NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Empagliflozin for treating chronic kidney disease [ID6131]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Boehringer Ingelheim:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Initial clarification response
   b. Further clarification response

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Diabetes UK
   b. Kidney Care UK
   c. Kidney Research UK
   d. UK Kidney Association

4. **External Assessment Report** prepared by Warwick Evidence

5. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

Document B

Company evidence submission

29th June 2023

File name	Version	Contains confidential information	Date
ID6131_EMPAGLIFLOZIN_Document B_[redacted].docx	1.0	No	29th June 2023

Contents

List of Tables

List of Figures

Abbreviations

Acronym	Definition
ACH	all-cause hospitalisations
ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
APD	automated peritoneal dialysis
ARB	angiotensin II receptor blockers
BI	Boehringer Ingelheim
BMD	bone mineral disorders
BMI	body mass index
BNF	British National Formulary
CAD	coronary artery disease
CAPD	continuous ambulatory peritoneal dialysis
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CKD	chronic kidney disease
CKD-PC	chronic kidney disease prognosis consortium
CPRD	Clinical practice research datalink
CRIC	Chronic Renal Insufficiency Cohort
CTR	clinical trial report
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DKD	diabetic kidney disease
DOF	data on file
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
EKPF	European Kidney Patients Federation
ESKD	end-stage kidney disease
FE	fixed effects
HbA1c	glycated haemoglobin
HCHS	Hospital and Community Health Services
HCRU	healthcare resource utilisation
HD	haemodialysis
HDL	high-density lipoproteins
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalisation for heart failure
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
JAGS	Just Another Gibbs Sampler
KCUK	Kidney Care UK
KDIGO	Kidney Disease Improving Global Outcomes
KRUK	Kidney Research UK

Acronym	Definition
LVEF	left ventricular ejection fraction
LY	life year
MAIC	matching adjusted indirect comparison
MI	myocardial infraction
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
OD	once daily
PD	peritoneal dialysis
PICOS	population, intervention, comparator, outcomes, and study
PID	patient identifiable data
PKD	polycystic kidney disease
PPPY	per patient per year
PVD	peripheral vascular disease
QoF	quality outcomes framework
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitor
RCT	randomised controlled trial
RRID	Renal risk in Derby
RRT	renal replacement therapy
RS	randomised set
SAE	serious adverse event
SE	Standard error
SGLT1	sodium-glucose cotransporter 1
SGLT2	sodium-glucose cotransporter 2
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
T2DM	type 2 diabetes mellitus
TA	technology appraisal
TC	total cholesterol
TIA	transient ischaemic attack
TLR	targeted literature review
uACR	urine albumin-to-creatine ratio
UK	United Kingdom
UKKA	United Kingdom Kidney Association
UKRR	UK Renal Registry
US	United States of America
USRDS	United States Renal Data System
WTP	willingness-to-pay

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

B.1.1 Decision problem

This submission covers a population of adults with chronic kidney disease (CKD) (patients with or without type 2 diabetes mellitus [T2DM], with a broad range of estimated glomerular filtration rate [eGFR] from 20 to 90 mL/min/1.73m^2, and varying levels of albuminuria). This population falls within the full anticipated marketing authorisation for empagliflozin in this indication i.e., for the treatment of adults with CKD.

EMPA-KIDNEY is the pivotal randomised controlled trial (RCT) assessing the effect of empagliflozin 10mg oral once daily (OD) versus matching placebo on top of standard of care (SoC) on the progression of kidney disease in a broad population of CKD patients at risk of further disease progression. This submission further addresses the cost-effectiveness, comparative effectiveness, clinical efficacy, and safety of empagliflozin versus SoC in adult patients with CKD in alignment with the final National Institute for Health and Care Excellence (NICE) scope as outlined in Table 1.

