179.00	£32,046.00

LTC = long term conditions; QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

For the metformin background analysis the LTCs are the biggest contributor to the total QALYs and costs. There does not appear to be many significant differences between the options. The main differences are associated with strokes (sitagliptin100mg has the fewest) and non-severe hypoglycaemic events – sitagliptin 100mg is associated the fewest, while canagliflozin is associated with the most hypoglycaemic events. In terms of costs there are no significant differences. Canagliflozin 300mg is associated with higher costs for the first treatment since it is the most expensive treatment considered. Empagliflozin 10mg is the second most expensive treatment due the cost of subsequent treatment combinations mainly due to the HbA1c control being slightly lower which resulted in earlier switches to subsequent treatment lines.

Table 83: Disaggregated QALYs and costs – metformin and SU

		Empagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 100 mg	Canagliflozin 300 mg	Sitagliptin 100 mg
Deaths	**Diabetes-related deaths**	0.268	0.269	0.269	0.267	0.271
	Other deaths	0.732	0.731	0.732	0.733	0.729
Life Years	**Total LYs**	9.370	9.360	9.360	9.360	9.34

QALYs	**Lost due to LTCs**					
	IHD	-0.065	-0.065	-0.065	-0.065	-0.0656
	MI	-0.045	-0.045	-0.044	-0.044	-0.0452
	CHF	-0.042	-0.042	-0.042	-0.041	-0.0434
	Strokes	-0.118	-0.122	-0.117	-0.122	-0.1185
	Amputation	-0.091	-0.091	-0.089	-0.087	-0.0907
	Blindness in one eye	-0.023	-0.024	-0.023	-0.023	-0.023
	Renal failure	-0.006	-0.006	-0.006	-0.006	-0.0062
	Subtotal	-0.389	-0.394	-0.386	-0.389	-0.3925
	Lost due to AEs					
	Hypoglycaemic events (non-severe)	-0.059	-0.066	-0.074	-0.082	-0.0704
	Hypoglycaemic events (severe)	-0.001	-0.001	-0.001	-0.001	-0.0013
	UTIs	-0.001	-0.001	0.000	0.000	-0.0003
	GenIs	0.000	0.000	0.000	0.000	0
	Weight gain	-0.013	-0.014	-0.013	-0.013	-0.0233
	Subtotal	-0.075	-0.082	-0.089	-0.097	-0.0953
	Lost QALYs due to deaths					
	Diabetes-related deaths	0.000	0.000	0.000	0.000	0
	Other deaths	0.000	0.000	0.000	0.000	0
	Subtotal	0.000	0.000	0.000	0.000	0
	Total QALYs	6.990	6.980	6.980	6.980	6.96
Costs						
	Diabetes w/o complications	£4,441	£4,437	£4,438	£4,439	£4,428
	LTCs					
	IHD	£4,161	£4,174	£4,184	£4,180	£4,215
	MI	£4,344	£4,352	£4,324	£4,268	£4,418
	CHF	£2,371	£2,374	£2,349	£2,336	£2,455
	Strokes	£3,665	£3,784	£3,623	£3,794	£3,692
	Amputation	£2,124	£2,139	£2,091	£2,043	£2,124
	Blindness in one eye	£1,455	£1,473	£1,443	£1,439	£1,433
	Renal failure	£1,958	£1,971	£1,962	£1,996	£1,978
	Subtotal	£20,078	£20,268	£19,976	£20,057	£20,314
	AEs					
	Hypoglycaemic events (non-severe)	£0	£0	£0	£0	£0

Hypoglycaemic events (severe)	£10	£10	£10	£9	£9
UTIs	£9	£8	£6	£6	£4
GenIs	£2	£4	£4	£4	£0
Subtotal	£21	£22	£19	£19	£14
Treatment costs					
First treatment	£1,696	£1,611	£1,757	£2,321	£1,801
Subsequent treatments	£4,735	£4,778	£4,592	£4,824	£4,369
Subtotal	£6,430	£6,390	£6,349	£7,145	£6,170
Deaths	£438	£440	£434	£428	£438
Total NHS and PSS costs	£31,408	£31,557	£31,217	£32,087	£31,365

LTC = long term conditions; QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

The main difference in QALYs was very marginal for all individual comparisons where the differences were at most by 0.004 QALYs. For costs the differences again varied less than £200 except for canagliflozin 300mg which again was associated with the highest cost due to the higher acquisition costs.

Table 84: Disaggregated QALYs and costs – metformin and TZD

		Empagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 100 mg	Canagliflozin 300 mg	Sitagliptin 100 mg
Deaths	**Diabetes-related deaths**	0.269	0.267	0.268	0.269	0.270
	Other deaths	0.731	0.733	0.732	0.731	0.730
Life Years	**Total LYs**	9.370	9.380	9.36	9.360	9.350
QALYs	**Lost due to LTCs**					
	IHD	-0.066	-0.065	-0.0651	-0.065	-0.065
	MI	-0.045	-0.045	-0.0442	-0.044	-0.045
	CHF	-0.042	-0.041	-0.0414	-0.041	-0.043
	Strokes	-0.117	-0.120	-0.1221	-0.124	-0.117
	Amputation	-0.090	-0.089	-0.0872	-0.086	-0.089
	Blindness in one eye	-0.024	-0.023	-0.0234	-0.023	-0.023
	Renal failure	-0.006	-0.006	-0.0062	-0.006	-0.006
	Subtotal	-0.389	-0.389	-0.3896	-0.390	-0.388
	Lost due to AEs					
	Hypoglycaemic events (non-severe)	-0.050	-0.057	-0.068	-0.074	-0.064

Hypoglycaemic events (severe)	-0.001	-0.001	-0.0009	-0.001	-0.001
UTIs	0.000	0.000	-0.0004	-0.001	0.000
GenIs	0.000	0.000	-0.0003	0.000	0.000
Weight gain	-0.012	-0.011	-0.0097	-0.008	-0.033
Subtotal	-0.064	-0.069	-0.0795	-0.084	-0.098
Lost QALYs due to deaths					
Diabetes-related deaths	-	-	0	-	-
Other deaths	-	-	0	-	-
Subtotal	-	-	0	-	-
Total QALYs	7.000	7.000	6.98	6.980	6.970
Costs					
Diabetes w/o complications	£4,441	£4,445	£4,438	£4,436	£4,433
LTCs					
IHD	£4,230	£4,197	£4,185	£4,183	£4,192
MI	£4,388	£4,354	£4,318	£4,264	£4,375
CHF	£2,349	£2,328	£2,340	£2,320	£2,425
Strokes	£3,630	£3,716	£3,793	£3,849	£3,626
Amputation	£2,117	£2,077	£2,049	£2,023	£2,086
Blindness in one eye	£1,463	£1,452	£1,459	£1,450	£1,437
Renal failure	£1,974	£1,961	£1,991	£1,981	£1,955
Subtotal	£20,152	£20,085	£20,133	£20,070	£20,096
AEs					
Hypoglycaemic events (non-severe)	£-	£-	£0	£-	£-
Hypoglycaemic events (severe)	£9	£8	£7	£6	£8
UTIs	£7	£6	£6	£7	£5
GenIs	£5	£4	£4	£4	£-
Subtotal	£20	£18	£17	£17	£13
Treatment costs					
First treatment	£1,819	£1,775	£1,693	£2,074	£1,870
Subsequent treatments	£5,003	£4,731	£4,615	£4,833	£4,457
Subtotal	£6,822	£6,506	£6,308	£6,907	£6,327
Deaths	£434	£432	£432	£436	£433
Total NHS and PSS costs	£31,869	£31,486	£31,329	£31,866	£31,302

LTC = long term conditions; QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

The biggest difference in QALYs was between sitagliptin and the SGLT2is in terms of weight gain. As can be seen in the evolution of weight over time this was caused by the significant differences in the weight profiles. In terms of the total costs the most expensive option was empagliflozin 10mg due to the cost of treatment (both initial and subsequent). This was caused by the longer duration of initial treatment on empagliflozin 10mg because of the lower discontinuation rates due to adverse events compared to other treatments as can be seen by the low QALYs associated with adverse events. Canagliflozin 300mg was associated with the highest initial cost due to its acquisition cost. All other differences were not significant.

Table 85: Disaggregated QALYs and costs – Insulin

		Empagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 100 mg	Canagliflozin 300 mg	Dapagliflozin 10 mg	Sitagliptin 100 mg
Deaths	**Diabetes-related deaths**	0.278	0.278	0.278	0.275	0.277	0.282
	Other deaths	0.722	0.722	0.722	0.725	0.723	0.718
Life Years	**Total LYs**	9.330	9.330	9.330	9.340	9.330	9.300
QALYs	**Lost due to LTCs**						
	IHD	-0.067	-0.067	-0.066	-0.066	-0.066	-0.067
	MI	-0.045	-0.045	-0.045	-0.045	-0.045	-0.045
	CHF	-0.043	-0.043	-0.042	-0.042	-0.042	-0.044
	Strokes	-0.126	-0.126	-0.126	-0.125	-0.126	-0.127
	Amputation	-0.093	-0.093	-0.092	-0.090	-0.093	-0.094
	Blindness in one eye	-0.024	-0.024	-0.024	-0.024	-0.024	-0.024
	Renal failure	-0.006	-0.006	-0.006	-0.006	-0.006	-0.006
	Subtotal	-0.404	-0.404	-0.401	-0.398	-0.403	-0.408
	Lost due to AEs						
	Hypoglycaemic events (non-severe)	-0.078	-0.082	-0.087	-0.093	-0.081	-0.089
	Hypoglycaemic events (severe)	-0.002	-0.002	-0.002	-0.002	-0.002	-0.002
	UTIs	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001
	GenIs	0.000	0.000	0.000	0.000	0.000	0.000
	Weight gain	0.000	0.000	0.000	0.000	0.000	-0.019
	Subtotal	-0.081	-0.085	-0.090	-0.096	-0.084	-0.110
	Lost QALYs due to deaths						

Diabetes-related deaths	0.000	0.000	0.000	0.000	0.000	0.000
Other deaths	0.000	0.000	0.000	0.000	0.000	0.000
Subtotal	0.000	0.000	0.000	0.000	0.000	0.000
Total QALYs	6.950	6.950	6.940	6.960	6.950	6.910
Costs						
Diabetes w/o complications	£4,420.00	£4,422.00	£4,420.00	£4,429.00	£4,425.00	£4,408.00
LTCs						
IHD	£4,280.00	£4,276.00	£4,261.00	£4,264.00	£4,268.00	£4,285.00
MI	£4,402.00	£4,396.00	£4,365.00	£4,355.00	£4,387.00	£4,405.00
CHF	£2,435.00	£2,426.00	£2,374.00	£2,346.00	£2,389.00	£2,515.00
Strokes	£3,909.00	£3,913.00	£3,910.00	£3,882.00	£3,925.00	£3,963.00
Amputation	£2,179.00	£2,189.00	£2,163.00	£2,122.00	£2,174.00	£2,208.00
Blindness in one eye	£1,504.00	£1,500.00	£1,487.00	£1,482.00	£1,491.00	£1,492.00
Renal failure	£1,981.00	£1,981.00	£1,993.00	£1,966.00	£1,975.00	£1,983.00
Subtotal	£20,688.00	£20,681.00	£20,552.00	£20,417.00	£20,610.00	£20,851.00
AEs						
Hypoglycaemic events (non-severe)	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Hypoglycaemic events (severe)	£16.00	£16.00	£16.00	£16.00	£16.00	£16.00
UTIs	£14.00	£14.00	£10.00	£10.00	£10.00	£11.00
GenIs	£2.00	£5.00	£3.00	£4.00	£4.00	£1.00
Subtotal	£32.00	£35.00	£29.00	£29.00	£29.00	£27.00
Treatment costs						
First treatment	£2,467.00	£2,636.00	£2,458.00	£3,121.00	£2,573.00	£2,538.00
Subsequent treatments	£2,507.00	£2,432.00	£2,511.00	£2,402.00	£2,463.00	£2,405.00
Subtotal	£4,974.00	£5,067.00	£4,969.00	£5,524.00	£5,035.00	£4,942.00
Deaths	£450.00	£448.00	£448.00	£442.00	£446.00	£453.00
Total NHS and PSS costs	£30,564.00	£30,653.00	£30,418.00	£30,842.00	£30,545.00	£30,682.00

LTC = long term conditions; QALY = quality adjusted life years; CHF = congestive heart failure; IHD = ischaemic heart disease; MI = myocardial infarction; UTIs = urinary tract infection; GTIs = genital infection

The biggest difference in QALYs was between sitagliptin and SGLT2i and was because of the differences in weight loss. The other main contributor to the differences was due to the number of non-severe hypoglycaemic events. However, the main differences were again very marginal

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

7.7.7 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The following sections present the results for each background therapy. The incremental analysis treatments are ranked from least expensive to most expensive and then remaining options were the compared to the next most cost effective option. Treatments were excluded if they were dominated (that is more expensive and less effective or if they were cost ineffective (i.e. if the treatment had an ICER of greater than £20,000 per QALY).

The results were first presented as low and high dose comparisons and then combined results are presented. This is to allow the comparison of similar treatment strategies, but also to give an overall picture of all the licensed doses.

In addition, net monetary benefits are presented at the £20,000 per QALY threshold along with 95% intervals to explore the variation in the estimates. Finally, cost effectiveness acceptability curves are presented to explore decision uncertainty.

Dual therapy – Metformin combinations

Table 86: Base-case results dual therapy – Low dose

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	133	Dominated by sitagliptin 100 mg
Met + Canagliflozin 100 mg	7.415	-0.01	£32,300	254	Dominated by sitagliptin 100 mg
Met + Empagliflozin 10 mg	7.424	-0.001	£32,654	608	Dominated by sitagliptin 100 mg

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year

Table 87: Base-case results dual therapy – High dose

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	133	Dominated by sitagliptin 100 mg
Met + Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
Met + Canagliflozin 300 mg	7.418	-0.015	£32,737	£384	Dominated by empagliflozin 25 mg

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year

Table 88: Base-case results dual therapy – combined results

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	£133	Dominated by sitagliptin 100 mg
Met + Canagliflozin 100 mg	7.415	-0.01	£32,300	£255	Dominated by sitagliptin 100 mg
Met + Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
Met + Empagliflozin 10 mg	7.424	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Met + Canagliflozin 300 mg	7.418	-0.015	£32,737	£384	Dominated by empagliflozin 25 mg

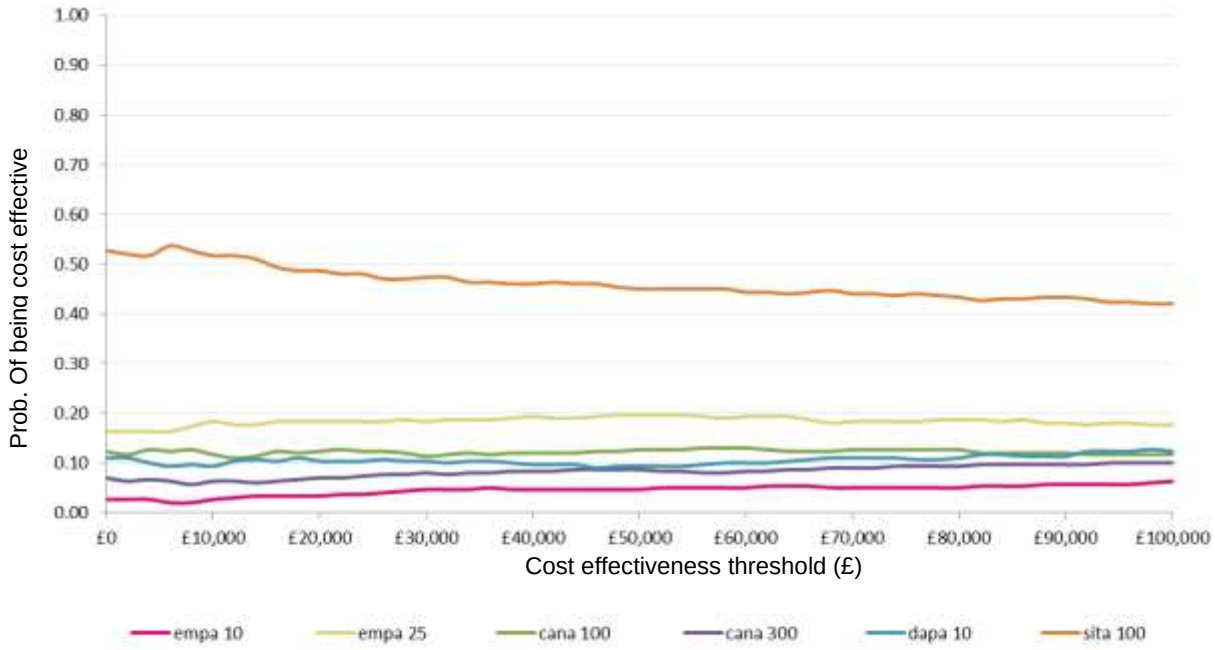
ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year

Table 89: Base-case results Net Monetary Benefit at £20,000 per QALY threshold for dual therapy

	NMB Mean	NMB LCI	NMB UCI
Met + Canagliflozin 300 mg	£115,834	£110,452	£226,287
Met + Empagliflozin 10 mg	£116,309	£110,933	£227,242
Met + Dapagliflozin 10 mg	£115,991	£110,614	£226,605
Met + Canagliflozin 100 mg	£115,631	£110,272	£225,903
Met + Empagliflozin 25 mg	£115,893	£110,506	£226,399
Met + Sitagliptin 100 mg	£116,446	£111,092	£227,538

LCI = lower confidence interval; Met = metformin; NMB = net monetary benefit; QALY = quality-adjusted life year; UCI = upper confidence interval

Figure 36: Cost effectiveness acceptability curve – dual therapy



The results indicate that sitagliptin 100mg is the most cost effective option, the only other option that was not dominated by sitagliptin was empagliflozin 25mg. The main cause of this difference was the significant difference in HbA1c change from baseline which for sitagliptin was 0.79 and for empagliflozin was approximately 0.7.

However, there does not appear to be any clinically significant differences between the options as the QALY differences are no more than 0.018 (between empagliflozin 25 mg and canagliflozin 100 mg). In addition, the cost differences are no more than £400. Both of these are over a 40 year horizon and therefore, are not significant.

The NMB results indicate the significant overlap in estimates demonstrating that no option is significantly more cost effective than the others. In addition, the cost effectiveness acceptability curve demonstrates that while sitagliptin has the highest probability of being cost effective it is around 50%. These results indicate that no option is expected to be clearly the most cost effective and in particular the differences between the SGLT2is are broadly equivalent.

Triple therapy – Metformin and sulphonylurea combinations

Table 90: Base-case results - Triple therapy Low dose – metformin plus SU

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met+SU+ Canagliflozin 100 mg	6.98	-	£31,217	-	-
Met+SU+ Sitagliptin 100 mg	6.959	-0.021	£31,365	£148	Dominated by canagliflozin 100 mg
Met+SU+ Empagliflozin 10 mg	6.991	0.011	£31,409	£192	£17,445

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; SU = sulphonylurea

Table 91: Base-case results – Triple therapy High dose - metformin plus SU

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met+SU+ Sitagliptin 100 mg	6.959		£31,365		
Met+SU+ Empagliflozin 25 mg	6.978	0.019	£31,557	£192	£10,105
Met+SU+ Canagliflozin 300 mg	6.976	-0.002	£32,087	£679	Dominated by empagliflozin 25mg

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; SU = sulphonylurea

Table 92: Base-case results triple therapy (met + SU combinations)

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met+SU+ Canagliflozin 100 mg	6.98	-	£31,217	-	-
Met+SU+ Sitagliptin 100 mg	6.959	-0.021	£31,365	£148	Dominated by canagliflozin 100 mg
Met+SU+ Empagliflozin 10 mg	6.991	0.011	£31,409	£192	£17,445
Met+SU+ Empagliflozin 25 mg	6.978	-0.013	£31,557	£148	Dominated by empagliflozin 10 mg
Met+SU+ Canagliflozin 300 mg	6.976	-0.015	£32,087	£679	Dominated by empagliflozin 10 mg

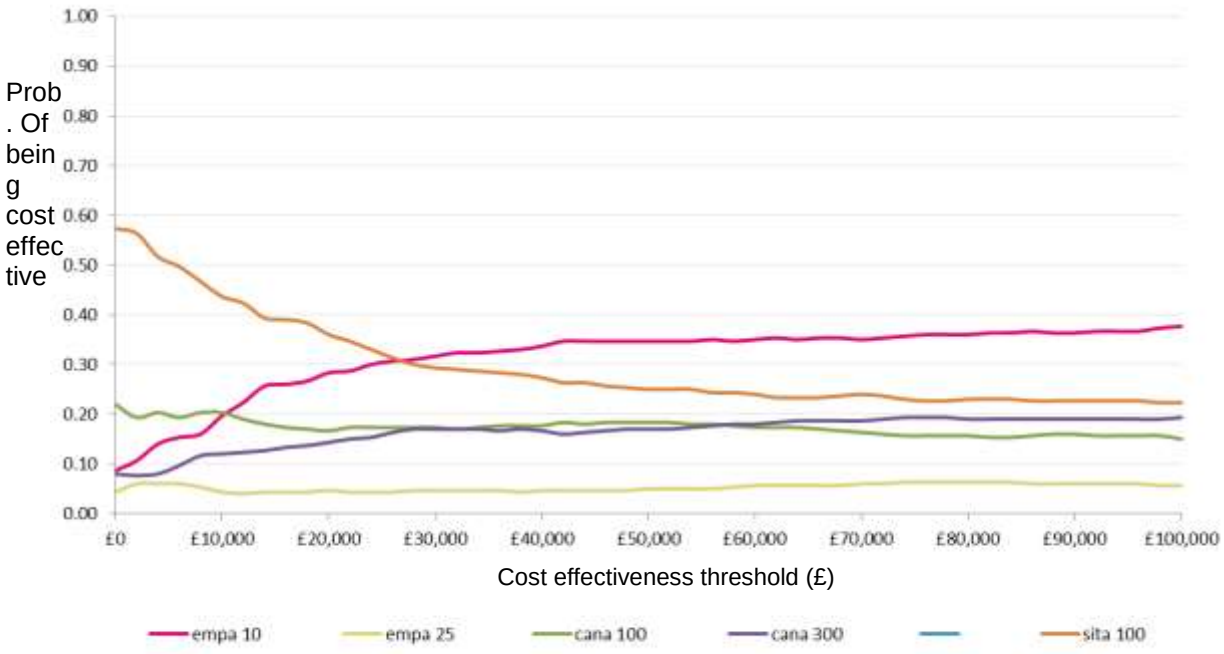
ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; SU = sulphonylurea

Table 93: Base-case results Net Monetary Benefit at £20,000 per QALY willingness to pay met + SU

	NMB Mean	NMB LCI	NMB UCI
Insulin + Empagliflozin 10 mg	£108,407	£103,540	£211,947
Insulin + Empagliflozin 25 mg	£108,005	£103,136	£211,141
Insulin + Canagliflozin 100 mg	£108,377	£103,520	£211,897
Insulin + Canagliflozin 300 mg	£107,433	£102,606	£210,039
Insulin + Sitagliptin 100 mg	£107,812	£102,937	£210,749

LCI = lower confidence interval; Met = metformin; NMB = net monetary benefit; QALY = quality-adjusted life year; SU = sulphonylurea; UCI = upper confidence interval

Figure 37: Cost Effectiveness Acceptability Curve - triple therapy (met + SU)



The results presented by dose indicate that empagliflozin is more cost effective than sitagliptin 100mg and that canagliflozin is dominated by empagliflozin. The combined results demonstrate that empagliflozin 10mg is the most effective and most cost effective treatment option being the only one that is not dominated.

This can be attributed to empagliflozin's 10mg being associated with lower hypoglycaemia rate and also its greater effectiveness in terms of SBP and HbA1c compared to the alternative treatments. Generally the remaining results are consistent with the estimates of clinical efficacy.

The variation around the NMB and CEAC both indicate that there is considerable decision uncertainty in which treatment is the optimum option. There is apparently significant overlap in the 95% intervals for the NMB and in addition the CEAC demonstrates that the probability of being cost effective for any one option is no greater than 30% between £20,000 and £30,000 per QALY. The two options with the highest probability of cost effectiveness are sitagliptin and empagliflozin 10mg, even though sitagliptin is dominated by canagliflozin 100mg reinforcing the marginal differences. These results imply that no option can be conclusively considered the most cost effective option.