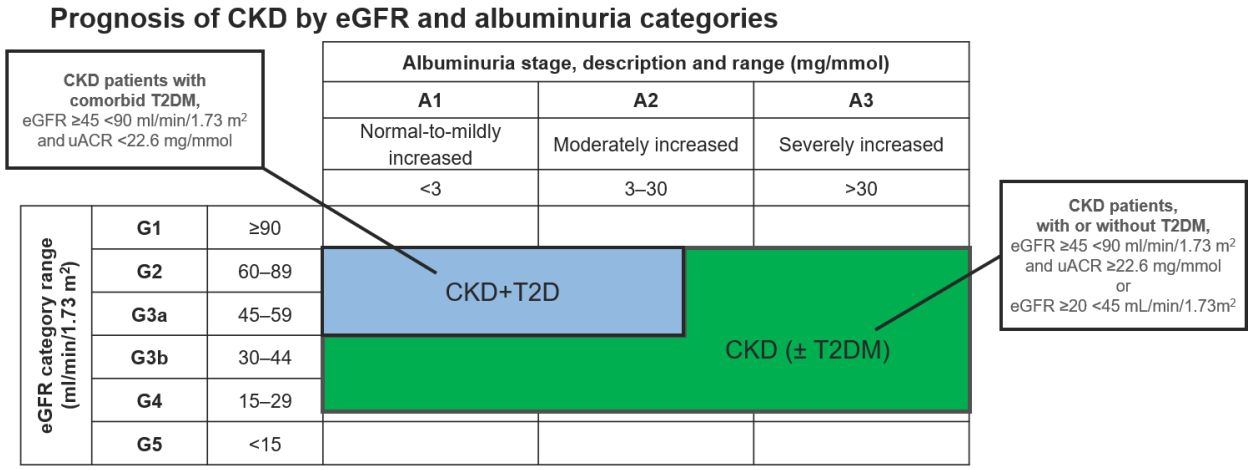
The intention to treat (ITT) population comprised of 6,609 randomised CKD patients with heterogenous baseline characteristics, including 46% and 54% with or without diabetes (DM), and 26% and 74% of patients with or without history of cardiovascular disease (CVD) at baseline respectively (1, 2). Mean eGFR at baseline was 37.4 mL/min/1.73m^2, with 34% of patients having eGFR <30 mL/min/1.73m^2; 44% with eGFR ≥30 to <45 mL/min/1.73m^2; and 22% with eGFR ≥45 mL/min/1.73m^2. Median urinary albumin-to-creatinine ratio (uACR) at baseline was 329 mg/g (37.2 mg/mmol), with 20% of patients having uACR <30 mg/g (3 mg/mmol; A1); 28% having uACR ≥30 to ≤300 mg/g (≥3 to ≤30 mg/mmol; A2); and 52% having uACR >300 mg/g (30 mg/mmol; A3) (2). EMPA-KIDNEY is the first CKD trial to include patients with low or no albuminuria (uACR <22.6 mg/mmol).

Empagliflozin is currently recommended by NICE for the treatment of adult patients with T2DM [NICE appraisal TA336] (3) and adult patients with heart failure (HF) with reduced ejection fraction (HFrEF), i.e., HF with left ventricular ejection fraction (LVEF) ≤40% [NICE appraisal TA773] (4), within the National Health Service (NHS) England. This means empagliflozin is already recommended for adult patients with comorbid CKD within these populations within the relevant marketing authorisations. Other disease-modifying sodium-glucose cotransporter 2 (SGLT2) inhibitors are already recommended in CKD/diabetic kidney disease (DKD), as per NICE Clinical Guideline NG203, NICE Clinical Guideline NG28, and NICE appraisal TA775 (dapagliflozin) (5-7).

However, recommendations are limited to patients with certain eGFR and uACR thresholds and/or T2DM, based on available evidence from pivotal RCTs (8, 9).

This submission provides evidence to support the inclusion of empagliflozin in NICE Clinical Guideline NG203 as an SGLT2 inhibitor treatment option for a broader population of adults with CKD (patients with or without T2DM, with a broad range of eGFR from 20 to 90 mL/min/1.73m^2 and varying levels of albuminuria) in line with the EMPA-KIDNEY ITT population and supporting data from EMPA-REG OUTCOME, thus addressing an important unmet need for patients who fall outside the scope of current recommendations (Figure 1).