Triple therapy – Metformin and TZD combinations

Table 94: Base case results: metformin and TZD for low doses

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-
Met + TZD + Canagliflozin 100 mg	6.983	0.016	£31,329	£26	£1,644
Met + TZD + Empagliflozin 10 mg	6.996	0.013	£31,869	£540	£41,538

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; TZD = thiazolidinedione

Table 95: Base case results: metformin and TZD for high doses

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-
Met + TZD + Empagliflozin 25 mg	6.999	0.032	£31,486	£183	£5719
Met + TZD + Canagliflozin 300 mg	6.978	-0.021	£31,866	£380	Dominated by empagliflozin 25 mg

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; TZD = thiazolidinedione

Table 96: Base case results: metformin and TZD for all doses

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-
Met + TZD + Canagliflozin 100 mg	6.983	0.016	£31,329	£26	£1,644
Met + TZD + Empagliflozin 25 mg	6.999	0.016	£31,486	£157	£9,806
Met + TZD + Canagliflozin 300 mg	6.978	-0.021	£31,866	£380	Dominated by empagliflozin 25 mg
Met + TZD + Empagliflozin 10 mg	6.996	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg

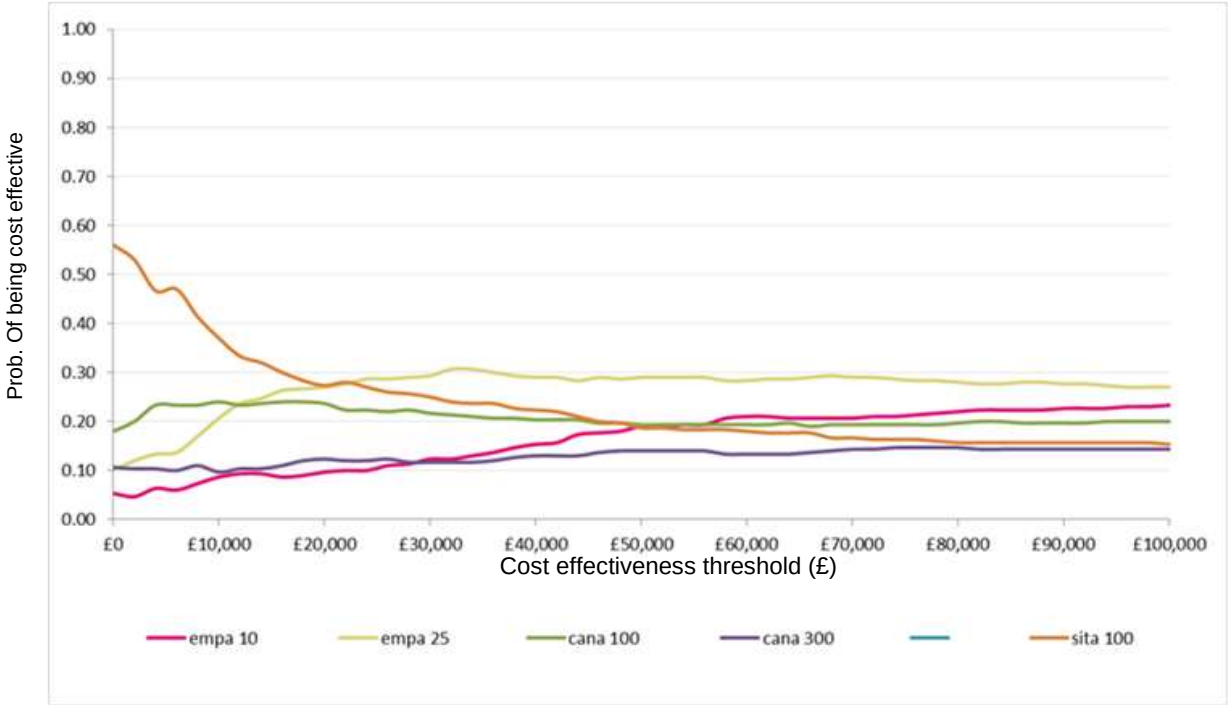
ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; TZD = thiazolidinedione

Table 97: Base-case results Net Monetary Benefit at £20,000 per QALY willingness to pay and 95% intervals for metformin and TZD combinations

	NMB Mean	NMB LCI	NMB UCI
Met + TZD + Empagliflozin 10 mg	£ 108,050	£ 103,208	£ 211,258
Met + TZD + Empagliflozin 25 mg	£ 108,493	£ 103,641	£ 212,135
Met + TZD + Canagliflozin 100 mg	£ 108,338	£ 103,465	£ 211,803
Met + TZD + Canagliflozin 300 mg	£ 107,700	£ 102,851	£ 210,551
Met + TZD + Sitagliptin 100 mg	£ 108,041	£ 103,168	£ 211,209

ICER = incremental costs-effectiveness ratio; Met = metformin; TZD = thiazolidinedione; NMB = net monetary benefit; LCL = lower confidence level; UCL = upper confidence level;

Figure 38: Cost effectiveness acceptability curve – triple therapy (met + TZD)



The results for metformin and TZD background split by dose suggest that canagliflozin 100mg is the most cost effective option in the low dose analysis, while empagliflozin 25mg is the most cost effective option in the high dose analysis. The combined analysis implies that empagliflozin is the most cost effective option.

These results are being driven by the superiority of the higher dose of empagliflozin compared to the other options and its relatively low hypoglycaemic events.

However, there is considerable uncertainty in the results as can be seen in the variation around the mean NMB at £20,000 threshold and also the CEAC

demonstrate that no option is associated with greater than 30% probability of being the most cost effective. This is consistent with the previous analyses where the SGLT2is are as good as each other with no clinically significant differences.

Insulin combinations

Table 98: Base case results for insulin combinations

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Insulin + Canagliflozin 100 mg	6.944	-	£30,418	-	-
Insulin + Dapagliflozin 10 mg	6.953	0.009	£30,545	£128	£14,178
Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg

ICER = incremental costs-effectiveness ratio; NHS = National Health Service QALY = quality-adjusted life year

Table 99: Base case results for insulin combinations – high dose

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Insulin + Dapagliflozin 10 mg	6.953	-	£30,545	-	-
Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Insulin + Canagliflozin 300 mg	6.957	0.004	£30,842	£296	£74,075

ICER = incremental costs-effectiveness ratio; NHS = National Health Service QALY = quality-adjusted life year

Table 100: Base case results for insulin combinations

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Insulin + Canagliflozin 100 mg	6.944	-	£30,418	-	-
Insulin + Dapagliflozin 10 mg	6.953	0.009	£30,545	£128	£14,178
Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Insulin + Canagliflozin 300 mg	6.957	0.004	£30,842	£296	£74,075

ICER = incremental costs-effectiveness ratio; NHS = National Health Service QALY = quality-adjusted life year

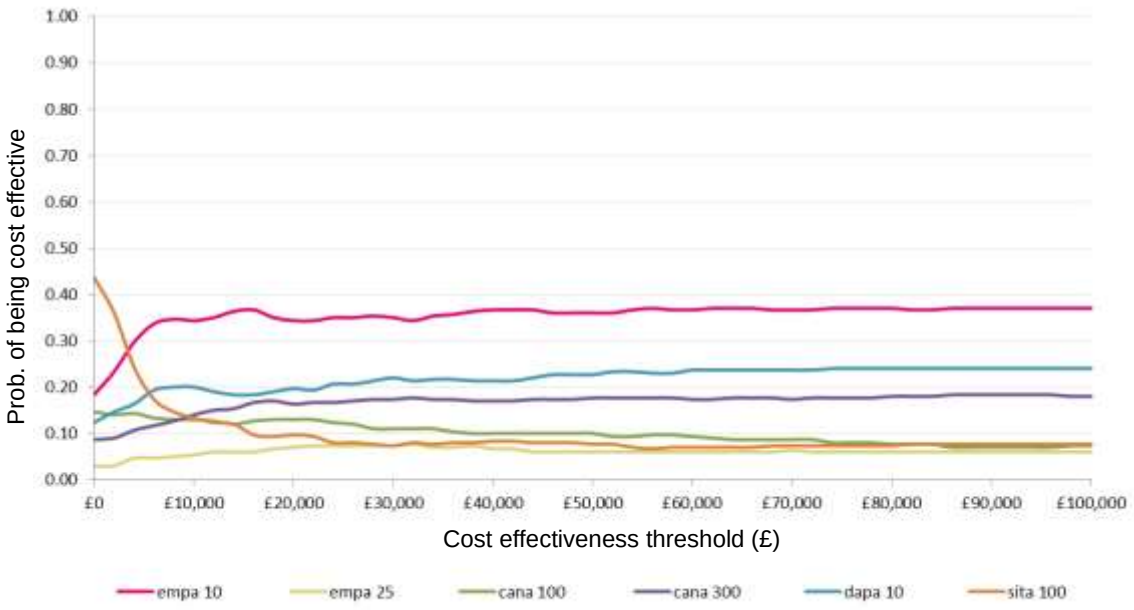
Table 101: Base-case results Net Monetary Benefit at £20,000 per QALY threshold for metformin and insulin combinations

	NMB Mean	NMB LCI	NMB UCI
Insulin + Empagliflozin 10 mg	£108,377	£103,407	£211,784
Insulin + Empagliflozin 25 mg	£108,298	£103,339	£211,637
Insulin + Canagliflozin 100 mg	£108,463	£103,506	£211,969

Insulin + Canagliflozin 300 mg	£108,301	£103,345	£211,646
Insulin + Dapagliflozin 10 mg	£108,523	£103,559	£212,083
Insulin + Sitagliptin 100 mg	£107,556	£102,589	£210,145

ICER = incremental costs-effectiveness ratio; NMB = net monetary benefit; LCL = lower confidence level; UCL = upper confidence level;

Figure 39: Cost effectiveness acceptability curve – insulin combinations



The base case results indicate that dapagliflozin is the only cost effective option in all scenarios. This is being driven by superior efficacy compared to empagliflozin, sitagliptin and canagliflozin 100mg. It is more cost effective than canagliflozin 300mg due to its lower price.

However, the CEAC demonstrates that while dapagliflozin is the most cost effective option it is not associated with the highest probability of being cost effective which is empagliflozin 10mg. The CEAC demonstrates that no treatment is associated with a greater than 50% probability of being the most cost effective.

One difference between this analysis and the previous three is that the absolute QALYs are significantly lower for this analysis. This is mainly due to the difference in the treatment pathway in that patients are switched to rescue insulin without having the option to have a treatment added on.

Sensitivity analyses

7.7.8 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results are presented in Section 9.11, Appendix 11 and are discussed in Section 7.7.10.

7.7.9 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

All CEACs are presented above. Scatter plots were considered inappropriate since they do not consider any correlation between variables when multiple comparisons are made.

7.7.10 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

52 week data analysis

Table 102 presents the results for 52 weeks data. However, there was not enough evidence from the 52 week networks for metformin and TZD therefore, results are presented for metformin, metformin and SU and Insulin

Table 102: Cost effectiveness results with 52 week data from network meta-analyses

	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Met + Sitagliptin 100mg	7.24		£28,143		
Met + Dapagliflozin 10mg	7.26	0.027	£28,354	£211	£7893
Met + Empagliflozin 10mg	7.27	0.001	£28,465	£111	£82,766
Met + Empagliflozin 25	7.27	0.007	£28,559	£205	£31,016
Met + Canagliflozin 100mg	7.26	-0.009	£28,575	£221	Dominated by dapagliflozin 10mg
Met + Canagliflozin 300mg	7.28	0.011	£29,322	£968	£88,784
Met + SU + Sitagliptin 100 mg	6.81	-	£26,581	-	-
Met + SU + Canagliflozin 100 mg	6.83	0.028	£26,622	£41	£1440
Met + SU + Empagliflozin 25 mg	6.79	-0.046	£26,853	£231	Dominated by canagliflozin 100mg
Met + SU + Empagliflozin 10 mg	6.82	-0.009	£26,872	£250	Dominated by canagliflozin 100mg
Met + SU + Canagliflozin 300 mg	6.81	-0.023	£27,681	£1060	Dominated by canagliflozin 100mg
Insulin + Sitagliptin 100 mg	6.78		£25,593		
Insulin + Dapagliflozin 10 mg	6.81	0.03	£25,750	£157	5214.397
Insulin + Canagliflozin 100 mg	6.79	-0.025	£25,752	£1.66	Dominated by dapagliflozin 10mg
Insulin + Empagliflozin 25 mg	6.80	-0.017	£25,904	£154	Dominated by dapagliflozin 10mg
Insulin + Empagliflozin 10 mg	6.76	-0.055	£25,960	£210	Dominated by dapagliflozin 10mg
Insulin + Canagliflozin 300 mg	6.79	-0.023	£26,134	£383	Dominated by dapagliflozin 10mg

ICER = incremental costs-effectiveness ratio; Met = metformin; NHS = National Health Service QALY = quality-adjusted life year; SU = sulphonylurea

These results are broadly similar to the results for 24 weeks. There are fewer results that are counter intuitive where the higher dose of interventions are less effective than lower doses, except for met + su combinations. The results reinforce the small differences in QALYS and costs and the lack of clinically significant differences. It also indicates that no differences develop over at least one year of treatment.

7.7.11 What were the main findings of each of the sensitivity analyses?

The sensitivity analyses are presented in Section 9.11, Appendix 11. For metformin, metformin plus SU and Metformin plus TZD there was no impact on any of the results. The absolute values changed, for example the removal of the impact of BMI reducing the QALYs. The one analysis that did impact on the results was for the insulin background therapy when the treatment duration was increased to two years and this resulted in empagliflozin becoming the baseline treatment. However, dapagliflozin was remained the most cost effective option.

7.7.12 What are the key drivers of the cost-effectiveness results?

The results of the sensitivity analysis and also the main results suggest that the results are robust to a number of sensitivity analysis and that the key drivers are the clinical effectiveness and adverse events rather than any of the assumptions.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Internal verification of the model was conducted throughout the model implementation process. Patient characteristics, values of risk factors and the occurrence of adverse events and complications were checked to ensure they were changing as expected, and that patients were following expected routes. The costs and utility value outputs per cycle were checked against the patient status outputs for face validity. The aggregated outputs were also cross checked against the sum of individual patient outputs. Additional validation conducted in the model consisted on undergoing extreme sensitivity analyses to ensure the consistency of the results. As part of these extreme analyses, the following scenarios were tested:

- Drug costs were first set to zero and then set to be equal for both compared interventions to confirm that no cost for these categories were accrued over time and no incremental drug cost were accrued over time, respectively.
- Costs for different resource categories were set to zero to confirm that no costs for these categories were accrued over time.
- Efficacy parameters for the interventions of interest were set to zero to demonstrate that accrued health benefits over time were equal for compared interventions and that those incremental benefits were zero.
- The baseline utility estimate was set to 1 and the utility decrements for long term complications were set to zero to demonstrate that LYs and QALYs were equal over time.
- The probabilities of experiencing AEs were set to zero to confirm that no AE occurred and no cost associated with AEs was incurred over time.
- The probabilities of treatment failure and treatment discontinuation were set to 1 to ensure that all patients experiencing treatment discontinuation would be moved to the next treatment in the sequence.
- Discount rates were set to null and non-null percent values for cost and effects to confirm that undiscounted costs were higher than discounted cost estimates.

All performed sensitivity analyses confirmed accurate programming of the model and the findings made logical and intuitive sense.

Moreover, based on previously published cost-effectiveness analysis, similar inputs were used to assess whether the obtained results were similar to those from other studies published in the target population of interest. For example, a validation exercise was conducted to replicate the analyses presented as part of one of the health economic evaluations conducted in the T2DM NICE clinical guidelines.

For this, the objective was to use the empagliflozin pharmacoeconomic model to replicate the comparison between exenatide versus NPH as third line treatments. The results of this exercise are presented in Table 15 below. As it can be observed, although qualitatively both models obtained similar results since in both

cases exenatide would result in higher number of QALYs when compared to NPH, although at a very high cost, resulting in NPH being the cost-effective strategy, there are some relevant differences in terms of total values obtained. It should be noted that these differences may be due to the impossibility of fully replicating the analyses and the type of assumptions formulated in the model presented as part of the clinical guidelines due to lack of complete information in some cases. For example, not all baseline characteristics required to populate the model were reported in the guidelines (e.g. proportion of population that was smoking at baseline). Utility adjustments for hypoglycaemias and nausea under the clinical guidelines cost-effectiveness assessment seemed to have been conducted differently than for the empagliflozin model and in some cases the required information to replicate the model was unclear.

Therefore, these adjustments were not implemented as part of the analysis using empagliflozin model, which may have been reflected in the higher number of QALYs and lower costs obtained through the empagliflozin cost-effectiveness model. Moreover, utility adjustments for weight loss were not considered in the empagliflozin model, only disutility associated to weight gain. A final point to mention is that the set of specifications used in empagliflozin model may not have been fully consistent with those used in the analysis presented in the NICE clinical guidelines (for example, in terms of the specification of adverse events –i.e. whether each adverse event was to be considered for all cycles while the patient was on a specific treatment, or only at the initiation of treatment-).

Table 103: Replication of analysis presented in T2DM clinical guidelines using the empagliflozin model

	Total QALYs	Total costs NHS (£)	Δ QALY	Δ cost	ICER
Results from T2DM NICE clinical guidelines:					
NPH	8.05	£19,527			
Exenatide	8.08	£29,001	0.034	£9,474	£280,495
Results obtained by replicating the analysis using the empagliflozin pharmacoeconomic model:					
NPH	8.45	£17,829			
Exenatide	8.55	£23,938	0.09	£6,109	£66,325

IMS CORE model validation

The results from using the IMS CORE model are presented in Table 104 to Table 106.

There are a number of differences in the absolute figures derived from the CORE model and those from the ECEM. In the CORE model the absolute QALYs are larger than those obtained from the ECEM. This is because the CORE model is run over a longer time horizon (80 years) and also due to its structure it had to utilise a higher baseline utility. This results in the accumulation of a greater number of QALYs over a lifetime. The overall costs in the CORE model are also significantly higher; this is likely because of the greater detail in calculating the costs for LTCs such as for ulcers, where a separate Markov model is used to model this condition. This would allow a greater number of costs to be included.

However, the incremental QALYs and costs are broadly similar to the outcomes from the ECEM. The differences in QALYs in the ECEM varied from 0.001 to 0.04 and in the CORE model the differences varied from 0 to 0.02. The cost differences were also similar.

Overall the conclusions of the ECEM and CORE model are that there is no significant differences between the SGLT2is in terms of QALYs or costs and therefore, implies the conclusion of the cost effectiveness analysis is robust.

Table 104: IMS CORE model results

	Costs (£)			QALYs			ICER (£)
	Empagliflozin	**Comparator**	**Difference**	**Empagliflozin**	**Comparator**	**Difference**	**Cost/QALY gained**
2nd line, patients who are no longer responding adequately to metformin (MET)							
Empagliflozin 10mg +MET vs. Dapagliflozin 10 mg +MET	£61,462	£61,405	£57	8.463	8.463	0.000	**small QALY difference**
Empagliflozin 25mg +MET vs. Dapagliflozin 10 mg +MET	£61,192	£61,464	-£272	8.474	8.467	0.006	**Dominant**
3rd line, patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)							
Empagliflozin 10mg +MET+SU vs. Canagliflozin 100 mg +MET+SU	£61,752	£61,631	£121	8.461	8.459	0.002	**£63,974**
Empagliflozin 25mg +MET+SU vs. Canagliflozin 300 mg +MET+SU	£61,834	£61,599	£235	8.465	8.489	-0.024	**Dominated**
Patients who are no longer responding adequately to backbone insulin therapy (INS) plus other oral anti-diabetic drugs (OAD)							
Empagliflozin 10mg + MET + insulin vs. Dapagliflozin 10mg + MET + insulin	£62,284	£62,033	£251	8.462	8.481	-0.019	**Dominated**
Empagliflozin 25mg + MET + insulin vs. Dapagliflozin 10mg + MET + insulin	£62,116	£61,906	£209	8.477	8.485	-0.008	**Dominated**

Table 105: Breakdown of events in IMS CORE model

	Metformin dual therapy		Metformin and SU triple therapy		Insulin combination	
Change in baseline	Empagliflozin 10 mg	Dapagliflozin 10 mg	Empagliflozin 10 mg	Canagliflozin 100mg	Empagliflozin 10 mg	Dapagliflozin 10 mg
HbA1c	-0.70	-0.66	-0.76	-0.80	-0.83	-1.00
BMI	-0.71	-0.87	-0.78	-0.54	-0.72	-0.90
SBP	-0.71	-0.87	-0.78	-0.54	-0.72	-0.90
Hypos (non-severe)	3.99	1.32	33.85	45.70	109.05	104.68
UTIs	9.47	8.24	22.25	28.29	17.09	48.83
GTIs	0.08	0.25	0.06	0.13	0.12	0.17
	Empagliflozin 25 mg	Dapagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 300mg	Empagliflozin 25 mg	Dapagliflozin 10 mg
HbA1c	-0.77	-0.70	-0.74	-1.02	-0.97	-1.04
BMI	-0.84	-0.79	-0.80	-0.88	-0.74	-0.90
SBP	-5.20	-4.52	-2.90	-3.19	-3.77	-4.22
Hypos (non-severe)	3.04	1.46	27.96	60.11	110.01	104.51
UTIs	8.99	8.18	17.97	18.43	14.28	14.64
GTIs	0.10	0.25	0.05	0.13	0.25	0.17

Table 106: Breakdown of costs in IMS CORE model

	Metformin dual therapy		Metformin and SU triple therapy		Insulin combination	
	Empagliflozin 10 mg	Dapagliflozin 10 mg	Empagliflozin 10 mg	Canagliflozin 100mg	Empagliflozin 10 mg	Dapagliflozin 10 mg
Total Costs	£61,462	£61,405	£61,752	£61,631	£62,284	£62,033
Treatment	£6137	£6138	£6423	£6424	£7241	£7250
Management	£1080	£1080	£1081	£1081	£1081	£1083
CVD	£19,377	£19,285	£19,436	£19,407	£19,343	£19,287
Renal	£8119	£8124	£8091	£8062	£7981	£7868
Ulcer/Amputation/Neuropathy	£15,504	£15,537	£15,486	£15,465	£15,431	£15,373
Eye	£11,227	£11,208	£11,208	£11,152	£11,176	£11,103
Hypoglycaemia	£0	£0	£0	£0	£2	£4
GTI	£8	£25	£6	£13	£12	£17

	Empagliflozin 25 mg	Dapagliflozin 10 mg	Empagliflozin 25 mg	Canagliflozin 300mg	Empagliflozin 25 mg	Dapagliflozin 10 mg
Total Costs	£61,192	£61,464	£61,834	£61,599	£62,116	£61,906
Treatment	£6141	£6140	£6426	£6803	£7248	£7252
Management	£1081	£1081	£1081	£1084	£1083	£1083
CVD	£19,302	£19,371	£19,442	£19321	£19,361	£19,317
Renal	£8049	£8125	£8138	£7862	£7891	£7807
Ulcer/Amputation/Neuropathy	£15,465	£15,523	£15,502	£15381	£15,391	£15,379
Eye	£11,135	£11,191	£11,221	£11117	£11,097	£11,034
Hypoglycaemia	£0	£0	£0	£0	£6	£4
GTI	£10	£25	£5	£13	£25	£17

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis was conducted

7.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

N/A

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

N/A

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The overall findings of this analysis are that there are very few clinically significant differences between the treatments under consideration. The overall differences in QALYS and costs were marginal in all analyses and that no treatment was clearly the optimum choice. These results are consistent with the NMA in that there were no statistical significant differences between the treatments. Therefore, the optimum choice will be the one that best fits into the patients' requirements in terms of lifestyle and their acceptance and tolerability of adverse events and other factors.

These results are consistent with the findings of TA288 and also canagliflozin appraisal (ongoing). Therefore, on current evidence it appears that the SGLT2is are broadly equivalent in terms of clinical effectiveness and are of equivalent cost effectiveness.

Therefore, these results support empagliflozin being recommended in the same position as DPP-4is and SGLT2is as currently recommended in TA288 for dapagliflozin and the currently ongoing recommendations for canagliflozin.

7.10.2 Therefore, these results support empagliflozin being recommended in the same position as DPP-4is as currently recommended in TA288 and the current recommendations for canagliflozin*Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?*

The economic evaluation considers the cost effectiveness of empagliflozin in combination with metformin, metformin and sulphonylurea, metformin and TZD and in combination with insulin. This covers all the patients who could potentially receive empagliflozin other than those on dual therapy with sulphonylureas which is not expected to be commonly used.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of this evaluation is its consistency with previous assessments of SGLT2is and other oral antidiabetic agents, by using consistent inputs and also where possible consistent methods. The validation with the IMS CORE model allows comparison with previous assessments and also ensures that the De Novo model is validated against another commonly used diabetes cost effectiveness model. This ensures that the results are comparable to those obtained in previous appraisals and guidelines

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

It would be useful to conduct further analyses that could incorporate the 104 week data that the majority of the SGLT2is will eventually have along with information from long-term cardiovascular outcome studies. Unfortunately it is not clear when this data will be available for all options and whether all the relevant outcomes will

be collected. Potentially this data could be analysed with a model based meta-analysis which would allow for a more informative extrapolation. This could also have been combined with a regression on baseline characteristics in the trials which could reduce heterogeneity between studies. This would further improve the extrapolation of the surrogate outcomes. The results could be enhanced if more simulations could be run, but as they are currently limited by the computational capabilities of Excel this was not possible. Using more samples per run, but also using different random number seeds to completely address all the uncertainty. The analysis could also be strengthen by the inclusion of the UKPDS 82 equations which would allow the incorporation of eGFR status impact on long term complications which obviously impacts on the use of empagliflozin. However, there was a shortage of available data on the variables used in the analyses which limits the utility of these equations.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

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

Currently according to Cegedem market data there are 1.6 million patients on active treatment for diabetes. The current treatments these patients receive are presented in Table 107 potentially empagliflozin can be used in combination with any antidiabetic treatment and therefore, all patients are eligible. However, it is likely that empagliflozin will be used patients identified as suitable for dapagliflozin or canagliflozin

Table 107: Current use of combination treatments in England and Wales

Treatment	2013	2014
Dual	558,796	591,809
Met + SU	276,869	275,543
Met + TZD	35,281	26,063
Met + DPP-4is	75,942	89,985
Met+ SGLT2i	746	994
Met + GLP-1RA	15,958	18,609
Other dual	51,665	54,255
Triple	221,197	240,480
Met + SU + TZD	41,855	32,999
Met + SU + DPP-4is	88,613	107,081
Met + SU + GLP-1RA	19,220	22,264
Met + SU + SGLT2i	410	547
Other Triple	44,007	49,473
Insulin combinations	211,255	221,449

Insulin + TZD	4237	3257
Insulin + DPP-4is	11598	14872
Insulin + SGLT2i	389	519
Insulin + GLP-1	10895	12803

We expect that the number of patients on SGLT2is will increase over the next five years at a rate of approximately 20% per year. It appears that the majority of patients will come from DPP-4is and GLP-1RAs.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Over the next five years it has been assumed that there will not be significant changes within the oral antidiabetic treatment market given the relatively slow uptake of new technologies within the NHS (38). Therefore, the most common treatment options for add on therapy to metformin over the next five years will be sulphonylurea, DPP-4is, GLP-1 RA and SGLT2is.

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that for empagliflozin as a third in class will mainly be competing with the other SGLT2is for market share; it is assumed that the only treatments replaced will be the other SGLT2is.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

It is expected that there will be no additional costs over other SGLT2is.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Costs were obtained from MIMs 2014. For classes such as DPP-4is a weighted cost was calculated which are presented in Table 108.

Table 108: Unit costs of SGLT2is

Treatment	Weight unit cost (£)	Annual cost (£)
Dapagliflozin	1.31	478
Canagliflozin	1.49	305
Empagliflozin	1.31	478

For canagliflozin given the difference in cost between the 100 mg and 300 mg doses it as assumed that there was a 50:50 split between the doses

8.6 Were there any estimates of resource savings? If so, what were they?

N/A

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 109: The budget impact for the NHS in England and Wales without empagliflozin

Treatment	2015	2016	2017	2018	2019
SGLT2i	73,612	109,310	146,686	174,318	197,806
Dapagliflozin (% share)	89%	79%	71%	65%	62%
Cost	£31,432,627	£41,567,186	£49,557,166	£54,250,938	£58,357,760
Canagliflozin (% share)	11%	17%	29%	35%	38%
Cost	£4,309,627	£12,210,413	£23,463,087	£33,162,737	£41,274,233
Empagliflozin (% share)	0%	0%	0%	0%	0%
Cost	£0	£0	£0	£0	£0
Total cost	£35,742,254	£53,777,599	£73,020,253	£87,413,675	£99,631,993

Table 110: The budget impact for the NHS in England and Wales with empagliflozin

Treatment	2015	2016	2017	2018	2019
SGLT2i	73,612	109,310	146,686	174,318	197,806
Dapagliflozin (% share)	82%	70%	60%	53%	49%
Cost	£29,055,696	£36,578,104	£41,951,931	£44,224,061	£46,074,573
Canagliflozin (% share)	4%	11%	19%	23%	25%
Cost	£1,606,095	£6,535,809	£14,812,858	£21,758,120	£27,303,280
Empagliflozin (% share)	13%	19%	22%	24%	26%
Cost	£4,753,862	£9,978,163	£15,210,470	£20,053,755	£24,566,374
Total cost	£35,415,653	£53,092,076	£71,975,259	£86,035,936	£97,944,226

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As presented in Section 7.4 patients are most concerned that diabetes treatments should have side effects that do not affect their day-to-day lives. For example patients are very concerned with weight gain, and hypoglycaemia. This might result in patient not complying with their treatment. This can result in significant drug wastage and therefore, empagliflozin could result in long term savings as patients stay on initial oral treatment.

9 Appendices

9.1 Appendix 1

9.1.1 *SPC/IFU, scientific discussion or drafts.*

9.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

9.2.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

A systematic search of the medical literature using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register was conducted.

9.2.2 *The date on which the search was conducted.*

The systematic literature review was conducted in December 2013.

9.2.3 *The date span of the search.*

The search of the medical literature was conducted from inception to December 7 2013.

9.2.4 *The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

The complete search algorithm for the MEDLINE and EMBASE search can be seen in Table 111.

Table 111: MEDLINE and EMBASE search strategy

Search		
1	Hypoglycemic drugs/	43672
2	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.	18535
3	Thiazolidinediones/	20045
4	(glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab.	25169
5	(122320-73-4 or 155141-29-0).rn.	17617
6	Dipeptidyl-Peptidase IV Inhibitors/	4826

Search		
7	(sitagliptin or Januvia or Janumet or gliptin or incretin agent*).ti,ab.	2494
8	486460-32-6.rn.	3031
9	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.	1486
10	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.	1047
11	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.	1407
12	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.	559
13	(dpp adj IV adj inhibitor*).ti,ab.	990
14	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.	749
15	DPP-4 inhibitors.ti,ab.	1483
16	dipeptidyl peptidase-4 inhibitors.ti,ab.	676
17	exp Sulfonylurea Compounds/	65823
18	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.	43809
19	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.	49732
20	exp insulin/	410653
21	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.	2552
22	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.	7550
23	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.	2934
24	(nph insulin or humulin or novolin).ti,ab.	2276
25	11061-68-0.rn.	3327
26	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.	2669
27	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.	4859
28	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.	4025
29	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.	1249
30	or/1-29	519459
31	exp Diabetes Mellitus, Type 2/	223869
32	Diabetes mellitus/	433582
33	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.	224078
34	(Mody or niddm or t2dm).ti,ab.	33683
35	or/31-34	680015
36	Metformin/	39433
37	Metformin.ti,ab.	23798
38	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.	246
39	(657-24-9 or 1115-70-4).rn.	36195
40	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.	212
41	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.	341
42	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.	475
43	or/36-42	44538
44	30 and 35 and 43	24134
45	Antidiabetic agent/	76876
46	Oral Antidiabetic agent/	12870
47	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.	18535

Search		
48	exp *glitazone derivative/	7532
49	(glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab.	25156
50	(122320-73-4 or 155141-29-0).rn.	17617
51	exp *Dipeptidyl Peptidase IV Inhibitor/	4254
52	(sitagliptin or Januvia or Janumet or gliptin or incretin agent*).ti,ab.	2494
53	486460-32-6.rn.	3031
54	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.	1486
55	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.	1047
56	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab.	886
57	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.	559
58	(dpp adj IV adj inhibitor*).ti,ab.	990
59	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.	749
60	DPP-4 inhibitors.ti,ab.	1483
61	dipeptidyl peptidase-4 inhibitors.ti,ab.	676
62	exp *sulfonylurea derivative/	18552
63	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.	43809
64	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.	49732
65	*biphasic insulin/ or *human insulin/ or *insulin/ or *insulin aspart/ or *insulin detemir/ or *insulin glargine/ or *insulin glulisine/ or *insulin lispro/ or *isophane insulin/ or *long acting insulin/ or *monocomponent insulin/ or *neutral insulin/ or *recombinant human insulin/ or *synthetic insulin/	196348
66	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.	2552
67	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.	7550
68	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.	2934
69	(nph insulin or humulin or novolin).ti,ab.	2276
70	11061-68-0.rn.	3327
71	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.	2669
72	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.	4859
73	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.	4025
74	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.	1249
75	or/45-74	346418
76	*Diabetes Mellitus/	232122
77	*Maturity Onset Diabetes Mellitus/	70185
78	*Non Insulin Dependent Diabetes Mellitus/	152205
79	*Lipoatrophic Diabetes Mellitus/	296
80	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.	224078
81	(Mody or niddm or t2dm).ti,ab.	33683
82	or/76-81	461651
83	Metformin/	39433
84	Metformin.ti,ab.	23798
85	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.	246
86	(657-24-9 or 1115-70-4).rn.	36195
87	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.	341
88	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.	212
89	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or	475

Search		
	Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or imethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.	
90	or/83-89	44538
91	75 and 82 and 90	19170
92	44 or 91	24795
93	limit 92 to english	21717
94	exp animals/	37343670
95	exp animal experimentation/	1744223
96	exp models animal/	1166747
97	exp animal experiment/	1744223
98	nonhuman/	4185230
99	exp vertebrate/	36373867
100	exp animals/	37343670
101	or/94-100	38557739
102	exp humans/	28905541
103	exp human experiment/	319239
104	exp humans/	28905541
105	or/102-104	28906982
106	101 not 105	9651736
107	93 not 106	20862
108	meta-analysis.pt.	52483
109	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	215994
110	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	135391
111	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	12204
112	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	25714
113	(data synthes* or data extraction* or data abstraction*).ti,ab.	30792
114	(handsearch* or hand search*).ti,ab.	13433
115	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	30567
116	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	7365
117	(meta regression* or metaregression* or mega regression*).ti,ab.	5772
118	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	308059
119	(medline or Cochrane or pubmed or medlars).ti.	6697
120	(cochrane or (health adj2 technology assessment) or evidence report).jw.	38564
121	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	308059
122	or/108-121	413205
123	Randomized Controlled Trial.pt.	391739
124	Randomized Controlled Trials as Topic/	146424
125	Randomized Controlled Trial/	756048
126	Randomization/	146068
127	Random Allocation/	146068
128	Double-Blind Method/	253826
129	Double Blind Procedure/	121614
130	Double-Blind Studies/	211513
131	Single-Blind Method/	38330
132	Single Blind Procedure/	18633
133	Single-Blind Studies/	38330
134	Placebos/	277080
135	Placebo/	243259
136	(random* or sham or placebo*).ti,ab,hw.	2277165
137	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	398665
138	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.	211
139	or/123-138	2324861

Search		
140	107 and 122	1340
141	140 not conference abstract.pt.	1226
142	107 and 139	7208
143	142 not conference abstract.pt.	6568
144	141 or 143	6969

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Searches of the bibliographies of published systematic literature reviews and HTAs were also carried out. In addition the websites of selected pharmaceuticals companies were searched as well as clinicaltrials.gov in order to identify any unpublished clinical trials that may be eligible for inclusion. All searches were performed independently and in duplicate.

9.2.6 The inclusion and exclusion criteria.

Table 112: PICOS criteria for study inclusion

Criteria	Eligibility
Population	• Adult patients T2DM experiencing inadequate (HbA_{1C} control) despite a diet and exercise program and a stable regimen of metformin plus sulphonylurea.
Interventions	• SGLT2is: • Empagliflozin 10 mg and 25 mg • DPP4is: • Sitagliptin 100 mg • Saxagliptin 5 mg • Linagliptin 5 mg • TZD: • Pioglitazone 30 mg • Rosiglitazone 6 mg • Bolus insulin: • Insulin aspart 40 U • Insulin lispro 40 U • Insulin glulisine 40 U • Human insulin 40 U • Basal insulin: • Insulin NPH 40 U • Insulin detemir 40 U • Insulin glargine 40 U • Biphasic insulin: • Premixed regular NPH 40 U • Biphasic insulin aspart 40 U • Biphasic insulin lispro 40 U • If multiple arms of same treatment were available, World Health Organization Defined Dose was used.1

Criteria	Eligibility
Comparison	• Usual care, placebo, or any of the interventions listed above
Outcomes	• Primary outcomes: • HbA1c change from baseline • SBP change from baseline • Body weight change from baseline • Secondary outcomes: • Hypoglycemias (severe and non severe, separate and as a composite) • UTIs (any) • Genital infections (any)
Study design	• RCTS

DPP-4is = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = Glucagon-like peptide-1 receptor agonists; HBA_{1C} = glycated haemoglobin; RCTS = randomised controlled trial study; SBP = systolic blood pressure; SGLT2s = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus; U = units; UTI = urinary tract infection

9.2.7 The data abstraction strategy

Two reviewers independently extracted and recorded data in a Microsoft Excel spreadsheet, which was then verified by a third reviewer. The extracted efficacy data included change from baseline in HbA_{1C}, body weight and systolic blood pressure. The extracted safety data included hypoglycaemic events, non-severe hypoglycaemic events, severe hypoglycaemic events, UTIs, genital infections.

Continuous outcomes were recorded using mean or median difference from baseline. In cases where measurements at baseline and time of measurement were provided, rather than change from baseline, the difference in means was used as a measure of change. In such cases, the standard error of change was estimated by combining the standard errors at both time points and assuming a correlation of 0.8 between baseline and follow-up measurements. In practice, the correlation for pre and post measurements tend to be closer to 0.9, so using 0.8 is a reasonable compromise to acknowledge a non-measurement. In cases where standard deviations were not provided, the average standard deviation among reported studies was used

For each trial, the following trial characteristics were extracted: treatment duration (weeks), location, number of patients randomised. For second line treatment, the following additional trial characteristics were extracted: metformin dose (mg/d),

metformin duration with stable dose, criteria for defining metformin failure. For third line treatment, the following additional trial characteristics were extracted: glycaemic target and criteria for defining combination therapy failure.

9.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 113: Quality assessment of the RCTs

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
1245.19 (EMPA-REG PIO)	Yes – patients were randomised using an interactive voice and web response system (IXRS)	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	Yes – premature discontinuations: placebo: 10.9%; empagliflozin 10 mg: 6.7%; empagliflozin 25 mg: 7.1%	No	Yes – the analysis was undertaken using data from the full analysis set (FAS), which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set (TS), which comprised all patients who received ≥1 dose of randomised study medication
1245.23 (EMPA-REG MET, EMPA-REG METSU)	Yes – patients were randomised using an IXRS	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	Yes - premature discontinuations: placebo: 10.7%; empagliflozin 10 mg: 7.6%; empagliflozin 25 mg: 7.9%	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
							patients who received ≥1 dose of randomised study medication
1245.28 (EMPA-REG H2H-SU)	Yes – patients were randomised using an IXRS	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	No	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication
1245.31 (EMPA-REG EXTEND	Patients continued with the treatment they had been randomised to in the preceding trial				No	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
1245.33 (EMPA-REG BASAL)	Yes – patients were randomised using an IXRS	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	Yes - premature discontinuations: placebo: 30.6%; empagliflozin 10 mg: 22.5%; empagliflozin 25 mg: 28.4%	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication
1245.36 (EMPA-REG RENAL)	Yes – patients were randomised using an IXRS	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	No	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication
1245.48	Yes – patients	Yes – treatment	Yes –	Yes – the patients,	No	No	Yes – the analysis was

Trial no. (acronym)	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
(EMPA-REG BP)	were randomised using an IXRS	allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	demographic data and baseline efficacy variable were balanced between randomised treatment groups	investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment			undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication
1245.49 (EMPA-REG MDI)	Yes – patients were randomised using an IXRS	Yes – treatment allocation was via the IXRS which randomly assigns patients to a corresponding medication kit. This procedure was chosen to ensure that all relevant parties were blinded to the treatment group assignment	Yes – demographic data and baseline efficacy variable were balanced between randomised treatment groups	Yes – the patients, investigator, and anyone involved in the analysis of trial data or with an interest in the study were unaware of the patient's allocated treatment	Yes - premature discontinuations: placebo: 16.5%; empagliflozin10 mg: 16.7%; empagliflozin 25 mg: 13.8%	No	Yes – the analysis was undertaken using data from the FAS, which comprised all patients who received ≥1 dose of study medication and had a baseline HbA_{1C} value. All safety endpoints were analysed using data based on the treated set TS, which comprised all patients who received ≥1 dose of randomised study medication

FAS = full analysis set; IXRS = interactive voice and web response system; TS = treated set

9.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

Details of the identification of the studies used to carry out the indirect treatment comparison can be seen in Section 9.2.

9.4.2 The date on which the search was conducted.

N/A

9.4.3 The date span of the search.

N/A

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

9.4.6 The inclusion and exclusion criteria.

N/A

9.4.7 The data abstraction strategy.

N/A

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Excluded studies

Table 114: List of studies excluded following full-text review

Study	Exclusion Rationale
Barnett et al 2007(132)	Does not assess interventions of interest
Bergenstal et al 2009(133)	Does not assess interventions of interest, Intraclass comparison
Berndt-Zipfel et al 2013(134)	Does not assess interventions of interest, Endonodal
Blevins et al 2011(135)	Does not assess interventions of interest
Blonde et al 2009(136)	Does not assess outcomes of interest, TDZ not stratified
Bolli et al 2009(137)	Does not assess interventions of interest, Endonodal
Brazg et al 2007(138)	Does not assess outcomes of interest
Bunck et al 2009(139)	Does not assess interventions of interest, Endonodal
Cefalu et al 2013(140)	Does not assess interventions of interest, Endonodal
De Mattia et al 2009(141)	Does not assess interventions of interest, Intraclass comparison
DeFronzo et al 2005(142)	Does not assess interventions of interest, Endonodal
Derosa et al 2013(143)	Does not assess interventions of interest, Endonodal
Diamant et al 2010(144)	Does not assess interventions of interest, Endonodal
Diamant et al 2012(145)	Does not assess interventions of interest, Endonodal
Esposito et al 2008(146)	Does not assess interventions of interest, Intraclass comparison
Fadini et al 2011(147)	Does not assess interventions of interest, Intraclass comparison
Ferrannini et al 2009(58)	Does not assess interventions of interest, Endonodal
Filozof et al 2010(59)	Does not assess interventions of interest, Endonodal
Gallwitz et al 2011(148)	Does not assess interventions of interest, Endonodal
Goodman et al 2009(60)	Does not assess interventions of interest
Heine et al 2005(149)	Does not assess interventions of interest, Endonodal
Henry et al 2013(150)	Does not assess interventions of interest
Kendall et al 2005(151)	Does not assess interventions of interest
Lu et al 2013(152)	Does not assess interventions of interest, Endonodal
Matthews et al 2005(153)	Additional publication of Charbonnel 2005, no additional outcomes
Poon et al 2005(154)	Does not assess interventions of interest
Pratley et al 2010(155)	Does not assess interventions of interest, Endonodal
Ristic et al 2007(156)	Does not assess interventions of interest, Endonodal
Rosenstock et al 2013a(157)	Does not assess interventions of interest
Rosenstock et al 2013b(158)	Does not assess interventions of interest, Endonodal
Schernthaner et al 2004(159)	Does not assess interventions of interest, Intraclass comparison
Schernthaner et al 2013(160)	Does not assess interventions of interest, Endonodal
Standl et al 2001(161)	Does not assess interventions of interest, Endonodal
Stehouwer et al 2003(162)	Does not assess interventions of interest, Intraclass comparison
Vinik et al 2007(163)	Additional publication of Rosenstock 2006, no additional

Study	Exclusion Rationale
	outcomes
Wang et al 2011(164)	Does not assess interventions of interest, Endonodal
White et al 2013(165)	Does not assess population of interest, Juvenile

TDZ = Thiazolidinedione

9.7 Appendix 7: Data extraction tables

Efficacy outcomes (24 weeks)

Second line

For second line:

1 = Metformin
2 = Metformin+SU
3 = Empa 10 mg
4 = Empa 25 mg
5 = Sitagliptin 100 mg
6 = Saxagliptin 5 mg
7 = Linagliptin 5 mg
8 = Vildagliptin 100 mg
9= Alogliptin 12.5 mg
10= Alogliptin 25 mg
11 = DAP 5 mg + MET
12 = DAP 10 mg + MET
13 = CAN 100 mg + MET
14 = CAN 300 mg + MET

Table 115: Second line efficacy outcomes – HbA_{1C}

Study	Treatment					HbA_{1C}											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
Charpentier et al. 2001 (56)	20	1	2							0.07	-0.74			0.14	0.08		
BI GMBH (1245-23) 2012 (9)	24	1	3	4		224	217	225		-0.13	-0.70	-0.77		0.05	0.05	0.05	
Charbonnel et al. 2006 (51)	24	1	5							-0.02	-0.67			0.06	0.05		
Defronzo et al. 2009 (47)	24	1	6			179	191			0.13	-0.69			0.07	0.07		
Raz et al. 2008 (53)	24	1	5							0.04	-1.08			0.10	0.09		
Taskinen et al. 2011 (46)	24	1	7			177	523			0.15	-0.49			0.06	0.04		

Study	Treatment					HbA1c										
	Time point					Population at risk (N)			Change from baseline (y)				Standard error (SE)			
Yang et al. 2011 (49)	24	1	6			287	283		-0.37	-0.78			0.06	0.06		
Yang et al. 2012 (55)	24	1	5			198	197		-0.14	-1.02			0.07	0.07		
BI GMBH (1245-28) 2013 (11)	28	2	4			780	765		-0.85	-0.77			0.03	0.03		
Arechavaleta et al. 2011 (50)	24	2	5			518	516		-0.54	-0.40			0.03	0.02		
Gallwitz et al. 2012 (45)	28	2	7						-0.84	-0.55			0.02	0.02		
Goke et al. 2010(48)	24	2	6						-0.94	-0.76			0.03	0.03		
Nauck et al. 2007 (52)	24	2	5			584	588		-0.96	-0.87			0.05	0.05		
Bosi et al. 2007 (57)	24	1	8			182	185		0.20	-0.90			0.10	0.10		
Ferrannini et al 2009 (58)	24	2	8						-0.73	-0.55			0.02	0.02		
Filozof et al 2010 (59)	24	2	8						-0.37	-0.51			0.06	0.06		
Goodman et al 2009 (60)	26	1	8			122	248		0.17	-0.53			0.11	0.11		
Pan et al 2012 (61)	24	1	8			144	148		-0.54	-1.05			0.08	0.08		
Janssen (DIA3009) 2013 (62)	26	2	13	14		484	483	485	-0.94	-0.81	-0.91		0.04	0.04	0.03	
Janssen (DIA3006) 2013(63)	26	1	5	13	14	183	366	368	-0.17		-0.79	-0.94	0.06	0.05	0.05	0.05
Bolinder et al 2012 (64)	24	1	12			91	91		-0.10	-0.39			0.09	0.09		
Henry et al 2012a(65)	24	1	12			208	211		-1.44	-1.98			0.08	0.08		

Study	Treatment					HbA1c											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
Henry et al 2012b(65)	24	1	11			201	194			-1.35	-2.05			0.09	0.09		
Bailey et al 2010 (66)	24	1	11	12		137	137	135		-0.32	-0.69	-0.98		0.08	0.08	0.08	
Nauck et al 2011 (67)	26	2	12			408	406			-0.73	-0.50			0.03	0.03		
Nauck et al. 2009(166)	26	1	9	10						-0.10	-0.60	-0.60		0.10	0.10	0.10	

SE = standard error

Table 116: Second line efficacy outcomes – Body weight

Study	Treatment					Body weight											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
Charpentier et al. 2001 (56)	20	1	2			75	147			-0.74	0.60			0.30	0.24		
BI GMBH (1245-23) 2012 (9)	24	1	3	4		224	217	225		-0.45	-2.08	-2.46		0.17	0.17	0.17	
Charbonnel et al. 2006 (51)	24	1	5														
Defronzo et al. 2009 (47)	24	1	6			179	191			-0.92	-0.87			0.33	0.32		
Raz et al. 2008 (53)	24	1	5														
Taskinen et al. 2011 (46)	24	1	7			177	523			-0.50	-0.40			0.56	0.34		
Yang et al. 2011 (49)	24	1	6			287	283			-0.97	-1.05			0.10	0.10		
Yang et al. 2012 (55)	24	1	5			198	197			-0.50	0.00			0.20	0.18		
BI GMBH	28	2	4			780	765			1.50	-3.28			0.11	0.07		

Study	Treatment					Body weight											
	Time point					Population at risk (N)				Change from baseline (y)			Standard error (SE)			
(1245-28) 2013 (11)																
Arechavaleta et al. 2011 (50)	24	2	5			518	516			1.20	-0.62		0.15	0.16		
Gallwitz et al. 2012 (45)	28	2	7													
Goke et al. 2010(48)	24	2	6													
Nauck et al. 2007 (52)	24	2	5			584	588			1.21	-1.31		0.22	0.21		
Bosi et al. 2007 (57)	24	1	8			182	185			-1.00	0.20		0.30	0.30		
Ferrannini et al 2009 (58)	24	2	8													
Filozof et al 2010 (59)	24	2	8													
Goodman et al 2009 (60)	26	1	8			122	248			-0.69	0.06		0.02	0.02		
Pan et al 2012 (61)	24	1	8			144	148			-1.00	-0.70		0.00	0.25		
Janssen (DIA3009) 2013 (62)	26	2	13	14		484	483	485		0.87	-3.38	-4.33	0.17	0.17	0.17	
Janssen (DIA3006) 2013(63)	26	1	5	13	14	183	366	368	367	-1.04		-3.22	0.22	0.18	0.18	0.18
Bolinder et al 2012 (64)	24	1	12			91	91			-0.88	-2.96		0.28	0.28		
Henry et al 2012a (65)	24	1	12			208	211			-1.36	-3.33		0.24	0.24		
Henry et al 2012b (65)	24	1	11			201	194			-1.29	-2.66		0.24	0.24		
Bailey et al 2010 (66)	24	1	11	12		137	137	135		-0.90	-3.00	-2.90	0.26	0.23	0.23	

Study	Treatment					Body weight											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
Nauck et al 2011 (67)	26	2	12			408	406			1.40	-3.15			0.14	0.14		
Nauck et al. 2009 (166	26	1	9	10						-0.74	0.60						

SE = standard error

Table 117: Second line efficacy outcomes – Systolic blood pressure

Study	Treatment					Systolic blood pressure											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
Charpentier et al. 2001 (56)	20	1	2			75	147			-0.65	-0.14			1.52	1.01		
BI GMBH (1245-23) 2012 (9)	24	1	3	4		224	217	225		-0.40	-4.50	-5.20		0.70	0.70	0.70	
Charbonnel et al. 2006 (51)	24	1	5														
Defronzo et al. 2009 (47)	24	1	6			179	191			-4.50	-3.60			1.30	1.20		
Raz et al. 2008 (53)	24	1	5														
Taskinen et al. 2011 (46)	24	1	7			177	523										
Yang et al. 2011 (49)	24	1	6			287	283			-3.10	-5.22			0.78	0.78		
Yang et al. 2012 (55)	24	1	5			198	197										
BI GMBH (1245-28) 2013 (11)	28	2	4			780	765			1.09	-4.39			0.51	0.49		

Study	Treatment					Systolic blood pressure										
	Time point					Population at risk (N)				Change from baseline (y)			Standard error (SE)			
Arechavaleta et al. 2011 (50)	24	2	5			518	516									
Gallwitz et al. 2012 (45)	28	2	7													
Goke et al. 2010(48)	24	2	6													
Nauck et al. 2007 (52)	24	2	5			584	588									
Bosi et al. 2007 (57)	24	1	8			182	185			-0.30	-2.00		0.60	0.60		
Ferrannini et al 2009 (58)	24	2	8													
Filozof et al 2010 (59)	24	2	8													
Goodman et al 2009 (60)	26	1	8			122	248									
Pan et al 2012 (61)	24	1	8			144	148									
Janssen (DIA3009) 2013 (62)	26	2	13	14		484	483	485		0.20	-3.30	-4.60	0.56	0.56	0.56	
Janssen (DIA3006) 2013(63)	26	1	5	13	14	183	366	368	367	1.50	-3.80	-5.10	0.82	0.61	0.61	
Bolinder et al 2012 (64)	24	1	12			91	91			0.10	-2.70		1.30	1.30		
Henry et al 2012a (65)	24	1	12			208	211			-1.20	-3.30		1.00	0.90		
Henry et al 2012b (65)	24	1	11			201	194			-1.80	-2.90		0.90	0.90		
Bailey et al 2010 (66)	24	1	11	12		137	137	135		-0.20	-4.30	-5.10	1.20	1.30	1.30	
Nauck et al 2011 (67)	26	2	12			408	406			0.80	-4.30		0.55	0.58		