Figure 1. Patient population addressed in the submission, according to KIDGO categories



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus
Source: Adapted from KDIGO 2013 (10)

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CKD having individually optimised standard of care	Adults with CKD having individually optimised standard of care, and having: [redacted]	This population represents a subset of the original scope, following advice received during the Decision Problem Meeting. Available evidence does support the use of empagliflozin in the anticipated marketing authorisation for the full population (i.e., in adults with CKD). [redacted]
Intervention	Empagliflozin in combination with optimised standard of care	Empagliflozin in combination with individually optimised standard of care (treatment with or without ACE inhibitors or ARB).	Intervention is in alignment with NICE final scope.
Comparator(s)	Established clinical management with or without dapagliflozin.	As per NICE final scope.	N/A
Outcomes	The outcome measures to be considered include: • morbidity including CV outcomes, disease progression (such as kidney replacement, kidney failure), and markers of disease progression (such as eGFR, albuminuria) • mortality • hospitalisation • adverse effects of treatment • health-related quality of life.	As per NICE final scope.	N/A
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of	As per NICE final scope.	N/A

	incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. • 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.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People with diabetes • People with CVD • People with other causes of CKD	• People with diabetes	Of the proposed subgroups, only 'people with diabetes' was a pre-specified key subgroup in the EMPA-KIDNEY trial. The benefit in the primary outcome – a significant reduction in the composite of time to first occurrence of kidney disease progression [defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization], or CV death) was consistently observed irrespective of diabetes status, as detailed in Section B.2.7. 'People with CVD' was another (non-key) pre-specified subgroup. There was a significant and consistent reduction in the primary outcome irrespective of CVD history as baseline, as detailed in Section B.2.7. 'People with other causes of CKD', which is interpreted as 'people without T2D or CVD' was not a pre-specified subgroup. A subgroup analysis by cause

			of CKD is detailed in Section B.2.7, which includes patients with 'other/unknown' causes, however this is not mutually exclusive with CVD or T2D. The heterogenous nature of CKD should be noted; of patients with diabetes enrolled in EMPA-KIDNEY, one third of them had a primary cause of kidney disease other than diabetes (e.g., glomerular and hypertensive/renovascular). In this submission, economic analyses are presented for the ITT population and the diabetes subgroups, which are relevant for decision making. Additional economic analyses in people with and without CVD are not considered necessary. The comparator treatment for these subgroups would not differ from the overall target population. Further, as cost-effectiveness analysis demonstrates that empagliflozin is cost-effective in the overall ITT population, an exploration of the cost-effectiveness of further subgroups is deemed inappropriate.
Special considerations including issues related to equity or equality	None.	Consideration should be given to equity and equality implications related to the availability of empagliflozin across primary and secondary care settings for patients with CKD.	Principle 9 of NICE's Social Value judgements as part of its statement highlights the goal to reduce health inequalities across protected characteristics as well as considering those arising from socioeconomic factors (11). Socioeconomic disparities are associated with health inequalities in England, with more socially advantaged patients often receiving better access to secondary and specialist care in the NHS (12). Resource constraints in a post-COVID-19 healthcare system may further exacerbate pre-existing inequalities in access to secondary and specialist care in the NHS. Secondary care in CKD is largely focussed on patients with ESKD, and barriers in ease and affordability of travel may further complicate access to these settings.

			A positive NICE recommendation for empagliflozin in CKD that facilitates broad access for patients across primary and secondary care settings and the multidisciplinary care team can help alleviate health inequalities, as CKD patients may be seen by a variety of specialists in clinical practice. Broad access is important for alleviating any health inequalities in terms of access to nephroprotective treatments for CKD patients.

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney failure; HR, hazard ratio; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; N/A, not applicable; T2D, Type 2 diabetes; uACR, urine albumin-to-creatinine ratio.

B.1.2 Description of the technology being evaluated

A description of the technology being evaluated is presented in Table 2. The current summary of product characteristics (SmPC) for empagliflozin is available in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Empagliflozin (Jardiance®)
Mechanism of action	• Empagliflozin is an orally bioavailable, reversible, highly potent, and selective inhibitor of SGLT2. SGLT2 is highly expressed in the kidney and is the predominant cotransporter responsible for the reabsorption of sodium and glucose from the glomerular filtrate back into the circulation. • Empagliflozin-mediated SGLT2 inhibition reduces renal reabsorption of sodium and glucose in the proximal tubules of the kidney, leading to increased distal delivery of sodium to the macula densa and increased urinary excretion of sodium (natriuresis) and glucose. • CKD results from progressive damage and loss of nephrons, which are the core structural and functional units of the kidney. Nephron loss and damage leads to glomerular hypertension and hyperfiltration, which trigger a proinflammatory and profibrotic cascade, interstitial scarring, and further nephron loss. • Increased empagliflozin-mediated sodium excretion impacts several physiological functions in the context of CKD, including (but not restricted to) increased tubulo-glomerular feedback which leads to a reduction in glomerular hypertension and hyperfiltration, and an attenuation of the proinflammatory and profibrotic cascade. This also reduces albuminuria, possibly mediating a reduction on direct toxic effects on renal tubules. • SGLT2 inhibitors have further been associated with weight loss, decreased blood pressure, and a reduction in HbA1c, which have all been associated with a reduction in CKD disease progression (13-15).
Marketing authorisation/CE mark status	An application for UK MHRA marketing authorisation in adults with CKD was made on [redacted]. MHRA marketing authorisation is [redacted]. An application for EMA marketing authorisation for the same indication was made on [redacted], and the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 22 June 2023.
Indications and any restriction(s) as described in the SmPC	**Indication relevant to this submission:** Empagliflozin is expected to be indicated in adults for the treatment of CKD. **Other indications:** **T2DM** – Jardiance® (empagliflozin) is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes **Heart failure** – Jardiance® (empagliflozin) is indicated in adults for the treatment of symptomatic chronic heart failure.