Study	Treatment				Systolic blood pressure		
	Time point				Population at risk (N)	Change from baseline (y)	Standard error (SE)
Nauck et al. 2009 (166)	26	1	9	10			

SE = standard error

Third line

Table 118: Third line - HbA1c

Study	Treatment				HbA1C								
	Time point				Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
Haring et al. 2013 (9)	24	Met+ SU	Empa 10mg	Empa 25mg	225	224	217	-0.17	-0.82	-0.77	0.05	0.05	0.05
Owens et al. 2011 (68)	24	Met+ SU	DPP4		263	792		-0.1	-0.72		0.05	0.03	
Hermansen et al. 2007 (69)	26	Met+ SU	DPP4		109	115		0.3	-0.59		0.08	0.08	
Moses et al. 2013 (70)	26	Met+ SU	DPP4		128	129		-0.08	-0.74		0.08	0.07	
Janssen (DIA3015) 2013(63)	26	Sita 100mg	CAN 300 mg + Met		378	378		-0.93	-1.15		0.04	0.04	
Janssen (DIA3002) 2013(63)	26	Met+ SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156	-0.13	-0.85	-1.06	0.08	0.08	0.07653

DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error

Table 119: Third line - Body weight

Study		Treatment			Body weight								
	Time point				Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
Haring et al. 2013 (9)	24	Met+ SU	Empa 10 mg	Empa 25 mg	225	224	217	-0.39	-2.16	-2.39	0.15	0.15	0.16
Owens et al. 2011 (68)	24	Met+ SU	DPP4		263	792		-0.06	0.27		0.16	0.09	
Hermansen et al. 2007 (69)	26	Met+ SU	DPP4		109	115		-0.7	0.4		0.3316	0.2551	
Moses et al. 2013 (70)	26	Met+ SU	DPP4		128	129		-0.6	0.2		0.1849	0.1945	
Janssen (DIA3015) 2013(63)	26	Sita 100 mg	CAN 300 mg + Met		378	378		0.2649	-2.384		0.1325	0.1325	
Janssen (DIA3002) 2013(63)	26	Met+ SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156	-0.648	-1.945	-2.408	0.2362	0.2362	0.2362

DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; SU = sulphonylureas

Table 120: Third line - Systolic blood pressure

Study	Time point	Treatment			Systoic blood pressure								
					Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
Haring et al. 2013 (9)	24	Met+ SU	Empa 10mg	Empa 25mg	225	224	217	-1.4	-4.1	-3.5	0.70	0.70	0.70
Owens et al. 2011 (68)	24	Met+ SU	DPP4		263	792		0.63	-0.31		0.75	0.43	
Hermansen et al. 2007 (69)	26	Met+ SU	DPP4		109	115							
Moses et al. 2013 (70)	26	Met+ SU	DPP4		128	129							
Janssen (DIA3015) 2013(63)	26	Sita 100 mg	CAN 300 mg + Met		378	378		0.9	-5.1		0.66	0.66	
Janssen (DIA3002) 2013(63)	26	Met+ SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156	-2.6	-4.9	-4.3	0.92	0.97	0.97

DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; SU = sulphonylureas

TZD failure

For TZD failure:

1 = TZD

2 = TZD + MET

3 = Empa 10 mg + T

4 = Empa 25 mg + T

5 = Empa 10 mg + T + M

6 = Empa 25 mg + T +M

7 = DAP 5 mg + T

8 = DAP 10 mg + T

9 = CAN 100 mg + T + M

10 = CAN 300 mg + T + M

11 = ALO 12.5 mg +T

12 = ALO 25 mg +T

13 = SAX 2.5 mg + T

14 = SAX 5 mg + T

15 = SIT 100 mg + T

16 = VIL 50 mg + T

17 = VIL 100 mg + T

18 = ALO 25 mg + T + M

Table 121: TZD failure - HbA1C

Study	Treatment							HbA$_{1C}$																	
	Time point							Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	24	1	2	3	4	5	6	41	125	40	41	125	127	-0.11	-0.11	-0.66	-0.78	-0.55	-0.70	0.14	0.08	0.14	0.14	0.08	0.07
Rosenstock et al. 2012 (71)	24	1	7	8				139	141	140				-0.42	-0.82	-0.97				0.08	0.08	0.08			
Janssen (DIA3012) 2013(63)	26	2	9	10				115	115	114				-0.26	-0.89	-1.03				0.07	0.07	0.04			
Pratley et al 2009 (72)	26	1	11	12										-0.19	-0.66	-0.80				0.12	0.09	0.09			
Hollander et al 2009 (73)	24	1	13	14										-0.30	-0.66	-0.94				0.07	0.07	0.07			
Derosa et al 2010 (74)	26	2	15											-0.60	-0.80					0.06	0.07				
Garber et al 2007 (75)	24	1	16	17										-0.30	-0.80	-1.00				0.10	0.10	0.10			
Bosi et al 2011 (76)	26	2	18											-0.42	-0.89					0.04	0.04				

Table 122: TZD failure - Body weight

Study	Time point	Treatment						Body weight																	
								Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	24	1	2	3	4	5	6	41	125	40	41	125	127	0.15	0.40	-1.18	-1.17	-1.74	-1.59	0.43	0.25	0.44	0.43	0.25	0.25
Rosenstock et al. 2012 (71)	24	1	7	8				139	141	140				1.64	0.09	-0.14				0.28	0.28	0.28			
Janssen (DIA3012) 2013 (63)	26	2	9	10				115	115	114				-0.09	-2.64	-3.58				0.29	0.29	0.29			
Pratley et al 2009 (72)	26	1	11	12																					
Hollander et al 2009 (73)	24	1	13	14										0.90	1.30	1.40				0.25	0.25	0.25			
Derosa et al 2010 (74)	26	2	15											-1.40	-1.10					0.37	0.44				
Garber et al 2007 (75)	24	1	16	17										1.40						0.30					
Bosi et al 2011 (76)	26	2	18											1.52	0.73					0.18	0.15				

SE = standard error

Table 123: TZD failure - Systolic blood pressure

Study	Time point	Treatment						Systolic blood pressure																	
								Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	24	1	2	3	4	5	6	41	125	40	41	125	127	0.67	0.76	-2.04	-6.3	-3.47	-3.3	1.72	0.97	1.74	1.72	0.97	0.96
Rosenstock et al. 2012 (71)	24	1	7	8				139	141	140				1.3	-0.8	-3.4				1.20	1.20	1.20			
Janssen (DIA3012) 2013 (63)	26	2	9	10				115	115	114				-1.2	-5.3	-4.7				1.02	1.07	1.07			
Pratley et al 2009 (72)	26	1	11	12										0.67	0.76	-2.04	-6.3	-3.47	-3.3						
Hollander et al 2009 (73)	24	1	13	14										1.3	-0.8	-3.4									
Derosa et al 2010 (74)	26	2	15											-1.2	-5.3	-4.7									
Garber et al 2007 (75)	24	1	16	17										0.67	0.76	-2.04	-6.3	-3.47	-3.3						
Bosi et al 2011 (76)	26	2	18											1.3	-0.8	-3.4									

SE = standard error

Insulin failure

For insulin failure:

1 = INS
2 = INS+MET
3 = Empa 10 mg +INS
4 = Empa 25 mg +INS
5 = CAN 100 mg +INS
6 = CAN 300 mg +INS
7 = DAP 2.5 mg + INS
8 = DAP 5 mg + INS
9 = DAP 10 mg + INS
10 = ALO 12.5 mg +INS
11 = ALO 25 mg +INS
12 = SAX+INS

13 = SIT+MET+INS 14 = VIL+INS

Table 124: Insulin failure - HbA1C

Study	Time point	Treatment				HbA1C											
						Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-49) 2013 (40)	18	1	3	4		189	187	190		-0.49	-0.96	-1.00		0.05	0.05	0.05	
BI GMBH (1245-33) 2013 (12)	18	1	3	4		170	169	155		-0.01	-0.57	-0.71		0.07	0.07	0.07	
Janssen (DIA3008) 2013 (63)	18	1	5	6		565	566	587		0.01	-0.63	-0.72		0.06	0.06	0.06	
Wilding et al 2012 (83)	24	1	7	8	9	197	202	212	196	-0.39	-0.79	-0.89	-0.96	0.06	0.06	0.05	0.05
Rosenstock et al 2009 (78)	26	1	10	11		130	131	129		-0.13	-0.63	-0.71		0.20	0.20	0.20	
Barnett et al 2012 (79)	24	1	12			151	304			-0.32	-0.73			0.07	0.05		
Vilsboll et al 2010 (80)	24	2	13			319	322			0.00	-0.60			0.07	0.07		
Fonseca et al 2007 (81)	24	1	14			152	144			-0.20	-0.50			0.10	0.10		

Table 125: Insulin failure - Body weight

Study	Time point	Treatment				Body weight											
						Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-49) 2013 (40)	18	1	3	4		189	187	190		0.34	-0.98	-1.52		0.16	0.17	0.21	
BI GMBH (1245-33) 2013 (12)	18	1	3	4		170	169	155		-0.05	-2.09	-0.92		0.68	0.66	0.72	
Janssen (DIA3008) 2013 (63)	18	1	5	6		565	566	587		0.10	-1.75	-2.23		0.23	0.19	0.19	
Wilding et al 2012 (83)	24	1	7	8	9	197	202	212	196	0.43	-0.92	-1.00	-1.61	0.20	0.20	0.19	0.19
Rosenstock et al 2009 (78)	26	1	10	11		130	131	129		0.60	0.70	0.60		0.20	0.20	0.20	
Barnett et al 2012 (79)	24	1	12			151	304			0.18	0.39			0.21	0.15		
Vilsboll et al 2010 (80)	24	2	13			319	322										
Fonseca et al 2007 (81)	24	1	14			152	144			0.60	1.30			0.30	0.30		

SE = standard error

Table 126: Insulin failure - Systolic blood pressure

Study	Time point	Treatment				Systolic blood pressure											
						Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-49) 2013 (40)	18	1	3	4		189	187	190		-1.20	-3.60	-2.90		0.80	0.80	0.80	
BI GMBH (1245-33) 2013 (12)	18	1	3	4		170	169	155		-0.30	-3.70	-3.30		0.90	0.90	1.00	
Janssen (DIA3008) 2013 (63)	18	1	5	6		565	566	587		-2.5	-5.1	-6.9		1.07	1.035	1.10	
Wilding et al 2012 (83)	24	1	7	8	9	197	202	212	196	-3.56	-4.21	-5.93	-6.66	0.98	0.96	0.92	0.95
Rosenstock et al 2009 (78)	26	1	10	11													
Barnett et al 2012 (79)	24	1	12														
Vilsboll et al 2010 (80)	24	2	13														
Fonseca et al 2007 (81)	24	1	14														

SE = standard error

Safety outcomes (24 weeks)

Second line

For second line:

1 = Metformin
2 = Metformin+SU
3 = Empa 10mg
4 = Empa 25 mg
5 = Sitagliptin 100 mg
6 = Saxagliptin 5 mg
7 = Linagliptin 5 mg
8 = Vildagliptin 100 mg
9= Alogliptin 12.5mg
10= Alogliptin 25mg
11 = DAP 5 mg + MET
12 = DAP 10 mg + MET
13 = CAN 100 mg + MET
14 = CAN 300 mg + MET

Table 127: Second line - Overall hypoglycaemia

Study	Treatment				Overall hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
Forst et al 2010 (167)	1	2	7		71	65	66		0	3	0	
Charpentier et al. 2001 (56)	1	2			75	147			11	22		
Feinglos et al 2005 (168)	1	2			61	61			2	9		
BI GMBH (1245-23) 2012 (9)	1	3	4		225	224	217		1	4	3	
Scott et al. 2008 (54)	1	6			92	94			2	1		

Study	Treatment		Overall hypoglycaemia			
			Population at risk (N)		Observed cases (n)	
Charbonnel et al. 2006 (51)	1	5	237	464	5	6
Defronzo et al. 2009 (47)	1	6	179	191	9	10
Raz et al. 2008 (53)	1	5	94	96	0	1
Taskinen et al. 2011 (46)	1	7	177	523	5	3
Yang et al. 2011 (49)	1	6	287	283	4	4
Yang et al. 2012 (55)	1	6	198	197	3	1
BI GMBH (1245-28) 2013 (11)	2	4	780	765	165	15
Arechavaleta et al. 2011 (50)	2	5	518	516	114	36
Gallwitz et al. 2012 (45)	2	7	775	776	280	58
Goke et al. 2010(48)	2	6	430	428	156	13
Nauck et al. 2007 (52)	2	5	584	588	187	29
Bosi et al. 2007 (57)	1	8	182	185	0	1
Ferrannini et al 2009 (58)	2	8	1393	1396	224	23
Filozof et al 2010 (59)	2	8	494	513	11	6
Goodman et al 2009 (60)	1	8	122	248	0	2
Nauck et al 2006 (169)	1	2	36	36	0	1
Pan et al 2012 (61)	1	8	144	148	0	0

Study	Treatment				Overall hypoglycaemia					
					Population at risk (N)			Observed cases (n)		
Janssen (DIA3009) 2013 (62)	2	9	10		482	483	485	165	27	24
Janssen (DIA3006) 2013 (63)	1	5	9	10						
Bolinder et al 2012 (64)	1	12			91	91		3	2	
Henry et al 2012a (65)	1	12			208	211		6	7	
Henry et al 2012b (65)	1	11			201	194		0	5	
Bailey et al 2010 (66)	1	11	12		137	137	135	4	5	5
Nauck et al 2011 (67)	2	12			408	406		162	14	

Table 128: Second line – Non-severe hypoglycaemia

Study	Treatment				Non-severe hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
Forst et al 2010 (167)	1	2	7		71	65	66		0	3	0	
Charpentier et al. 2001 (56)	1	2			75	147			11	20		
Feinglos et al 2005 (168)	1	2			61	61			2	9		
BI GMBH (1245-23) 2012 (9)	1	3	4		206	217	214		1	4	3	

Study	Treatment		Non-severe hypoglycaemia			
			Population at risk (N)		Observed cases (n)	
Scott et al. 2008 (54)	1	6	92	94	2	1
Charbonnel et al. 2006 (51)	1	5	237	464	5	6
Defronzo et al. 2009 (47)	1	6	179	191	9	10
Raz et al. 2008 (53)	1	5	94	96	0	1
Taskinen et al. 2011 (46)	1	7	177	523	5	3
Yang et al. 2011 (49)	1	6	287	283	4	4
Yang et al. 2012 (55)	1	6	198	197	3	1
BI GMBH (1245-28) 2013 (11)	2	4	780	765	164	15
Arechavaleta et al. 2011 (50)	2	5	518	516	111	35
Gallwitz et al. 2012 (45)	2	7	755	764	268	57
Goke et al. 2010(48)	2	6	430	428	149	13
Nauck et al. 2007 (52)	2	5	584	588	180	28
Bosi et al. 2007 (57)	1	8	182	185	0	1
Ferrannini et al 2009 (58)	2	8	1393	1396	214	23
Filozof et al 2010 (59)	2	8	494	513		
Goodman et al 2009 (60)	1	8	122	248	0	2
Nauck et al 2006 (169)	1	2	36	36	0	1

Study	Treatment				Non-severe hypoglycaemia					
					Population at risk (N)			Observed cases (n)		
Pan et al 2012 (61)	1	8			144	148		0	0	
Janssen (DIA3009) 2013 (62)	2	9	10		482	483	485			
Janssen (DIA3006) 2013 (63)	1	5	9	10						
Bolinder et al 2012 (64)	1	12			91	91		2	2	
Henry et al 2012a (65)	1	12			208	211		6	7	
Henry et al 2012b (65)	1	11			201	194		0	5	
Bailey et al 2010 (66)	1	11	12		137	137	135	4	5	5
Nauck et al 2011 (67)	2	12			408	406		147	7	

Table 129: Second line - Severe hypoglycaemia

Study	Treatment				Severe hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
Forst et al 2010 (167)	1	2	7		71	65	66		0	0	0	
Charpentier et al. 2001 (56)	1	2			75	147			0	2		
Feinglos et al 2005 (168)	1	2			61	61			0	0		

Study	Treatment			Severe hypoglycaemia							
				Population at risk (N)			Observed cases (n)				
BI GMBH (1245-23) 2012 (9)	1	3	4	217	214	206	0	0	0		
Scott et al. 2008 (54)	1	6		92	94		0	0			
Charbonnel et al. 2006 (51)	1	5		237	464		0	0		0	
Defronzo et al. 2009 (47)	1	6		179	191		0	0			
Raz et al. 2008 (53)	1	5		94	96		0	0			
Taskinen et al. 2011 (46)	1	7		177	523		0	0			
Yang et al. 2011 (49)	1	6		287	283		0	0			
Yang et al. 2012 (55)	1	6		198	197		0	0			
BI GMBH (1245-28) 2013 (11)	2	4		780	765		1	0			
Arechavaleta et al. 2011 (50)	2	5		518	516		3	1			
Gallwitz et al. 2012 (45)	2	7		755	764		12	1			
Goke et al. 2010(48)	2	6		430	428		7	0			
Nauck et al. 2007 (52)	2	5		584	588		7	1			
Bosi et al. 2007 (57)	1	8		182	185		0	0			
Ferrannini et al 2009 (58)	2	8		1393	1396						
Filozof et al 2010 (59)	2	8		494	513						
Goodman et al 2009 (60)	1	8		122	248		0	0			

Study	Treatment				Severe hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
Nauck et al 2006 (169)	1	2			36	36			0	0		
Pan et al 2012 (61)	1	8			144	148			0	0		
Janssen (DIA3009) 2013 (62)	2	9	10		482	483	485					
Janssen (DIA3006) 2013 (63)	1	5	9	10								
Bolinder et al 2012 (64)	1	12			91	91			0	0		
Henry et al 2012a (65)	1	12			208	211			0	0		
Henry et al 2012b (65)	1	11			201	194			0	0		
Bailey et al 2010 (66)	1	11	12		137	137	135		0	0	0	
Nauck et al 2011 (67)	2	12			408	406			0	0		

Table 130: Second line - Urinary tract infections

Study	Treatment				Urinary tract infections							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
Forst et al 2010 (167)	1	2	7		65	71	66		1	0	0	
Charpentier et al. 2001 (56)	1	2										
Feinglos et al 2005 (168)	1	2										

Study	Treatment			Urinary tract infections					
				Population at risk (N)			Observed cases (n)		
BI GMBH (1245-23) 2012 (9)	1	3	4	214	206	217	8	9	9
Scott et al. 2008 (54)	1	6							
Charbonnel et al. 2006 (51)	1	5		237	464		13	22	
Defronzo et al. 2009 (47)	1	6		179	191		8	10	
Raz et al. 2008 (53)	1	5		94	96		3	4	
Taskinen et al. 2011 (46)	1	7		177	523		7	16	
Yang et al. 2011 (49)	1	6		287	283		8	13	
Yang et al. 2012 (55)	1	6							
BI GMBH (1245-28) 2013 (11)	2	4		780	765		67	81	
Arechavaleta et al. 2011 (50)	2	5							
Gallwitz et al. 2012 (45)	2	7		755	764		1	1	
Goke et al. 2010(48)	2	6							
Nauck et al. 2007 (52)	2	5		584	588		25	44	
Bosi et al. 2007 (57)	1	8		185			1	0	
Ferrannini et al 2009 (58)	2	8		1396					
Filozof et al 2010 (59)	2	8		513					
Goodman et al 2009 (60)	1	8		248					

Study	Treatment				Urinary tract infections			
					Population at risk (N)		Observed cases (n)	
Nauck et al 2006 (169)	1	2			36			
Pan et al 2012 (61)	1	8			148		0	1
Janssen (DIA3009) 2013 (62)	2	9	10		483	485		
Janssen (DIA3006) 2013 (63)	1	5	9	10				
Bolinder et al 2012 (64)	1	12			91		0	2
Henry et al 2012a (65)	1	12			211		4	6
Henry et al 2012b (65)	1	11			194		10	10
Bailey et al 2010 (66)	1	11	12		137	135		
Nauck et al 2011 (67)	2	12			406			

Table 131: Second line - Genital infections

Study	Treatment				Genital infections							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
Forst et al 2010 (167)	1	2	7									
Charpentier et al. 2001 (56)	1	2										
Feinglos et al 2005 (168)	1	2										

Study	Treatment			Genital infections					
				Population at risk (N)			Observed cases (n)		
BI GMBH (1245-23) 2012 (9)	1	3	4	214	206	217	0	1	1
Scott et al. 2008 (54)	1	6							
Charbonnel et al. 2006 (51)	1	5							
Defronzo et al. 2009 (47)	1	6							
Raz et al. 2008 (53)	1	5							
Taskinen et al. 2011 (46)	1	7							
Yang et al. 2011 (49)	1	6							
Yang et al. 2012 (55)	1	6							
BI GMBH (1245-28) 2013 (11)	2	4		780	765		13	71	
Arechavaleta et al. 2011 (50)	2	5							
Gallwitz et al. 2012 (45)	2	7							
Goke et al. 2010(48)	2	6							
Nauck et al. 2007 (52)	2	5							
Bosi et al. 2007 (57)	1	8							
Ferrannini et al 2009 (58)	2	8							
Filozof et al 2010 (59)	2	8							
Goodman et al 2009 (60)	1	8							

Study	Treatment				Genital infections	
					Population at risk (N)	Observed cases (n)
Nauck et al 2006 (169)	1	2				
Pan et al 2012 (61)	1	8				
Janssen (DIA3009) 2013 (62)	2	9	10			
Janssen (DIA3006) 2013 (63)	1	5	9	10		
Bolinder et al 2012 (64)	1	12				
Henry et al 2012a (65)	1	12				
Henry et al 2012b (65)	1	11				
Bailey et al 2010 (66)	1	11	12			
Nauck et al 2011 (67)	2	12				

Third line

Table 132: Third line - Overall hypoglycaemia

Study	Treatment			Overall hypoglycaemia					
				Population at risk (N)			Change from baseline (n)		
	Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	r[,1]	r[,2]	r[,3]
Haring et al. 2013 (9)	Met + SU	Empa 10mg	Empa 25mg	224	217	225	22	35	28
Owens et al. 2011 (68)	Met + SU	DPP4		263	792		39	180	
Hermansen et al. 2007 (69)	Met + SU	DPP4		109	115		1	19	
Moses et al. 2013 (70)	Met + SU	DPP4		128	129		8	13	
Janssen (DIA3015) 2013 (63)	Sita 100 mg	CAN 300 mg + Met		378	377		154	163	
Janssen (DIA3002) 2013 (63)	Met + SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156	24	43	47

DAP = Dapagliflozin; DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; Sita = sitagliptin; SU = Sulphonylureas

Table 133: 3rd line - Non-severe hypoglycaemia

Study	Treatment			Non-severe hypoglycaemia					
				Population at risk (N)			Change from baseline (n)		
	Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	r[,1]	r[,2]	r[,3]
Haring et al. 2013 (9)	Met + SU	Empa 10mg	Empa 25mg	225	224	217	22	35	28
Owens et al. 2011 (68)	Met + SU	DPP4		263	792		37	175	
Hermansen et al. 2007 (69)	Met + SU	DPP4		109	115		1	19	
Moses et al. 2013 (70)	Met + SU	DPP4		128	129		8	13	
Janssen (DIA3015) 2013 (63)	Sita 100mg	CAN 300 mg + Met		378	377		154	163	
Janssen (DIA3002) 2013 (63)	Met + SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156	24	43	47

DAP = Dapagliflozin; DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; Sita = sitagliptin; SU = Sulphonylureas

Table 134: Third line - Severe hypoglycaemia

Study	Treatment			Severe hypoglycaemia					
				Population at risk (N)			Change from baseline (n)		
	Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	r[,1]	r[,2]	r[,3]
Haring et al. 2013 (9)	Met + SU	Empa 10mg	Empa 25mg	225	224	217	0	0	0
Owens et al. 2011 (68)	Met + SU	DPP4		263	792		2	5	
Hermansen et al. 2007 (69)	Met + SU	DPP4		109	115		0	0	
Moses et al. 2013 (70)	Met + SU	DPP4		128	129		0	0	
Janssen (DIA3015) 2013 (63)	Sita 100 mg	CAN 300 mg + Met		378	377				
Janssen (DIA3002) 2013 (63)	Met + SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156			

DAP = Dapagliflozin; DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; Sita = sitagliptin; SU = Sulphonylureas

Table 135: Third line - Urinary tract infections

Study	Treatment			Urinary tract infections					
				Population at risk (N)			Change from baseline (n)		
	Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	r[,1]	r[,2]	r[,3]
Haring et al. 2013 (9)	Met + SU	Empa 10 mg	Empa 25 mg	225	224	217	18	23	18
Owens et al. 2011 (68)	Met + SU	DPP4		263	792		14	26	
Hermansen et al. 2007 (69)	Met + SU	DPP4		109	115				
Moses et al. 2013 (70)	Met + SU	DPP4		128	129		8	4	
Janssen (DIA3015) 2013 (63)	Sita 100 mg	CAN 300 mg + Met		378	377				
Janssen (DIA3002) 2013 (63)	Met + SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156			

DAP = Dapagliflozin; DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; Sita = sitagliptin; SU = Sulphonylureas

Table 136: Third line - Genital infections

Study	Treatment			Genital infections					
				Population at risk (N)			Change from baseline (n)		
	Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	r[,1]	r[,2]	r[,3]
Haring et al. 2013 (9)	Met + SU	Empa 10 mg	Empa 25 mg	225	224	217	2	6	5
Owens et al. 2011 (68)	Met + SU	DPP4		263	792				
Hermansen et al. 2007 (69)	Met + SU	DPP4		109	115				
Moses et al. 2013 (70)	Met + SU	DPP4		128	129				
Janssen (DIA3015) 2013 (63)	Sita 100 mg	CAN 300 mg + Met		378	377				
Janssen (DIA3002) 2013 (63)	Met + SU	DAP 5 mg + Met	DAP 10 mg + Met	156	157	156			

DAP = Dapagliflozin; DPP4 = Dipeptidyl peptidase-4 inhibitors; Met = metformin; SE = standard error; Sita = sitagliptin; SU = Sulphonylureas

TZD failure

For TZD failure:

1 = TZD
2 = TZD + MET
3 = Empa 10 mg + T
4 = Empa 25 mg + T
5 = Empa 10 mg + T + M
6 = Empa 25 mg + T +M
7 = DAP 5 mg + T
8 = DAP 10 mg + T
9 = CAN 100 mg + T + M
10 = CAN 300 mg + T + M
11 = ALO 12.5 mg +T
12 = ALO 25 mg +T
13 = SAX 2.5 mg + T
14 = SAX 5 mg + T
15 = SIT 100 mg + T
16 = VIL 50 mg + T
17 = VIL 100 mg + T
18 = ALO 25 mg + T + M

Table 137: TZD failure - Overall hypoglycaemia

Study	Treatment						Overall hypoglycaemia											
							Population at risk (N)						Change from baseline (y)					
	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	r[,6]
Kovacs et al. 2012 (7)	1	2	3	4	5	6	41	124	40	41	125	127	0	4	0	0	2	6
Rosenstock et al. 2012 (71)	1	7	8				139	141	140				1	3	0			
Janssen (DIA3012) 2013 (63)	2	9	10															
Pratley et al 2009 (72)	1	11	12				97	198	199				5	10	14			
Hollander et al 2009 (73)	1	13	14															
Derosa et al 2010 (74)	2	15																
Garber et al 2007 (75)	1	16	17				158	146	158				3	0	1			
Bosi et al 2011 (76)	2	18					399	404					6	18				

Table 138: TZD failure - Non-severe hypoglycaemia

Study	Treatment						Non-severe hypoglycaemia											
							Population at risk (N)						Change from baseline (y)					
	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	r[,6]
Kovacs et al. 2012 (7)	1	2	3	4	5	6	41	124	40	41	125	127	0	4	0	0	2	6
Rosenstock et al. 2012 (71)	1	7	8				139	141	140				1	3	0			
Janssen (DIA3012) 2013 (63)	2	9	10															
Pratley et al 2009 (72)	1	11	12				97	198	199				0	0	1			
Hollander et al 2009 (73)	1	13	14				184	195	186				0	1	0			
Derosa et al 2010 (74)	2	15																
Garber et al 2007 (75)	1	16	17				158	146	158				3	0	1			
Bosi et al 2011 (76)	2	18					399	404					6	16				

Table 139: TZD failure - Severe hypoglycaemia

Study	Treatment						Severe hypoglycaemia											
							Population at risk (N)						Change from baseline (y)					
	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	r[,6]
Kovacs et al. 2012 (7)	1	2	3	4	5	6	41	124	40	41	125	127	0	0	0	0	0	0
Rosenstock et al. 2012 (71)	1	7	8				139	141	140				0	0	0			
Janssen (DIA3012) 2013 (63)	2	9	10															
Pratley et al 2009 (72)	1	11	12				97	198	199				0	0	0			
Hollander et al 2009 (73)	1	13	14															
Derosa et al 2010 (74)	2	15																
Garber et al 2007 (75)	1	16	17				158	146	158				0	0	0			
Bosi et al 2011 (76)	2	18					399	404					0	2				

Table 140: TZD failure - Urinary tract infections

Study	Treatment						Urinary tract infections											
							Population at risk (N)						Change from baseline (y)					
	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	r[,6]
Kovacs et al. 2012 (7)	1	2	3	4	5	6	41	124	40	41	125	127	1	17	5	7	19	11
Rosenstock et al. 2012 (71)	1	7	8															
Janssen (DIA3012) 2013 (63)	2	9	10															

Study	Treatment			Urinary tract infections					
				Population at risk (N)			Change from baseline (y)		
Pratley et al 2009 (72)	1	11	12						
Hollander et al 2009 (73)	1	13	14	184	195	186	12	7	12
Derosa et al 2010 (74)	2	15							
Garber et al 2007 (75)	1	16	17	158	146	158	2	3	8
Bosi et al 2011 (76)	2	18		399	404		13	22	

Table 141: TZD failure - Genital infections

Study	Treatment						Genital infections											
							Population at risk (N)						Change from baseline (y)					
	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	r[,1]	r[,2]	r[,3]	r[,4]	r[,5]	r[,6]
Kovacs et al. 2012 (7)	1	2	3	4	5	6		124			125	127		1			0	0
Rosenstock et al. 2012 (71)	1	7	8															
Janssen (DIA3012) 2013 (63)	2	9	10															
Pratley et al 2009 (72)	1	11	12															
Hollander et al 2009 (73)	1	13	14															
Derosa et al 2010 (74)	2	15																
Garber et al 2007 (75)	1	16	17															
Bosi et al 2011 (76)	2	18																

Insulin failure

For insulin failure:

1 = INS
2 = INS+MET
3 = Empa 10 mg +INS
4 = Empa 25 mg +INS
5 = CAN 100 mg +INS
6 = CAN 300 mg +INS
7 = DAP 2.5 mg + INS
8 = DAP 5 mg + INS
9 = DAP 10 mg + INS
10 = ALO 12.5 mg +INS
11 = ALO 25 mg +INS
12 = SAX+INS
13 = SIT+MET+INS
14 = VIL+INS

Table 142: Insulin failure - Overall hypoglycaemia

Study	Treatment				Overall hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-49) 2013 (40)	1	3	4		188	186	189		70	74	78	
BI GMBH (1245-33) 2013 (12)	1	3	4		170	169	155		18	20	27	
Janssen (DIA3008) 2013 (63)	1	5	6		565	566	587		208	279	285	
Wilding et al 2012 (83)	1	7	8	9	197	202	212	196	102	122	118	105
Rosenstock et al 2009 (78)	1	10	11		130	131	129		31	35	35	
Barnett et al 2012 (79)	1	12			151	304			5	16		
Vilsboll et al 2010 (80)	2	13			319	322			76	155		

Study	Treatment				Overall hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
Fonseca et al 2007 (81)	1	14			152	144			45	33		

Table 143: Insulin failure - Non-severe hypoglycaemia

Study	Treatment				Non-severe hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-49) 2013 (40)	1	3	4		188	186	189		69	73	77	
BI GMBH (1245-33) 2013 (12)	1	3	4		170	169	155		60	61	54	
Janssen (DIA3008) 2013 (63)	1	5	6		565	566	587		208	279	283	
Wilding et al 2012 (83)	1	7	8	9	197	202	212	196	99	118	113	99
Rosenstock et al 2009 (78)	1	10	11		130	131	129		21	28	29	
Barnett et al 2012 (79)	1	12			151	304			5	16		
Vilsboll et al 2010 (80)	2	13			188	186	189		69	73	77	
Fonseca et al 2007 (81)	1	14			170	169	155		60	61	54	

Table 144: Insulin failure - Severe hypoglycaemia

Study	Treatment				Severe hypoglycaemia							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-49) 2013 (40)	1	3	4		188	186	189		1	1	1	
BI GMBH (1245-33) 2013 (12)	1	3	4		170	169	155		0	0	2	
Janssen (DIA3008) 2013 (63)	1	5	6		565	566	587		14	10	16	
Wilding et al 2012 (83)	1	7	8	9	197	202	212	196	2	3	2	3
Rosenstock et al 2009 (78)	1	10	11		130	131	129		2	0	1	
Barnett et al 2012 (79)	1	12			151	304			2	3		
Vilsboll et al 2010 (80)	2	13										
Fonseca et al 2007 (81)	1	14			152	144			4	0		

Table 145: Insulin failure - Urinary tract infections

Study	Treatment				Urinary tract infections							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-49) 2013 (40)	1	3	4		188	186	189		0	0	1	
BI GMBH (1245-33) 2013 (12)	1	3	4		170	169	155		13	21	16	

Study	Treatment				Urinary tract infections							
					Population at risk (N)				Observed cases (n)			
Janssen (DIA3008) 2013 (63)	1	5	6									
Wilding et al 2012 (83)	1	7	8	9	197	202	212	196	8	11	16	14
Rosenstock et al 2009 (78)	1	10	11		129	131	129		10	8	9	
Barnett et al 2012 (79)	1	12			151	304			9	18		
Vilsboll et al 2010 (80)	2	13										
Fonseca et al 2007 (81)	1	14										

Table 146: Insulin failure - Genital infections

Study	Treatment				Genital infections							
					Population at risk (N)				Observed cases (n)			
	Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-49) 2013 (40)	1	3	4		188	186	189		0	0	1	
BI GMBH (1245-33) 2013 (12)	1	3	4		170	169	155		3	13	8	
Janssen (DIA3008) 2013 (63)	1	5	6									
Wilding et al 2012 (83)	1	7	8	9								
Rosenstock et al 2009 (78)	1	10	11									
Barnett et al 2012 (79)	1	12										

Study	Treatment		Genital infections	
			Population at risk (N)	Observed cases (n)
Vilsboll et al 2010 (80)	2	13		
Fonseca et al 2007 (81)	1	14		

Efficacy outcomes (52 weeks)

Second line

For second line:

1 = Metformin
2 = Metformin+SU
3 = Empa 10mg
4 = Empa 25 mg
5 = Sitagliptin 100 mg
6 = Saxagliptin 5 mg
7 = Linagliptin 5 mg
8 = Vildagliptin 100 mg
9= Alogliptin 12.5mg
10= Alogliptin 25mg
11 = DAP 5 mg + MET
12 = DAP 10 mg + MET
13 = CAN 100 mg + MET
14 = CAN 300 mg + MET

Table 147: Second line – HbA_{1C}

Study	Treatment					HbA_{1C}											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-23) 2012 (9)	52	1	3	4		207	217	213		-0.08	-0.71	-0.74		0.06	0.05	0.06	
BI GMBH (1245-28) 2013 (11)	52	2	4			780	765			-0.66	-0.73			0.03	0.03		
Gallwitz et al. 2012 (45)	52	2	7			755	764			-0.57	-0.36			0.03	0.03		
Goke et al. 2010(48)	52	2	6			430	428			-0.80	-0.74			0.04	0.04		
Nauck et al. 2007 (52)	52	2	5			584	588			-0.67	-0.67			0.04	0.04		
Ferrannini et al 2009 (58)	52	2	8			1396	1393			-0.44	-0.53			0.02	0.02		
Filozof et al 2010 (59)	52	2	8			513	494			-0.81	-0.85			0.06	0.06		
Janssen (DIA3009) 2013 (62)	52	2	13	14		484	483	485		-0.81	-0.82	-0.93		0.04	0.04	0.03	
Janssen (DIA3006) 2013 (63)	52	1	5	13	14	183	366	368	367	NR	-0.73	-0.73	-0.88	NR	0.04	0.04	0.05
Nauck et al 2011 (67)	52	2	12			401	400			-0.52	-0.52			0.04	0.04		

SE = standard error

Table 148: Second line – Body Weight

Study	Treatment					Body Weight											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-23) 2012 (9)	52	1	3	4		207	217	213		-0.58	-2.27	-2.89		0.18	0.19	0.23	
BI GMBH (1245-28) 2013 (11)	52	2	4			780	765			1.60	-3.21			0.11	0.11		
Gallwitz et al. 2012 (45)	52	2	7			755	764			1.40	-1.20			0.10	0.10		
Goke et al. 2010(48)	52	2	6			430	428			1.10	-1.10			0.18	0.18		
Nauck et al. 2007 (52)	52	2	5			584	588			1.10	-1.50			0.28	0.28		
Ferrannini et al 2009 (58)	52	2	8			1396	1393			-0.23	1.56			0.11	0.12		
Filozof et al 2010 (59)	52	2	8			513	494			0.08	1.36			0.24	0.24		
Janssen (DIA3009) 2013 (62)	52	2	13	14		484	483	485		1.00	-4.20	-4.70		0.20	0.20	0.20	
Janssen (DIA3006) 2013 (63)	52	1	5	13	14	183	366	368	367	NR	-1.30	-3.80	-4.20	NR	0.20	0.20	0.20
Nauck et al 2011 (67)	52	2	12			401	400			1.44	-3.22			0.18	0.17		

SE = standard error

Table 149: Second line – Systolic blood pressure

Study	Treatment					Systolic blood pressure											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-23) 2012 (9)	52	1	3	4		207	217	213		-0.40	-3.70	-5.30		0.80	0.70	0.80	
BI GMBH (1245-28) 2013 (11)	52	2	4			780	765			2.20	-3.60			0.50	0.50		
Gallwitz et al. 2012 (45)	52	2	7														
Goke et al. 2010(48)	52	2	6			430	428			-1.20	-4.10			0.59	0.59		
Nauck et al. 2007 (52)	52	2	5														
Ferrannini et al 2009 (58)	52	2	8														
Filozof et al 2010 (59)	52	2	8														
Janssen (DIA3009) 2013 (62)	52	2	13	14		484	483	485		0.20	-3.30	-4.60		0.56	0.56	0.56	
Janssen (DIA3006) 2013 (63)	52	1	5	13	14	183	366	368	367	NR	-0.74	-3.69	-4.72	NR	0.65	0.51	0.68
Nauck et al 2011 (67)	52	2	12			408	406			0.80	-4.30			0.55	0.58		

SE = standard error

Third line

For 3rd line:

1 = Metformin+SU

3 = Empa 10mg

4 = Empa 25 mg

5 = Sitagliptin 100 mg

6 = Saxagliptin 5 mg

7 = Linagliptin 5 mg

8 = Vildagliptin 100 mg

9 = CAN 100 mg + MET

10 = CAN 300 mg + MET

11 = DAP 5 mg + MET

12 = DAP 10 mg + MET

Table 150: Third line – HbA1C

Study		Treatment			HbA$_{1C}$								
	Time point				Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
BI GMBH (1245-23) 2012 (9)	52	1	3	4	225	225	216	-0.05	-0.76	-0.74	0.06	0.06	0.06
Janssen (DIA3015) 2013 (63)	52	5	10		378	378		-0.66	-1.03		0.05	0.05	
Janssen (DIA3002) 2013 (63)	52	1	11	12	156	157	156	0.01	-0.74	-0.96	0.08	0.60	0.08

SE = standard error

Table 151: Third line – Body weight

Study	Time point	Treatment			Body weight								
					Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
BI GMBH (1245-23) 2012 (9)	52	1	3	4	225	225	216	-0.28	-2.28	-2.33	0.16	0.19	0.2
Janssen (DIA3015) 2013 (63)	52	5	10		378	378		0.2649	-2.384		0.1325	0.1325	
Janssen (DIA3002) 2013 (63)	52	1	11	12	156	157	156	-0.912	-2.191	-3.191	0.29	0.31	0.31

SE = standard error

Table 152: Third line – Systolic blood pressure

Study	Time point	Treatment			Systolic blood pressure								
					Population at risk (N)			Change from baseline (y)			Standard error (SE)		
		Arm 1	Arm 2	Arm 3	n[,1]	n[,2]	n[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]
BI GMBH (1245-23) 2012 (9)	52	1	3	4	225	225	216	-0.2	-3	-2.9	0.80	0.70	0.80
Janssen (DIA3015) 2013 (63)	52	5	10		378	378		0.9	-5.1		0.66	0.66	
Janssen (DIA3002) 2013 (63)	52	1	11	12	156	157	156	0.1	-3.71	-2.9	1.05	1.08	0.97

SE = standard error

TZD failure

For TZD failure:

1 = TZD
2 = TZD + MET
3 = Empa 10 mg + T
4 = Empa 25 mg + T
5 = Empa 10 mg + T + M
6 = Empa 25 mg + T +M
7 = DAP 5 mg + T
8 = DAP 10 mg + T
9 = CAN 100 mg + T + M
10 = CAN 300 mg + T + M
11 = ALO 12.5 mg +T
12 = ALO 25 mg +T
13 = SAX 2.5 mg + T
14 = SAX 5 mg + T
15 = SIT 100 mg + T
16 = VIL 50 mg + T
17 = VIL 100 mg + T
18 = ALO 25 mg + T + M

Table 153: TZD failure – HbA_{1C}

Study	Treatment							HbA_{1C}																	
	Time point							Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	52	1	2	3	4	5	6	NR	165	NR	NR	165	168	NR	-0.06	NR	NR	-0.62	-0.69	NR	0.08	NR	NR	0.07	0.07
Janssen (DIA3012) 2013 (63)	52	2	9	10				115	113	113				NR	-0.95	-1.07				NR	0.80	0.07			
Bosi et al 2011 (76)	52	2	18					399	404					-0.29	-0.70					0.04	0.04				

SE = standard error

Table 154: TZD failure – Body weight

Study	Time point	Treatment						Body weight																	
								Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n,[2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	52	1	2	3	4	5	6	NR	165	NR	NR	165	168	NR	0.60	NR	NR	-1.48	-1.42	NR	0.22	NR	NR	0.27	0.25
Janssen (DIA3012) 2013 (63)	52	2	9	10				115	115	114				NR	-2.90	-4.00				NR	0.49	0.52			
Bosi et al 2011 (76)	52	2	18					399	404					1.60	1.10					0.19	0.19				

SE = standard error

Table 155: TZD failure – Systolic blood pressure

Study	Time point	Treatment						Systolic blood pressure																	
								Population at risk (N)						Change from baseline (y)						Standard error (SE)					
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	n[,1]	n[,2]	n[,3]	n[,4]	n[,5]	n[,6]	y[,1]	y[,2]	y[,3]	y[,4]	y[,5]	y[,6]	se[,1]	se[,2]	se[,3]	se[,4]	se[,4]	se[,4]
Kovacs et al. 2012 (7)	52	1	2	3	4	5	6	NR	165	NR	NR	165	168	NR	0.8	NR	NR	-1.9	-3.3	NR	0.90	NR	NR	1.10	1.00
Janssen (DIA3012) 2013 (63)	52	2	9	10				115	115	114				-2.96	NR	-4.01				1.20	NR	1.10			
Bosi et al 2011 (76)	52	2	18					399	404					NR	NR										

SE = standard error

Insulin failure

For insulin failure:

1 = INS
2 = INS+MET
3 = Empa 10 mg +INS
4 = Empa 25 mg +INS
5 = CAN 100 mg +INS
6 = CAN 300 mg +INS
7 = DAP 2.5 mg + INS
8 = DAP 5 mg + INS
9 = DAP 10 mg + INS
10 = ALO 12.5 mg +INS
11 = ALO 25 mg +INS
12 = SAX+INS
13 = SIT+MET+INS
14 = VIL+INS

Table 156: Insulin failure – HbA_{1C}

Study		Treatment				HbA_{1C}											
Time point						Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		0.05	-0.55	-0.71		0.07	0.07	0.07	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		115	119	118		-0.81	-1.18	-1.27		0.08	0.08	0.08	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194	-0.48	-0.79	-0.96	-1.01				

SE = standard error

Table 157: Insulin failure – Body weight

Study		Treatment				Body weight											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		-0.17	-2.28	-2.34		0.33	0.33	0.35	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		115	119	118		0.44	-1.90	-1.97		0.36	0.36	0.36	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194	0.82	-0.96	-0.99	-1.60				

SE = standard error

Table 158: Insulin failure – Systolic blood pressure

Study		Treatment				Systolic blood pressure											
	Time point					Population at risk (N)				Change from baseline (y)				Standard error (SE)			
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n[,2]	n[,3]	n[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		0.00	-3.00	-3.70		1.10	1.10	1.10	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		188	186	189		-2.30	-4.40	-3.80		0.80	0.80	0.80	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194	-0.2			-5.2	1.32			1.15

SE = standard error

Safety outcomes (52 weeks)

Insulin failure

For insulin failure:

1 = INS
2 = INS+MET
3 = Empa 10 mg +INS
4 = Empa 25 mg +INS
5 = CAN 100 mg +INS
6 = CAN 300 mg +INS
7 = DAP 2.5 mg + INS
8 = DAP 5 mg + INS
9 = DAP 10 mg + INS
10 = ALO 12.5 mg +INS
11 = ALO 25 mg +INS
12 = SAX+INS
13 = SIT+MET+INS
14 = VIL+INS

Table 159: Insulin failure – hypoglycaemic events

Study		Treatment				Hypoglycaemic events							
	Time point												
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n,[2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		51	54.1	55.8	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		188	186	189		110	108	99.2	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194				

Table 160: Insulin failure – urinary tract infections

Study		Treatment				Urinary tract infections							
	Time point												
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n,[2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		10.2	20	16	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		188	186	189		29	29	29	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194				

Table 161: Insulin failure – genital infections

Study		Treatment				Genital infections							
	Time point												
		Arm 1	Arm 2	Arm 3	Arm 4	n[,1]	n,[2]	n[,3]	n[,4]	r[,1]	r[,2]	r[,3]	r[,4]
BI GMBH (1245-33) 2013 (12)	54	1 or 2	3	4		170	169	155		3	7	8	
BI GMBH (1245-49) 2013 (40)	52	2	3	4		188	186	189		3	8	18	
Wilding et al 2012 (77)	52	1	7	8	9	193	202	211	194				

9.8 Appendix 8: review of diabetes economic models

Table 162: Review of diabetes economic models

Model	CORE	UKPDS Outcomes Model	JADE	DiDACT	DMM	Eastman model	GDM	IMIB/ Accusim	Archimedes Model	EAGLE
Key reference paper describing the model	Palmer et al. 2004(93)	Clarke et al 2004 (UKPDS 68)(26)	Chen et al. 2008(91)	Bagust et al 2001(170)	Brandle et al. 2007 (on version 3.3)(171)	Eastman et al. 1997a(172); Eastman et al. 1997b(172)	Brown 2000 (on version 3.0)(173)	Palmer et al. 2000a(174); Palmer et al. 2000b(89)	Eddy et al. 2003(175)	Mueller et al. 2006(176)
Basic model structure	15 Markov models using Monte Carlo micro-simulation plus a treatment sequence sub-model	Probabilistic discrete time illness-death Monte Carlo micro-simulation model based on 14 risk equations	Probabilistic discrete event Monte Carlo micro-simulation model	Deterministic Markov chain models	Markov model using simulation techniques	Markov type model using probabilistic Monte Carlo simulation techniques	Continuous, stochastic, Monte Carlo micro-simulation model	Deterministic Markov model using time-, state-, and diabetes type-dependent probabilities	A continuous micro-simulation model with equations representing human physiology and the effects of diseases.	An object-oriented, probabilistic, discrete event Markov model using Monte Carlo micro-simulation
Basic components	A series of interconnect-ted time-dependent modules representing patient characteristics clinical parameters, risk factors, treatment effects, complication-ns and economic parameters over time	UKPDS risk engine: an integrated system of parametric equations based on patient characteristics time-varying risk factors and the patient's history of complications to predict the occurrence and timing of seven complications and death	A complex treatment algorithm (up to six treatment regimes over patient's lifetime) in addition to the UKPDS Outcomes Model risk equations and algorithms	A series of interconnected sub models representing patient characteristic complication-s and treatment effects, arranged into two linked models: a metabolic model and an economic model	An epidemiologic al model accompany-ed by separate cost models and utility models	A model predicting rates of microvascular complications, cardiovascular disease, and mortality that reflect the natural history of the vascular and neuropathic complications of diabetes	A continuous micro-simulator constructed from continuous prediction equations	A series of sub models simulating the effect of different interventions on microvascular complications, macrovascular complications and on lactic acidosis and hypoglycaemia	Different equations representing the continuous changes and interactions of biological variables and object-oriented programming representing all aspects of a health-care system such as protocols, care processes, providers, visits, resources, and costs.	An epidemiological model based on risk equations and a health economic model

Population used to construct the model		Type 1 and type 2 diabetes in European countries	UKPDS participants	UKPDS participants	UKPDS and CORE-2 participants	A cohort of patients in Switzerland without long-term complications	Hypothetical patients with diabetes in the US population aged 25-74 years	Individuals with diabetes and representative diabetic populations	The model, initially developed for patients with type 1 diabetes, and was adapted to study type 2 diabetes (European)	Simulated people living simulated lives, sometimes developing simulated diabetes and/or its complications that match real population on designated variables	Type 1 and type 2 patients in European countries
Interventions incorporated		A given treatment sequence where up to 3 switches can be incorporated	A given intervention	A given treatment sequence where up to 6 switches can be incorporated	A given treatment sequence where the number of switches are not clear	Various management strategies for diabetes and for diabetes complications where the number of switches are not clear	A given treatment sequence where the number of switches are not clear	An unlimited database of specific drugs and non-drug treatments	Various management strategies for diabetes and for diabetes complications where the number of switches are not clear	Various management strategies including prevention programs, screening tests, diagnostic tests, treatments etc**	A given treatment sequence where up to 5 switches can be incorporated
Validation	**Internal***	√	√	X	√	√	√	Not clear	Not clear	√	√
	External*	√	√	X	X	√	X	Not clear	Not clear	√	√
Software used		C++; DATA™; Excel	Excel; C++	Excel	Excel	Delphi	Simulation software and Excel	Visual Basic on Windows	"C"	An object-oriented language (Smalltalk)	Delphi and C++ for Windows
Availability		With licence	With licence	Publication	Publication	Publication	Publication	Details online	Publication	Details online	Publication
User interface		Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes
Use for T2D drugs	**Published economic evaluations**	√	√	√	√	√	√	√	√	√	√
	HTA submissions	√	√	√	X	X	X	X	X	X	√

CORE = Centre for Outcomes Research Diabetes Model; **UKPDS** = United Kingdom Prospective Diabetes Study; **JADE** = Januvia Diabetes Economic Model; **DiDCT** = Diabetes Decision Analysis and Complications Type 2 Model; **DMM** = Diabetes Mellitus Model; **Eastman model** = the model developed by Eastman et al. (1997)[10,11]; **GDM** = Global Diabetes Model; **IMIB** = Institute for Medical Informatics and Biostatistics Model; **Accusim** = Diabetes Disease Management model; **EAGLE** = Economic Assessment of Glycemic Control and Long-Term-Effects of Diabetes Model. **HTA** = Health Technology Assessment.

* Internal validation refers to internal mathematical logic tests and debugging, and the extent to which a model is able to reproduce the results of the studies or datasets used to populate the model; external validation refers to the extent to which a model accurately predicts the results of studies that were not used to populate the model.

** Other interventions that the Archimedes model can incorporate are care processes and protocols, patient behaviours and compliance, provider behaviours and performance, variations in practice patterns, financial incentives, guidelines, and information systems

9.9 Appendix 9: UKPDS equations

Table 163: Equations used to estimate annual risk factor values from diagnosis of diabetes (based on panel/longitudinal data in the case of HbA1c, SBP and lipid ration, and on a logistic distribution in the case of smoking)

	Coefficient	Covariance matrix				
HbA1c						
		Alpha	Ln(Years since diagnosis)	Year 2 after diagnosis	Ln(HbA1c)	HbA1c(0)
Alpha	-0.02373257	0.130384048	0	0	0	0
Ln(Years since diagnosis)	0.14409963	0	0.09486833	0	0	0
Year 2 after diagnosis	-0.33304106	0	0	0.223606798	0	0
Lag(HbA1c)	0.75883104	0	0	0	0.063245553	0
HbA1c(0)	0.085162	0	0	0	0	0.063245553
SBP						
		Alpha	Ln(SBP)	SBP(0)	Ln(Years since diagnosis)	
Alpha	0.03017134	0.118321596	0	0	0	
Lag(SBP)	0.71715161	0	0.063245553	0	0	
SBP(0)	0.1272436	0	0	0.063245553	0	
Ln(Years since diagnosis)	0.03940557	0	0	0	0.089442719	
Lipid ratio						
		Alpha	Ln(Total cholesterol : HDL cholesterol	Ln(Total cholesterol : HDL cholesterol		

	Coefficient	Covariance matrix		
			ratio)	ratio(0))
Alpha	-0.021426	0.083666003	0	0
Ln(Total cholesterol : HDL cholesterol ratio)	0.52609729	0	0.070710678	0
Total cholesterol : HDL cholesterol ratio(0)	0.25225889	0	0	0.077459667

Smoking behaviour							
		Alpha	Current smoker	Smoking(baseline)	Year after diagnosis	Age	Female
Alpha	-4.02	0.485798312	0	0	0	0	0
Current smoker	1.878	0	0.459347363	0	0	0	0
Smoking(0)	4.879	0	0	0.702851336	0	0	0
Year	-0.203	0	0	0	0.154919334	0	0
Age	-0.027	0	0	0	0	0.089442719	0
Female	-0.489	0	0	0	0	0	0.392428337

HbA1c = glycated haemoglobin; HDL = high density lipoprotein; SBP = systolic blood pressure

Table 164: Equations to estimate the probability of diabetes-related complications (based on Weibull distributions)

Parameter	Coefficient	Covariance matrix						
IHD								
		Lambda	Delta	Age at diagnosis	Female	HbA1c	SBP	Ln(Total cholesterol : HDL cholesterol ratio)
Lambda	-5.31	0.166915108	-0.049048144	0.000407848	-0.020217267	0.00099701	-0.001680079	-0.003704772
Delta	1.15	-0.049048144	0.044544751	-0.000963292	-0.004326761	-0.005051097	-0.004482312	-0.005315472
Age at diagnosis	0.031	0.000407848	-0.000963292	0.007867604	-0.000616564	0.000708049	-0.002486266	0.00044072
Female	-0.471	-0.020217267	-0.004326761	-0.000616564	0.137694943	-0.002177805	-0.005904058	0.008253796
HbA1c	0.125	0.00099701	-0.005051097	0.000708049	-0.002177805	0.034667449	0.000707812	0.002946898
SBP	0.098	-0.001680079	-0.004482312	-0.002486266	-0.005904058	0.000707812	0.035295837	-0.003006777
Ln(Total cholesterol : HDL cholesterol ratio)	1.498	-0.003704772	-0.005315472	0.00044072	0.008253796	0.002946898	-0.003006777	0.207480795

MI												
		Lambda	Delta	Age at diagnosis	Female	Afro-Caribbean	Smoker	HbA1c	SBP	Ln(Total cholesterol : HDL cholesterol ratio)	IHD	CHF
Lambda	-4.977	0.148752893	-0.044814919	-0.001055088	-0.001055088	-0.017203519	-0.011994516	-0.013438336	-0.000780686	-0.00156795	-0.002758241	0.004452208
Delta	1.257	-0.044814919	0.036359995	-	-	-	0.002094541	-	-	-	-	-

Parameter	Coefficient		Covariance matrix									
				0.000848302	0.000848302	0.001322665		0.003540547	0.001643991	0.002046092	0.002214394	0.007737944
Age at diagnosis	0.055	-0.001055088	-0.000848302	0.004107477	0.004107477	-0.000373154	-6.66295E-05	7.93623E-05	0.000548542	-0.001727462	0.000253743	-0.00090053
Female	-0.826	-0.001055088	-0.000848302	0.004107477	0.004107477	-0.000373154	-6.66295E-05	7.93623E-05	0.000548542	-0.001727462	0.000253743	-0.00090053
Afro-Caribbean	-1.312	-0.017203519	-0.001322665	-0.000373154	-0.000373154	0.101734098	0.004886433	-0.003652307	-0.001423243	-0.002688831	-0.005158701	0.003611815
Smoker	0.346	-0.011994516	0.002094541	-6.66295E-05	-6.66295E-05	0.004886433	0.369562195	-0.003101621	-0.000520943	-0.00026376	0.021321072	0.006626725
HbA1c	0.118	-0.013438336	-0.003540547	7.93623E-05	7.93623E-05	-0.003652307	-0.003101621	0.093491029	5.51267E-05	5.92942E-05	-0.006097192	-0.002115608
SBP	0.101	-0.000780686	-0.001643991	0.000548542	0.000548542	-0.001423243	-0.000520943	5.51267E-05	0.023603299	-0.00025027	-0.002466825	-0.001808707
Ln(Total cholesterol : HDL cholesterol ratio)	1.19	-0.00156795	-0.002046092	-0.001727462	-0.001727462	-0.002688831	-0.00026376	5.92942E-05	-0.00025027	0.025760485	0.000786584	0.000563868
IHD	0.914	-0.002758241	-0.002214394	0.000253743	0.000253743	-0.005158701	0.021321072	-0.006097192	-0.002466825	0.000786584	0.165474267	-0.009875004
CHF	1.558	0.004452208	-0.007737944	-0.00090053	-0.00090053	0.003611815	0.006626725	-0.002115608	-0.001808707	0.000563868	-0.009875004	0.14265571

CHF						
		Lambda	Delta	Age at diagnosis	BMI	HbA1c	SBP
Lambda	-8.018	0.426592871	-0.140285334	-0.005070715	-0.002712017	-0.004830645	-0.001325083
Delta	1.711	-0.140285334	0.102982345	-0.004473011	-0.002335246	-0.004944051	-0.008321523
Age at diagnosis	0.093	-0.005070715	-0.004473011	0.014052164	0.001469463	0.00056281	-0.005242293
BMI	0.066	-0.002712017	-0.002335246	0.001469463	0.017891735	-0.003450657	-0.002453781
HbA1c	0.157	-0.004830645	-	0.00056281	-	0.055245284	6.34131E-05

Parameter	Coefficient		Covariance matrix								
			0.004944051		0.003450657						
SBP	0.114	-0.001325083	-0.008321523	-0.005242293	-0.002453781	6.34131E-05	0.060355801				

Stroke											
		Lambda	Delta	Age	Female	Smoker	Atrial fibrillation	HbA1c	SBP	Total cholesterol : HDL cholesterol ratio	CHF
Lambda	-7.163	0.326497364	-0.097626309	-0.003136399	-0.003136399	-0.02750949	-0.03464953	-0.014061373	0.000342279	-0.007508124	-0.003288164
Delta	1.497	-0.097626309	0.078848498	-0.00421443	-0.00421443	-0.008143581	-0.000932147	0.003287632	-0.006509032	-0.00513528	-0.000472609
Age at diagnosis	0.085	-0.003136399	-0.00421443	0.008607951	0.008607951	0.000700867	-0.00098465	0.00052066	0.000813865	-0.003844194	0.000606534
Female	-0.516	-0.003136399	-0.00421443	0.008607951	0.008607951	0.000700867	-0.00098465	0.00052066	0.000813865	-0.003844194	0.000606534
Smoker	0.355	-0.02750949	-0.008143581	0.000700867	0.000700867	0.17045739	0.012064357	-0.007118853	-0.002688707	-0.008147929	0.001880166
Atrial fibrillation	1.428	-0.03464953	-0.000932147	-0.00098465	-0.00098465	0.012064357	0.169648652	-0.003278547	0.002539336	0.000487604	-0.0030616
HbA1c	0.128	-0.014061373	0.003287632	0.00052066	0.00052066	-0.007118853	-0.003278547	1.411131995	0.000491733	0.002461566	0.003172595
SBP	0.276	0.000342279	-0.006509032	0.000813865	0.000813865	-0.002688707	0.002539336	0.000491733	0.041080378	-0.000114327	-0.001828078
Total cholesterol : HDL cholesterol ratio	0.113	-0.007508124	-0.00513528	-0.003844194	-0.003844194	-0.008147929	0.000487604	0.002461566	-0.000114327	0.043004169	-0.002588405
CHF	1.742	-0.003288164	-0.000472609	0.000606534	0.000606534	0.001880166	-0.0030616	0.003172595	-0.001828078	-0.002588405	0.04131839

Parameter	Coefficient	Covariance matrix					
Amputation							
		Lambda	Delta	PVD	HbA1c	SBP	Blind
Lambda	-8.718	0.640751673	-0.200949517	0.153297658	-0.023057203	-0.01434599	-0.020321297
Delta	1.451	-0.200949517	0.153061117	-0.063897249	-0.013393468	-0.009167305	-0.013333083
PVD	2.436	0.153297658	-0.063897249	1.495543544	0.00268966	-0.008477884	-0.005933272
HbA1c	0.435	-0.023057203	-0.013393468	0.00268966	0.061246614	0.003828987	0.008329385
SBP	0.228	-0.01434599	-0.009167305	-0.008477884	0.003828987	0.07394117	-0.00437163
Blind	1.812	-0.020321297	-0.013333083	-0.005933272	0.008329385	-0.00437163	0.73088977
Blind							
		Lambda	Delta	Age at diagnosis	HbA1c		
Lambda	-6.464	0.327020585	-0.101182796	-0.005807573	-0.010697928		
Delta	1.154	-0.101182796	0.076130519	-0.002782536	-0.003246959		
Age at diagnosis	0.069	-0.005807573	-0.002782536	0.013072986	-0.000404637		
HbA1c	0.221	-0.010697928	-0.003246959	-0.000404637	0.049675375		
Renal							
		Lambda	Delta	SBP	Blind		
Lambda	-10.016	0.959693126	-0.333190497	-0.003771542	0.008235651		

Parameter	Coefficient		Covariance matrix		
Delta	1.865	-0.333190497	0.238775613	-0.038038463	-0.009363722
SBP	0.404	-0.003771542	-0.038038463	0.103252019	-0.005000735
Blind	2.082	0.008235651	-0.009363722	-0.005000735	2.271038952

It should be noted that for the transformation applied to the term Ln (Total cholesterol: HDL cholesterol ratio), included in the IHD and CHF equations, instead of estimating it as:
log(total:hdl – 5.23)
it was conducted in the following way:
log (TOTAL:HDL) – log(5.23)
since otherwise it could result in the model attempting to evaluate the logarithm of a negative number, which would result in a model error (similarly to what was reported by the Decision Support Unit evaluating the pharmacoeconomic model presented in the dapagliflozin submission). (Davies, S. A review of the Bristol_Myers Squibb/Astrazeneca economic model on the cost-effectiveness of dapagliflozin. Report by the Decision Support Unit, November 2012. Available at: http://www.nicedsu.org.uk/Dapagliflozin%20DSU%20final%20report%20Nov%202012% 20(NICE%20version).pdf; accessed on: 25th October 2013.)
For validation, the main author of the paper reporting the UKPDS system of risk equations, Prof Philips Clarke, was contacted, and it was confirmed that the transformation conducted was appropriate (personal communication on 14/02/2013).
BMI = body mass index; CHF= congestive heart failure; HbA1c = glycated haemoglobin; HDL = high density lipoprotein; MI = myocardial infarction; PVD= peripheral vascular disease; SBP = systolic blood pressure

Table 165: Equations to estimate the probability of mortality (based on a logistic distribution in the case of event-related death and a Gompert distribution in the cases of diabetes-related death and other death

Parameter	Coefficient	Covariance matrix				
Event-related death						
		Lambda	HbA1c	MI last year	Stroke last year	Ln(Age at event)
Lambda	-3.251	0.247990842	-0.011199427	-0.175611786	-0.13416797	-0.115452442
HbA1c	0.114	-0.011199427	0.050417312	0.003451768	0.003667002	0.001079304
MI last year	2.64	-0.175611786	0.003451768	0.255077535	0.132569418	0.011398089
Stroke last year	1.048	-0.13416797	0.003667002	0.132569418	0.382297725	-0.031201682
Ln(Age at event)	2.772	-0.115452442	0.001079304	0.011398089	-0.031201682	0.730316073

Diabetes-related death										
		Lambda	Delta	Total cholesterol : HDL cholesterol ratio	MI within last year	MI > 1 year ago	Stroke last year	Renal	Amputation	Ln(Age at event)
Lambda	-5.124	0.290491218	-0.024244169	-0.007148449	-0.094797247	-0.099555971	0.016691978	-0.026365658	-0.045892087	-0.229868208
Delta	0.003	-0.024244169	0.030416017	-0.002302342	-0.001975796	-0.010252499	-0.004593418	-0.003328947	-0.009611326	0.000197322
Total cholesterol : HDL cholesterol ratio	0.109	-0.007148449	-0.002302342	0.051278794	-0.003016024	-0.008642042	-0.00028877	-0.003320973	0.004721395	0.005416553
MI within last year	3.939	-0.094797247	-0.001975796	-0.003016024	0.263650346	0.091390987	0.003764677	-0.01326561	0.028762997	-0.04383947
MI > 1 year ago	1.119	-0.099555971	-0.010252499	-0.008642042	0.091390987	0.254089646	-0.012151518	0.023209446	0.047056467	0.024403449

Parameter	Coefficient	Covariance matrix								
Stroke last year	2.807	0.016691978	-0.004593418	-0.00028877	0.003764677	-0.012151518	0.661615282	-0.001127228	-0.013716166	-0.052270169
Renal	1.585	-0.026365658	-0.003328947	-0.003320973	-0.01326561	0.023209446	-0.001127228	0.364717292	0.039533624	-0.001943068
Amputation	1.032	-0.045892087	-0.009611326	0.004721395	0.028762997	0.047056467	-0.013716166	0.039533624	0.404524826	0.054105865
Ln(Age at event)	4.731	-0.229868208	0.000197322	0.005416553	-0.04383947	0.024403449	-0.052270169	-0.001943068	0.054105865	1.096705995

Other death						
		Lambda	Delta	Age*Female	Age*(1-Female)	Smoker
Lambda	-6.373	0.154450486	-0.012207094	-0.004272579	-0.003496795	-0.036946091
Delta	0.154	-0.012207094	0.009338349	-0.001823669	-0.002034344	0.000358839
Age*Female	0.081	-0.004272579	-0.001823669	0.013773284	0.001082692	0.001116123
Age*(1-Female)	0.104	-0.003496795	-0.002034344	0.001082692	0.012205782	-0.000695372
Smoker	0.307	-0.036946091	0.000358839	0.001116123	-0.000695372	0.141373733

HbA1c = glycated haemoglobin; HDL = high density lipoprotein; MI = myocardial infarction

9.10 Appendix 10: Clinical outcomes over time

Figure 40: Dual therapy – Metformin - HbA1c level over time:

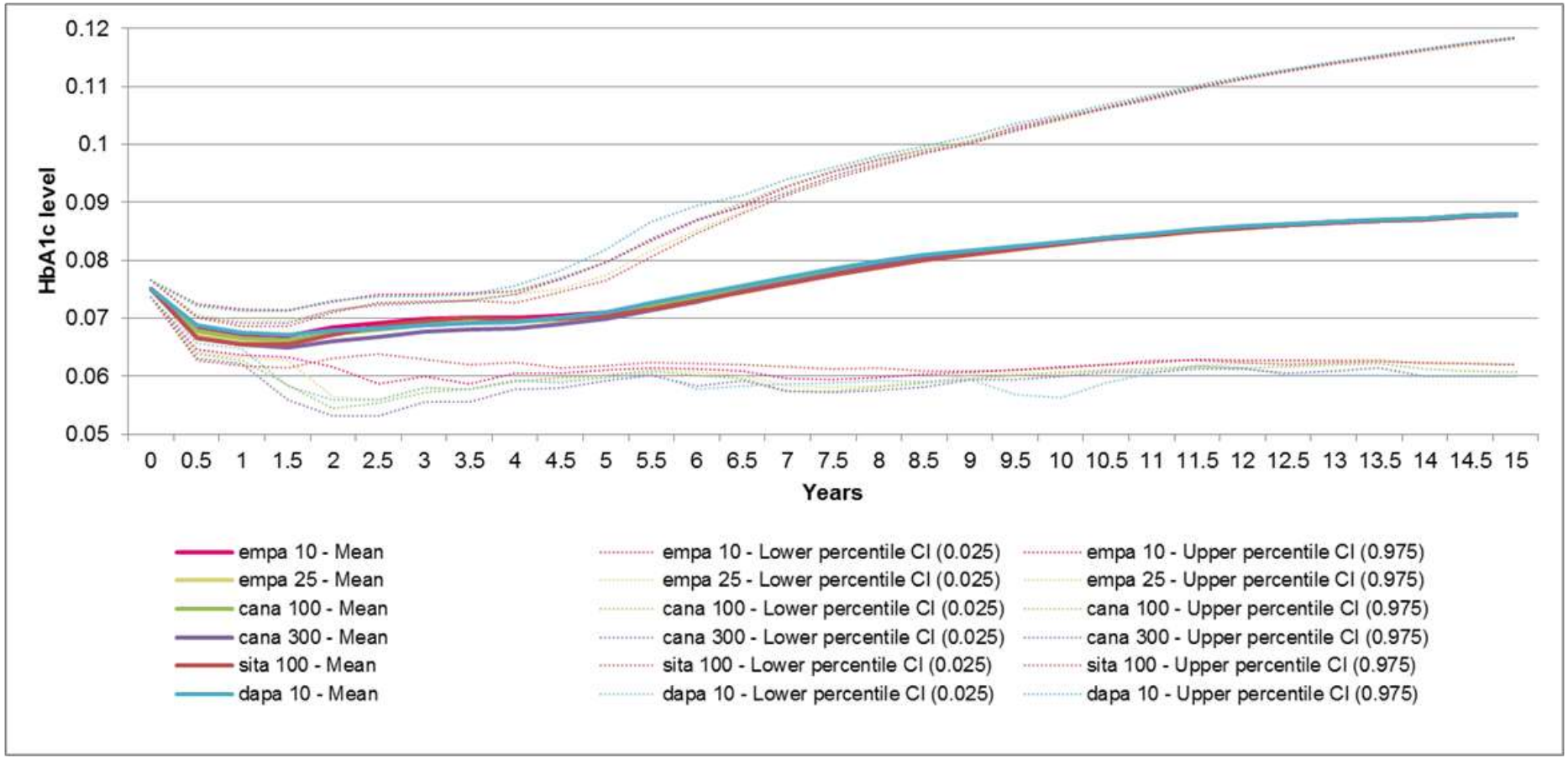


Figure 41: Dual therapy – Metformin – Systolic Blood Pressure

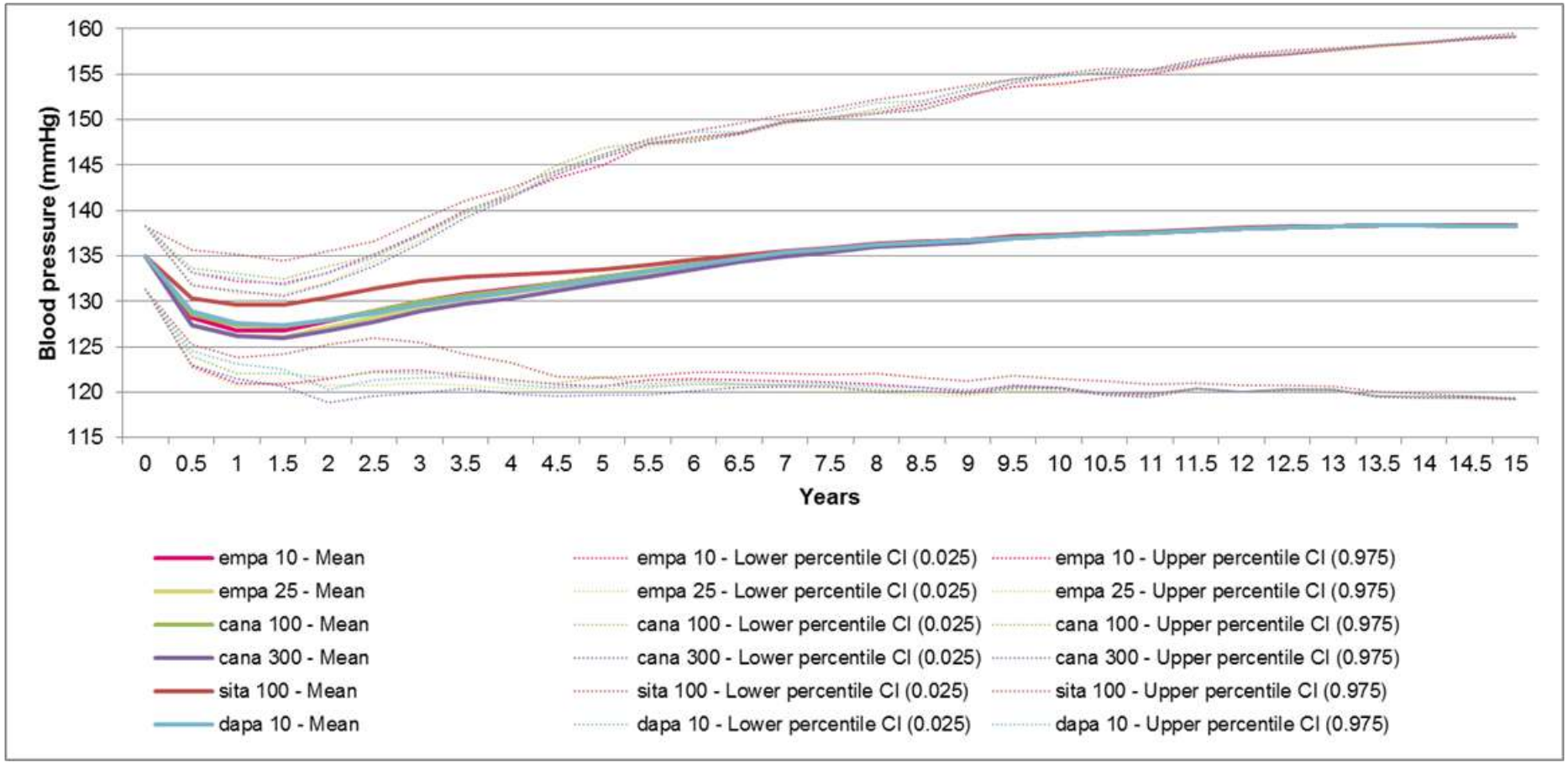
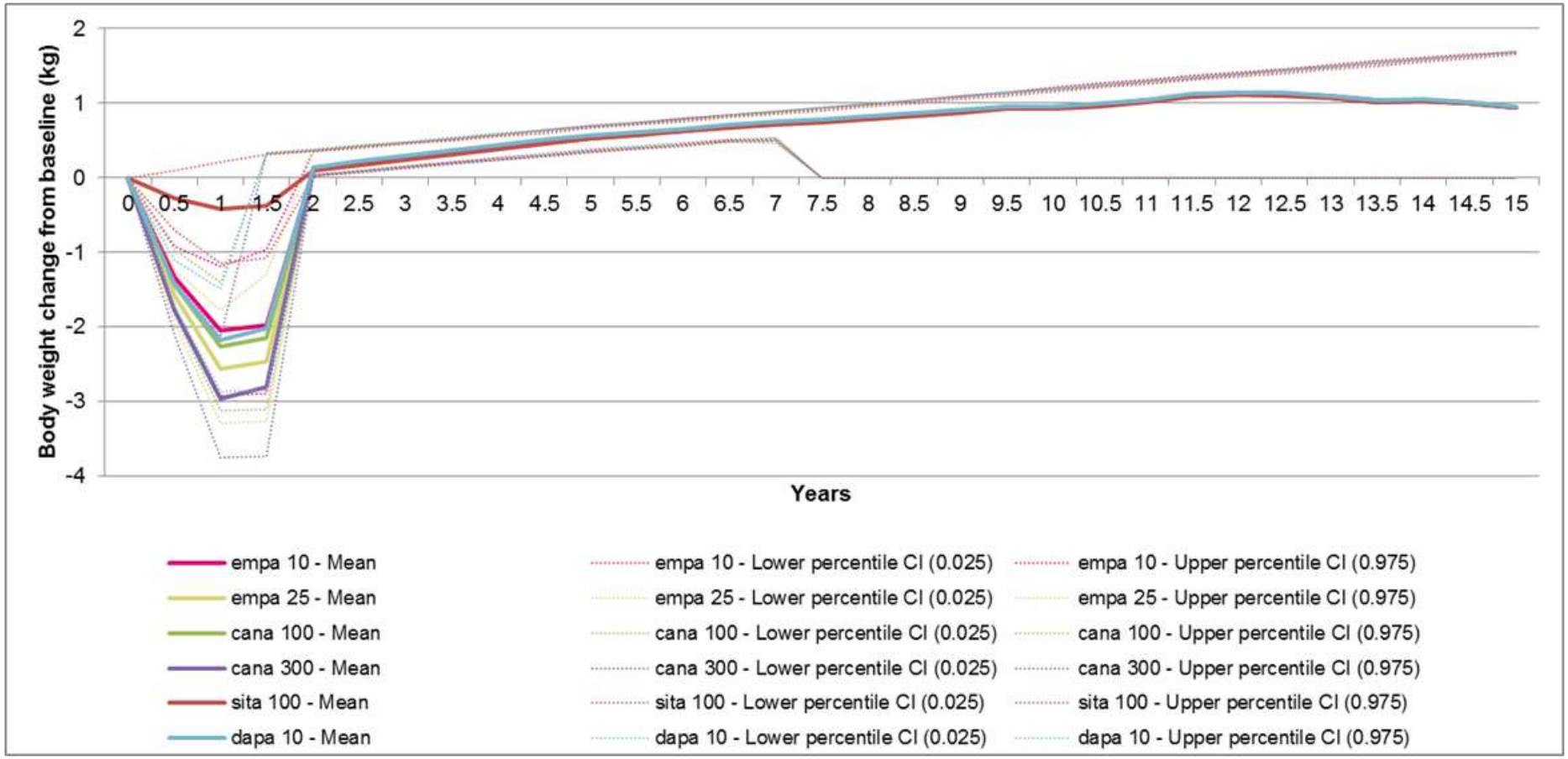


Figure 42: Dual therapy – Metformin – Weight



Triple therapy – metformin and SU

Figure 43: Triple therapy – Metformin and SU - HbA1c level over time

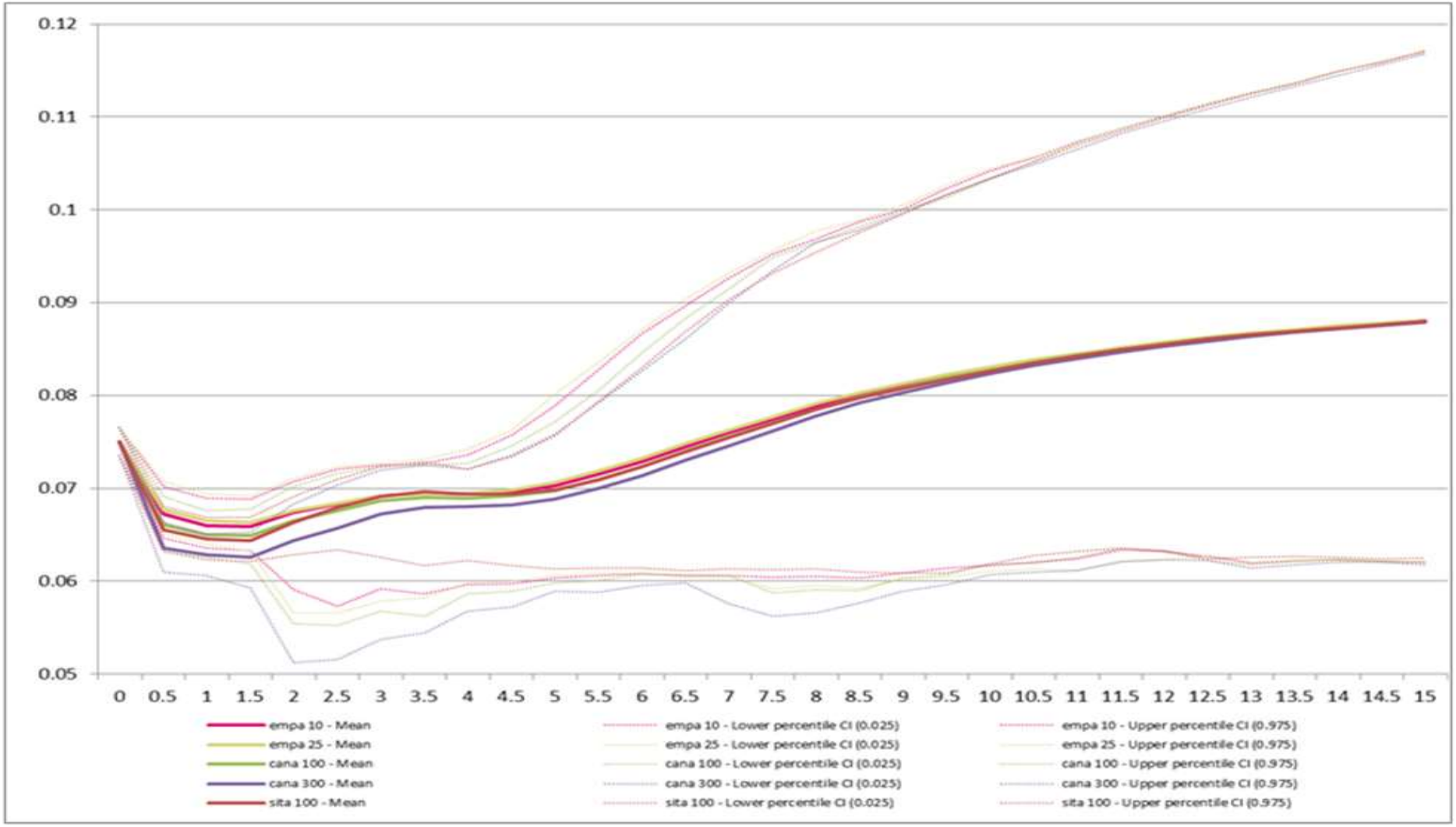


Figure 44: Metformin and SU – SBP over time

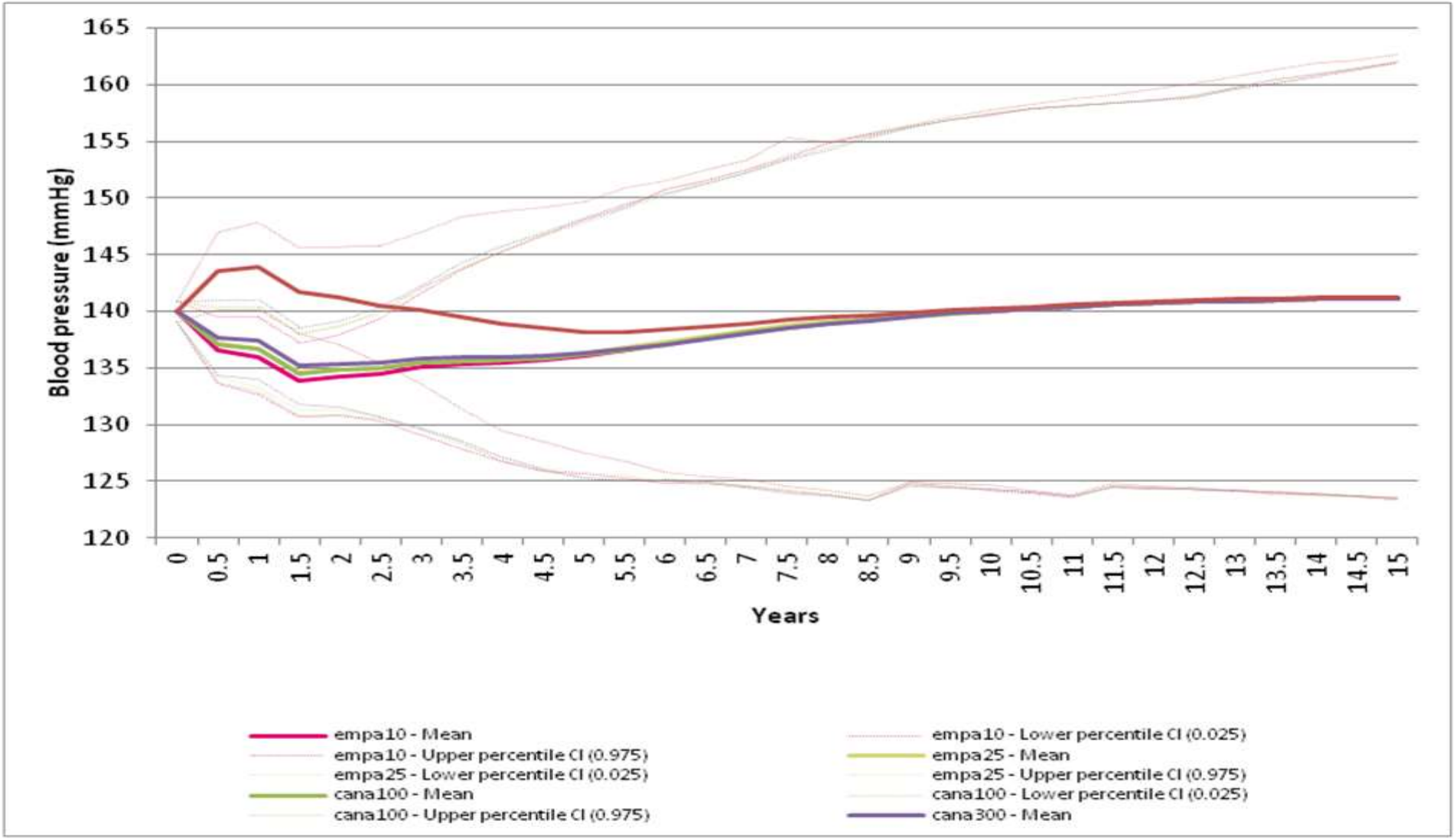
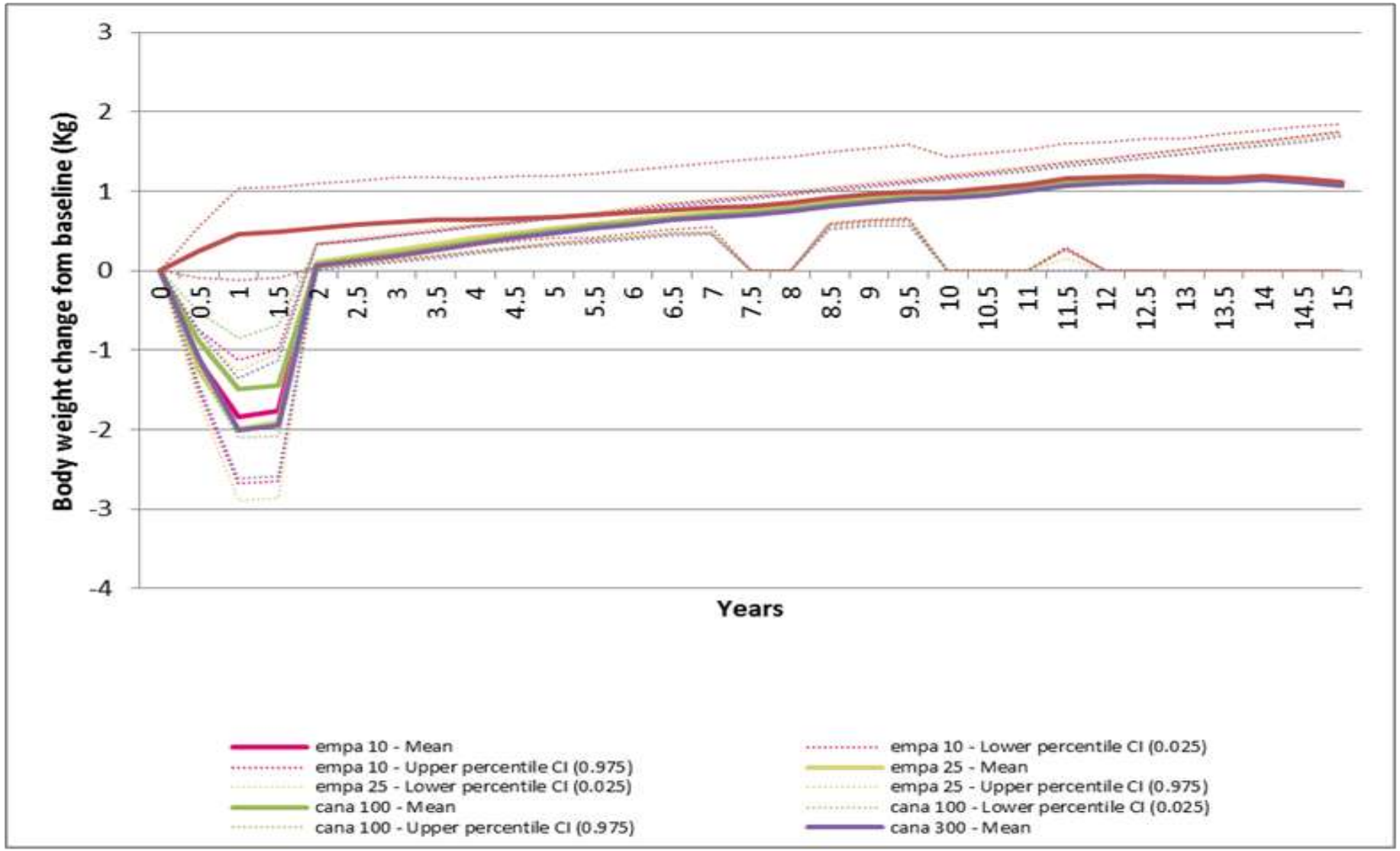


Figure 45: Triple therapy – Metformin and SU – Weight over time



Triple therapy – metformin and TZD

Figure 46: Triple therapy – metformin and TZD - HbA1c level over time

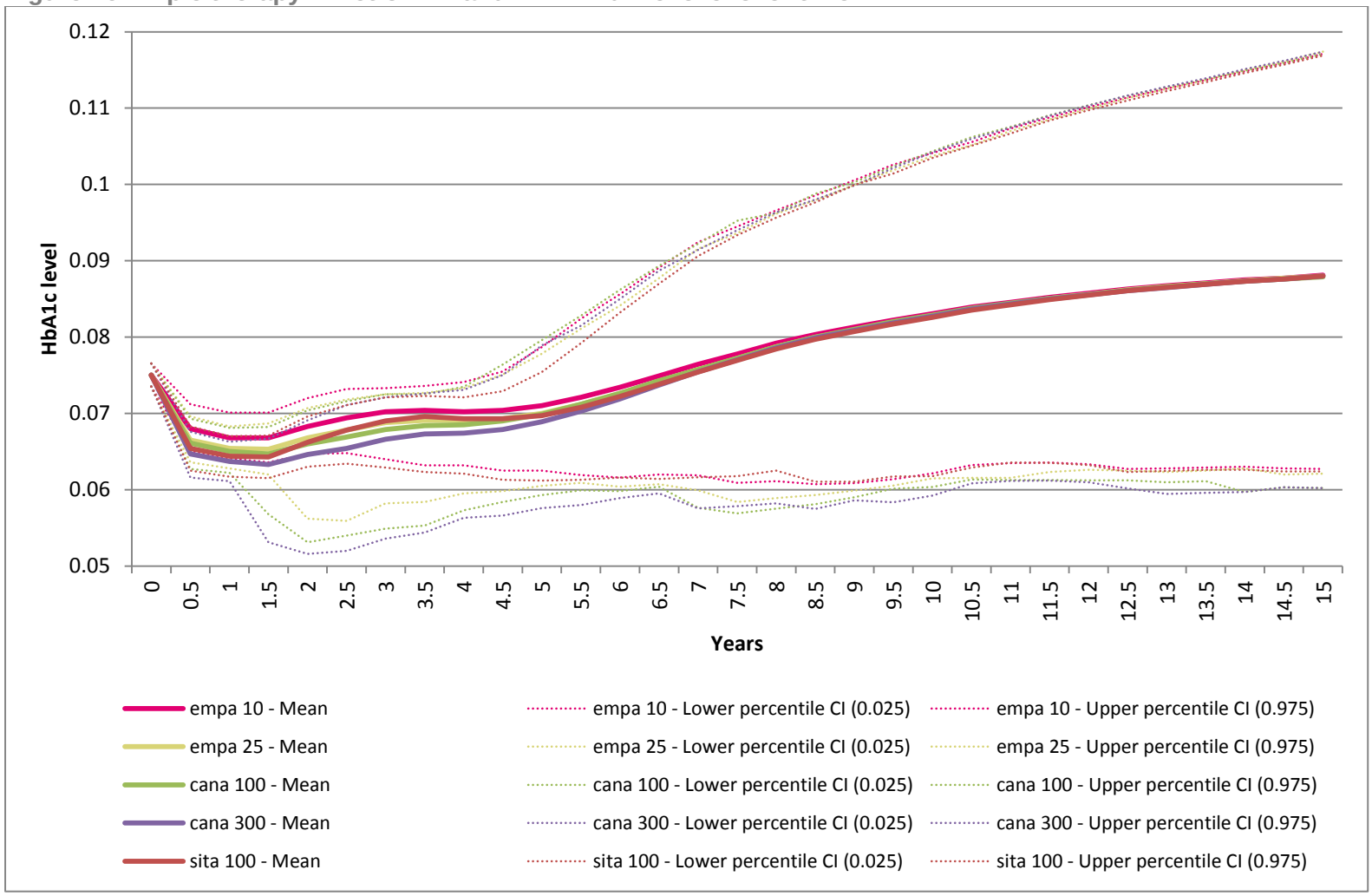


Figure 47: Triple therapy – metformin and TZD – SBP over time

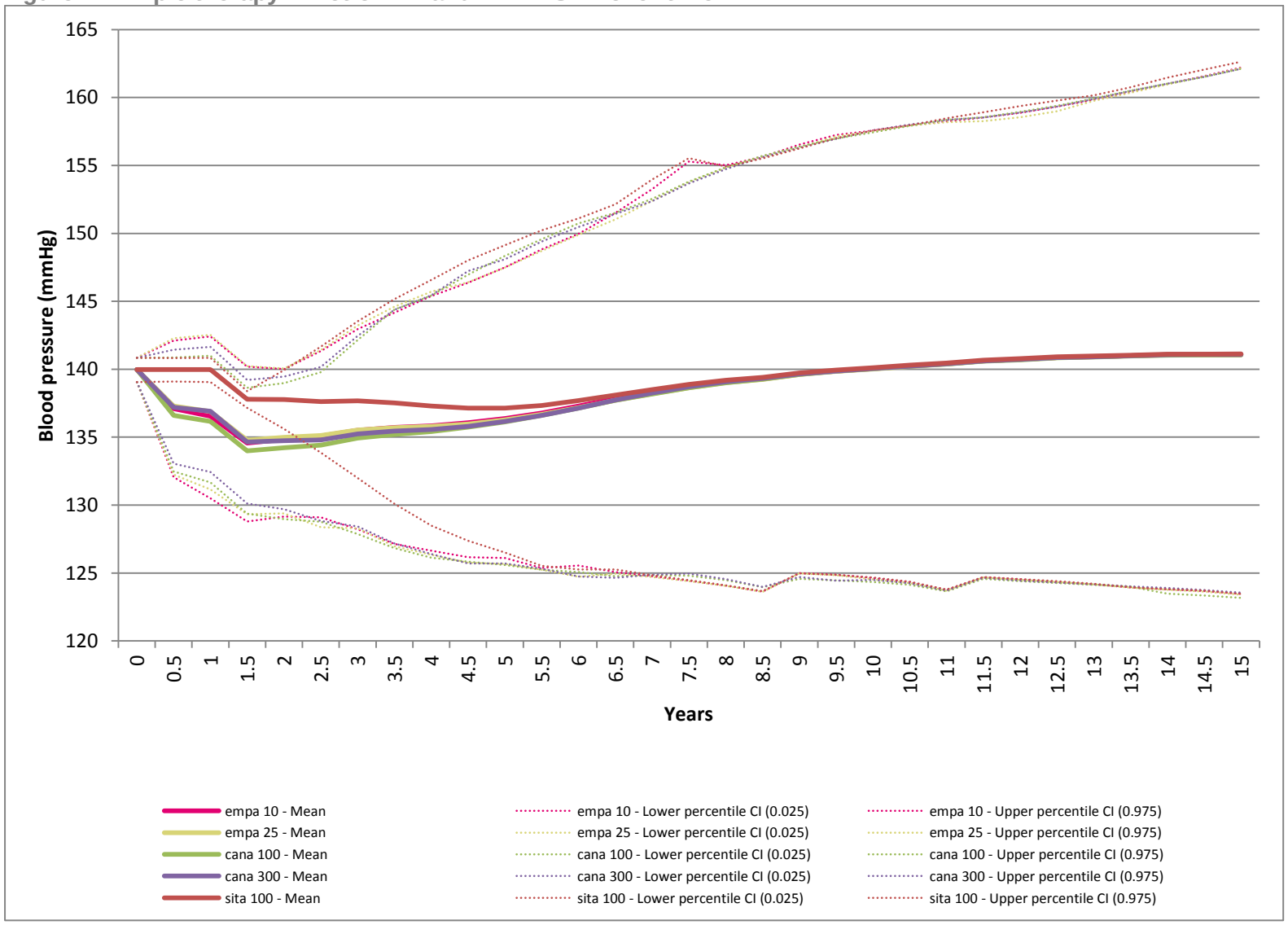
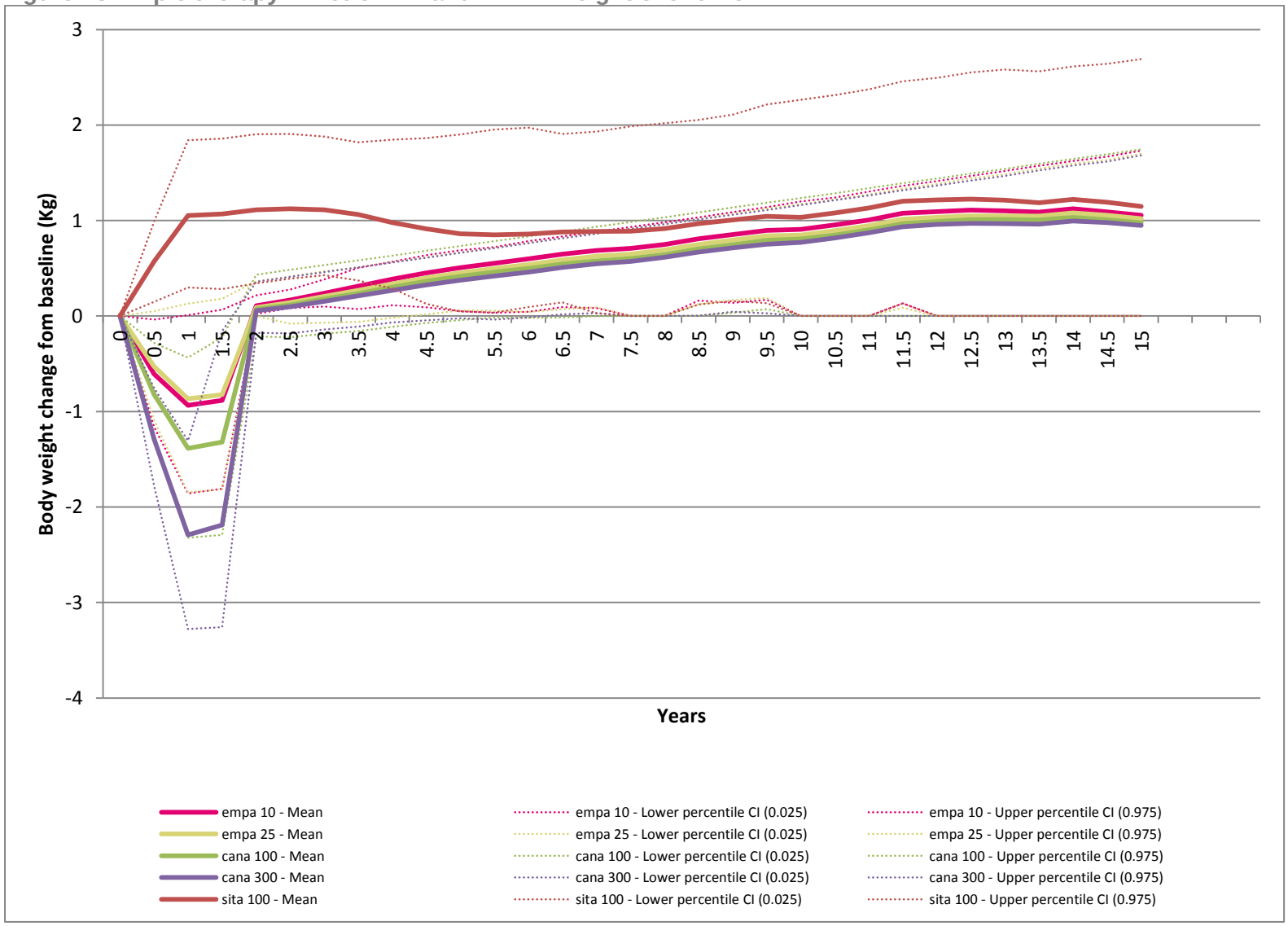


Figure 48: Triple therapy – metformin and TZD – Weight over time



Insulin combination

Figure 49: Insulin combination - HbA1c level over time

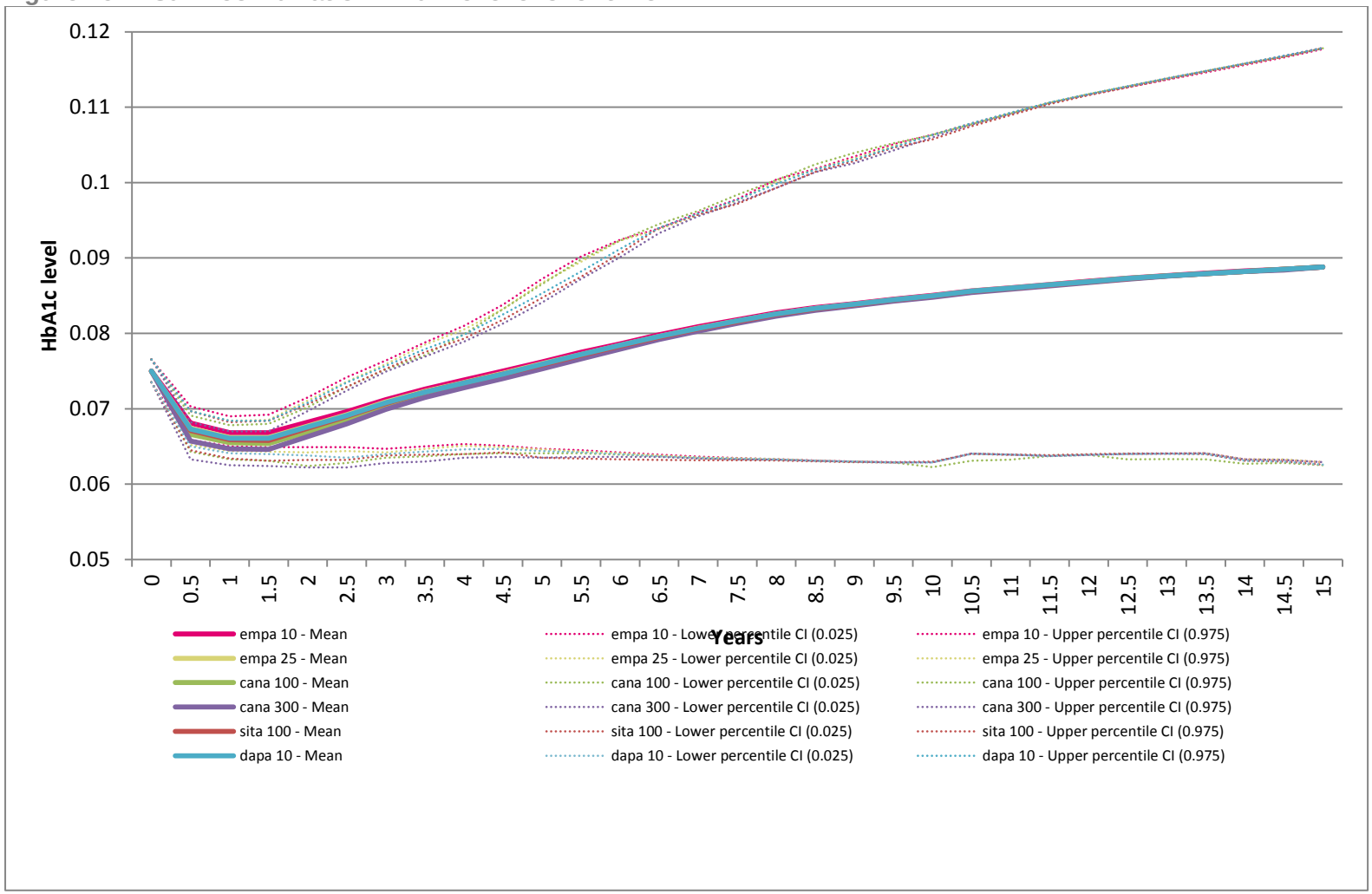


Figure 50: Insulin combination – SBP over time

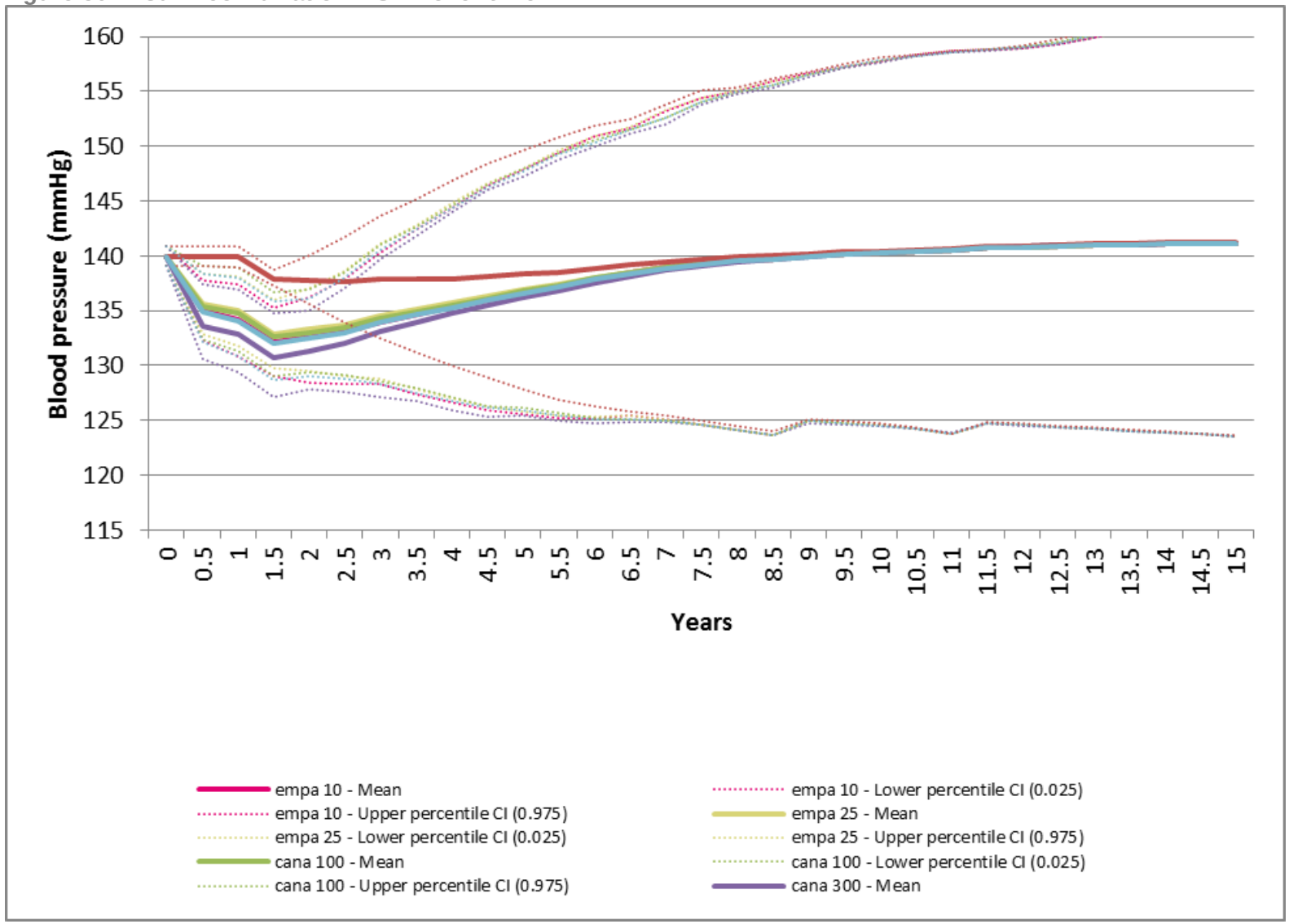
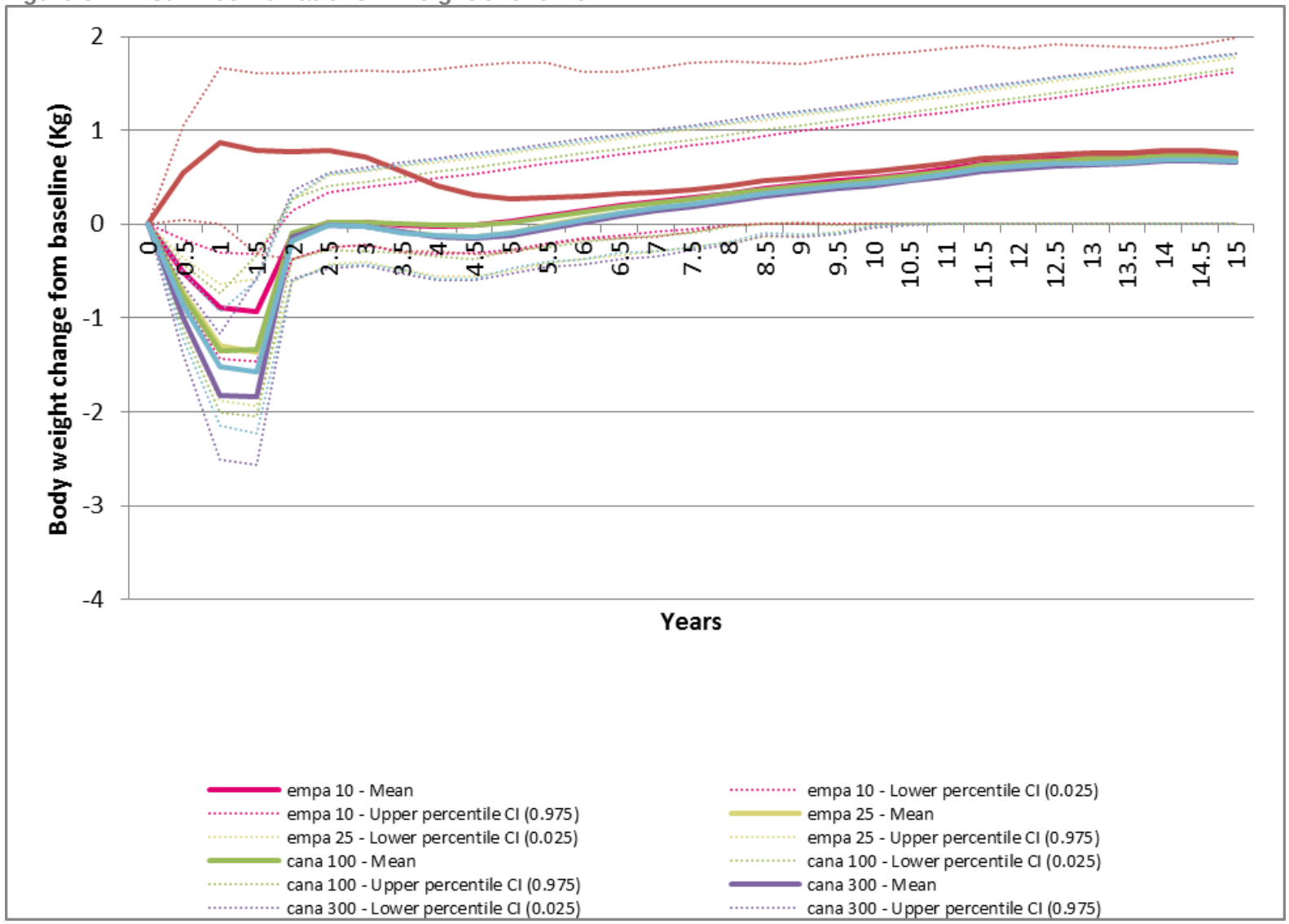


Figure 51: Insulin combinations – Weight over time



9.11 Appendix 11: Sensitivity analysis

Table 166: The sensitivity analysis for dual therapy

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Base case	Met + Sitagliptin 100 mg	7.425	-	£32,046	-	-
	Met + Dapagliflozin 10 mg	7.404	-0.021	£32,179	£133	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
	Met + Empagliflozin 10 mg	7.424	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Utilities Sullivan et al	Met + Sitagliptin 100 mg	7.479	-	£32,046	-	-
	Met + Dapagliflozin 10 mg	7.460	-0.019	£32,179	£133	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	7.490	0.011	£32,353	£307	£27,945
	Met+ Empagliflozin 10 mg	7.481	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Utilities Sullivan et al, age related	Met + Sitagliptin 100 mg	6.416	-	£32,046	-	-
	Met + Dapagliflozin 10 mg	6.400	-0.016	£32,179	£133	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	6.425	0.009	£32,353	£307	£34,156
	Met+ Empagliflozin 10 mg	6.417	-0.008	£32,654	£ 301	Dominated by empagliflozin 25 mg
BMI	Met + Sitagliptin 100 mg	7.432	-	£32,022	-	-
	Met + Dapagliflozin 10 mg	7.411	-0.021	£32,183	£161	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	7.440	0.008	£32,349	£327	£40,825
	Met + Empagliflozin 10 mg	7.432	-0.008	£32,644	£295	Dominated by empagliflozin 25 mg
Weight changes	Met + Sitagliptin 100 mg	7.425	-	£32,036	-	-
	Met + Dapagliflozin 10 mg	7.404	-0.021	£32,130	£94	Dominated by sitagliptin 100 mg

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
	Met + Empagliflozin 25 mg	7.434	0.009	£32,320	£284	£31,589
	Met + Empagliflozin 10 mg	7.425	-0.009	£32,617	£296	Dominated by empagliflozin 25 mg
Number of AEs	Met + Sitagliptin 100 mg	7.426	-	£32,045	-	-
	Met + Dapagliflozin 10 mg	7.414	-0.012	£32,173	£128	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	7.441	0.015	£32,349	£305	£20,300
	Met + Empagliflozin 10 mg	7.433	-0.008	£32,650	£301	Dominated by empagliflozin 25 mg
Discontinuation rates	Met + Sitagliptin 100 mg	7.424	-	£31,872	-	-
	Met + Empagliflozin 25 mg	7.437	0.013	£32,354	£482	£37,077
	Met + Dapagliflozin 10 mg	7.419	-0.005	£32,635	£763	Dominated by empagliflozin 25 mg
	Met + Empagliflozin 10 mg	7.424	-0.013	£32,654	£300	Dominated by empagliflozin 25 mg
10-year time horizon	Met + Sitagliptin 100 mg	5.472	-	£18,758	-	-
	Met + Dapagliflozin 10 mg	5.461	-0.011	£18,936	£178	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	5.475	0.003	£18,968	£210	£69,900
	Met + Empagliflozin 10 mg	5.466	-0.009	£19,209	£241	Dominated by empagliflozin 25 mg
Discount rate 0%	Met + Sitagliptin 100 mg	9.466	-	£44,215	-	-
	Met + Dapagliflozin 10 mg	9.436	-0.030	£44,323	£108	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	9.479	0.013	£44,611	£396	£30,469
	Met + Empagliflozin 10 mg	9.469	-0.010	£44,990	£378	Dominated by empagliflozin 25 mg
Discount rate 6%	Met + Sitagliptin 100 mg	6.405	-	£26,282	-	-
	Met + Dapagliflozin 10 mg	6.388	-0.017	£26,426	£144	Dominated by sitagliptin 100 mg

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
	Met + Empagliflozin 25 mg	6.412	0.007	£26,547	£265	£37,871
	Met + Empagliflozin 10 mg	6.403	-0.009	£26,808	£261	Dominated by empagliflozin 25 mg
Duration treatment effect	Met + Sitagliptin 100 mg	7.465	-	£31,820	-	-
	Met + Dapagliflozin 10 mg	7.424	-0.041	£31,848	£28	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 25 mg	7.463	-0.002	£32,090	£271	Dominated by sitagliptin 100 mg
	Met + Empagliflozin 10 mg	7.456	-0.009	£32,410	£590	Dominated by sitagliptin 100 mg

AE = adverse events; BMI = body mass index; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

Table 167: The sensitivity analysis for Metformin plus SU

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Base case	Met + SU + Sitagliptin 100 mg	6.959	-	£31,365	-	-
	Met + SU + Empagliflozin 10 mg	6.991	0.032	£31,409	£44	£1,372
	Met + SU + Empagliflozin 25 mg	6.978	-0.013	£31,557	£148	Dominated by empagliflozin 10 mg
Utilities Sullivan et al	Met + SU + Sitagliptin 100 mg	7.013	-	£31,365	-	-
	Met + SU + Empagliflozin 10 mg	7.045	0.032	£31,409	£44	£1,372
	Met + SU + Empagliflozin 25 mg	7.034	-0.011	£31,557	£148	Dominated by empagliflozin 10 mg
Utilities Sullivan et al, age related	Met + SU + Sitagliptin 100 mg	6.011	-	£31,365	-	-
	Met + SU + Empagliflozin 10 mg	6.040	0.029	£31,409	£44	£1,514
	Met + SU + Empagliflozin 25 mg	6.030	-0.010	£31,557	£148	Dominated by emapgliflozin 10 mg

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
BMI	Met + SU + Sitagliptin 100 mg	6.972	-	£31,348	-	-
	Met + SU + Empagliflozin 10 mg	6.998	0.026	£31,426	£78	£3,004
	Met + SU + Empagliflozin 25 mg	6.985	-0.013	£31,580	£155	Dominated by empagliflozin 10 mg
Weight changes	Met + SU + Sitagliptin 100 mg	6.958	-	£31,373	-	-
	Met + SU + Empagliflozin 10 mg	6.992	0.034	£31,377	£4	£112
	Met + SU + Empagliflozin 25 mg	6.979	-0.013	£31,541	£165	Dominated by empagliflozin 10 mg
Number of AEs	Met + SU + Sitagliptin 100 mg	6.960	-	£31,364	-	-
	Met + SU + Empagliflozin 10 mg	6.993	0.033	£31,407	£44	£1,321
	Met + SU + Empagliflozin 25 mg	6.985	-0.008	£31,555	£148	Dominated by empagliflozin 10 mg
Discontinuation rates	Met + SU + Sitagliptin 100 mg	6.954	-	£31,166	-	-
	Met + SU + Empagliflozin 10 mg	6.991	0.037	£31,409	£243	£6,554
	Met + SU + Empagliflozin 25 mg	6.982	-0.009	£31,523	£115	Dominated by empagliflozin 10 mg
10-year time horizon	Met + SU + Sitagliptin 100 mg	5.254	-	£19,103	-	-
	Met + SU + Empagliflozin 10 mg	5.278	0.024	£19,133	£30	£1,262
	Met + SU + Empagliflozin 25 mg	5.270	-0.008	£19,219	£85	Dominated by empagliflozin 10 mg
Discount rate 0%	Met + SU + Sitagliptin 100 mg	8.800	-	£42,819	-	-
	Met + SU + Empagliflozin 10 mg	8.841	0.041	£42,875	£55	£1,346
	Met + SU + Empagliflozin 25 mg	8.823	-0.018	£43,072	£198	Dominated by empagliflozin 10 mg
Discount rate 6%	Met + SU + Sitagliptin 100 mg	6.036	-	£25,900	-	-
	Met + SU + Empagliflozin 10 mg	6.063	0.027	£25,941	£41	£1,522
	Met + SU + Empagliflozin 25 mg	6.053	-0.010	£26,065	£124	Dominated by empagliflozin 10 mg

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Duration treatment effect	Met + SU + Sitagliptin 100 mg	6.998	-	£31,094	-	-
	Met + SU + Empagliflozin 10 mg	7.025	0.027	£31,201	£107	£3,959
	Met + SU + Empagliflozin 25 mg	7.008	-0.017	£31,281	£81	Dominated by empagliflozin 10 mg

AE = adverse events; BMI = body mass index; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SU = sulphonylureas

Table 168:The sensitivity analysis for Metformin plus TZD

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Base case	Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	£-	-
	Met + TZD + Empagliflozin 25 mg	6.999	0.032	£31,486	£183	£5,725
	Met + TZD + Empagliflozin 10 mg	6.996	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg
Utilities Sullivan et al	Met + TZD + Sitagliptin 100 mg	7.021	-	£31,303	-	-
	Met + TZD + Empagliflozin 25 mg	7.054	0.033	£31,486	£183	£5,552
	Met + TZD + Empagliflozin 10 mg	7.050	-0.004	£31,869	£383	Dominated by empagliflozin 25 mg
Utilities Sullivan et al, age related	Met + TZD + Sitagliptin 100 mg	6.018	-	£31,303	-	-
	Met + TZD + Empagliflozin 25 mg	6.048	0.030	£31,486	£183	£6,107
	Met + TZD + Empagliflozin 10 mg	6.045	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg
BMI	Met + TZD + Sitagliptin 100 mg	6.986	-	£31,240	-	-
	Met + TZD+ Empagliflozin 25 mg	7.005	0.019	£31,495	£256	£13,447
	Met + TZD + Empagliflozin 10 mg	7.003	-0.002	£31,874	£379	Dominated by empagliflozin 25 mg
Weight	Met + TZD + Sitagliptin 100 mg	6.967	-	£31,303	-	-

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
changes	Met + TZD + Empagliflozin 25 mg	7.000	0.033	£31,483	£180	£5,439
	Met + TZD + Empagliflozin 10 mg	6.996	-0.004	£31,866	£383	Dominated by empagliflozin 25 mg
Number of AEs	Met + TZD + Sitagliptin 100 mg	6.969	-	£31,302	-	-
	Met + TZD + Empagliflozin 25 mg	7.007	0.038	£31,484	£183	£4,803
	Met + TZD + Empagliflozin 10 mg	6.998	-0.009	£31,867	£383	Dominated by empagliflozin 25 mg
Discontinuation rates	Met + TZD + Sitagliptin 100 mg	6.969	-	£31,282	-	-
	Met + TZD + Empagliflozin 25 mg	7.003	0.034	£31,666	£384	£11,303
	Met + TZD + Empagliflozin 10 mg	6.996	-0.007	£31,869	£203	Dominated by empagliflozin 25 mg
10-year time horizon	Met + TZD + Sitagliptin 100 mg	5.260	-	£19,035	-	-
	Met + TZD + Empagliflozin 25 mg	5.284	0.024	£19,196	£161	£6,725
	Met + TZD + Empagliflozin 10 mg	5.283	-0.001	£19,459	£263	Dominated by empagliflozin 25 mg
Discount rate 0%	Met + TZD + Sitagliptin 100 mg	8.812	-	£42,749	-	-
	Met + TZD + Empagliflozin 25 mg	8.851	0.039	£42,968	£220	£5,631
	Met + TZD + Empagliflozin 10 mg	8.846	-0.005	£43,480	£511	Dominated by empagliflozin 25 mg
Discount rate 6%	Met + TZD + Sitagliptin 100 mg	6.042	-	£25,843	-	-
	Met + TZD + Empagliflozin 25 mg	6.070	0.028	£26,010	£167	£5,975
	Met + TZD + Empagliflozin 10 mg	6.068	-0.002	£26,330	£320	Dominated by empagliflozin 25 mg
Duration treatment effect	Met + TZD + Sitagliptin 100 mg	7.008	-	£30,985	-	£-
	Met + TZD + Empagliflozin 25 mg	7.028	0.020	£31,266	£282	£14,085
	Met + TZD + Empagliflozin 10 mg	7.038	0.010	£31,581	£315	£31,510

AE = adverse events; BMI = body mass index; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; TZD = thiazolidinedione

Table 169: Sensitivity analysis for insulin combinations

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Base case	Insulin + Dapagliflozin 10 mg	6.953	-	£30,545	-	-
	Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Utilities Sullivan et al	Insulin + Dapagliflozin 10 mg	7.011	-	£30,545	-	-
	Insulin + Empagliflozin 10 mg	7.004	-0.007	£30,564	£18	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	7.005	-0.006	£30,653	£108	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.970	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Utilities Sullivan et al, age related	Insulin + Dapagliflozin 10 mg	6.009	-	£30,545	-	-
	Insulin + Empagliflozin 10 mg	6.004	-0.005	£30,564	£18	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.004	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	5.972	-0.037	£30,682	£137	Dominated by dapagliflozin 10 mg
BMI	Insulin + Dapagliflozin 10 mg	6.953	-	£30,551	-	-
	Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,568	£17	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.923	-0.030	£30,644	£93	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,667	£116	Dominated by dapagliflozin 10 mg
Weight changes	Insulin + Dapagliflozin 10 mg	6.955	-	£30,507	-	-
	Insulin + Empagliflozin 10 mg	6.948	-0.007	£30,547	£40	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.949	-0.006	£30,627	£119	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.911	-0.044	£30,681	£174	Dominated by dapagliflozin 10 mg

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
Number of AEs	Insulin + Dapagliflozin 10 mg	6.953	-	£30,545	-	-
	Insulin + Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Discontinuation rates	Insulin + Dapagliflozin 10 mg	6.951	-	£30,526	-	-
	Insulin + Empagliflozin 10 mg	6.947	-0.004	£30,564	£38	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.947	-0.004	£30,591	£66	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.912	-0.039	£30,682	£157	Dominated by dapagliflozin 10 mg
10-year time horizon	Insulin + Dapagliflozin 10 mg	5.254	-	£18,873	-	-
	Insulin + Empagliflozin 10 mg	5.252	-0.002	£18,916	£43	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	5.251	-0.003	£18,985	£113	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	5.223	-0.031	£19,002	£130	Dominated by dapagliflozin 10 mg
Discount rate 0%	Insulin + Dapagliflozin 10 mg	8.791	-	£41,454	-	-
	Insulin + Empagliflozin 10 mg	8.780	-0.011	£41,465	£11	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	8.782	-0.009	£41,572	£118	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	8.739	-0.052	£41,626	£171	Dominated by dapagliflozin 10 mg
Discount rate 6%	Insulin + Dapagliflozin 10 mg	6.032	-	£25,346	-	-
	Insulin + Empagliflozin 10 mg	6.027	-0.005	£25,366	£20	Dominated by dapagliflozin 10 mg
	Insulin + Empagliflozin 25 mg	6.027	-0.005	£25,446	£100	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	5.996	-0.036	£25,463	£117	Dominated by dapagliflozin 10 mg
Duration	Insulin + Empagliflozin 10 mg	6.980	-	£30,358	-	-

Analysis	Treatment	QALY	Δ QALYs	Total costs NHS perspective	Δ Costs	ICER
treatment effect	Insulin + Dapagliflozin 10 mg	6.983	0.003	£30,358	£1	£200
	Insulin + Empagliflozin 25 mg	6.978	-0.005	£30,423	£65	Dominated by dapagliflozin 10 mg
	Insulin + Sitagliptin 100 mg	6.942	-0.041	£30,523	£165	Dominated by dapagliflozin 10 mg

AE = adverse events; BMI = body mass index; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

9.12 Appendix 12: IMS CORE model validation

Please see separate file: Empagliflozin CDM validation analyses – Technical report

9.13 Appendix 13 : WinBUGS code

Please see separate files

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the ACD or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- The checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed

during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing

will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

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