	The full list of contraindications, special warnings and precautions for use can be found in the draft SmPC in Appendix C.
Method of administration and dosage	10 mg oral empagliflozin OD.
Additional tests or investigations	None.
List price and average cost of a course of treatment	List price of a pack of 28 tablets (10 mg) is £36.59. This equates to a cost of £1.31 per tablet per day for each patient (16).
Patient access scheme (if applicable)	Not applicable.

Abbreviations: CKD, chronic kidney disease; EMA, European Medical Agency; HbA1c, glycated haemoglobin; MHRA, Medicines and Healthcare products Regulatory Agency; OD; Once daily; SGLT2, Sodium-glucose cotransporter 2; SmPC, Summary of product characteristics; T2DM; Type 2 diabetes Mellitus; UK, United Kingdom.

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

Summary of health condition and position of the technology in the treatment pathway

- CKD is a chronic progressive condition in which kidney function deteriorates over time, potentially leading to end-stage kidney disease (ESKD) (17, 18).
- The 2021 NICE CKD guidelines (NG203) define CKD as a condition in which kidney structural or functional abnormalities are present for ≥3 months and has implications on health. This includes all people with markers of kidney damage and those with an eGFR of <60 mL/min/1.73m^2 on at least two occasions separated by a period of ≥90 days (with or without markers of kidney damage) (7).
- CKD may result from various underlying systemic conditions and primary kidney diseases, with T2DM and hypertension cited as the most common causes (19).
- The prevalence of CKD in the UK is estimated at 3.5 million (37), although a new report by Kidney Research UK (KRUK) suggests up to 7.19 million may be affected (38).It is projected that CKD may affect 14% of the total UK population by 2025 (20).
- The NHS Quality and Outcomes Framework (QoF) 2021-2022 estimated the prevalence of CKD stages G3a to G5 as 3.98% (1.9 million) among adults aged ≥18 years in England (21).
- CKD is associated with a considerable number of comorbidities and complications that increase the disease burden. Patients with CKD are at a higher risk of experiencing adverse CV (HF, coronary artery disease, stroke, MI) and non-CV events (anaemia, infections, metabolic and bone mineral disorders [BMD]) as compared to non-CKD patients (22, 23).
- Patients with CKD demonstrate higher rates of hospitalisation as compared to patients without CKD (24). In the UK, patients with CKD have reported two-to-three-fold increased rates of emergency hospitalisation as compared to non-CKD patients, and a 2-fold higher risk of hospital readmission or death within 30 days of discharge across all disease stages (25).
- This burden of disease imposes substantial costs to the NHS, with RRT costs estimated to be £32,259 per patient per year (PPPY) for dialysis and £27,033 for the initial cost of renal transplantation (20).
- A 2009-2010 study estimates direct healthcare costs for CKD at £1.45 billion per annum (half of which accruing to RRT), representing approximately 1.3% of the total NHS budget (26).
- CKD also impacts patients' QoL, with the extent of decrement varying by disease stage, treatment modality, and patients' comorbidity profile (27).
- Patients with CKD's risk of all-cause and CV mortality increases with eGFR decline and increasing albuminuria (28). This risk is evident in early stages of CKD and increases as the disease progresses to later stages with particularly poor outcomes for patients with ESKD receiving RRT (29).
- Management of CKD in the NHS is informed by NICE clinical guidelines (NG203 and NG28) and NICE-accredited guidelines from the UK Kidney Association (UKKA), which can be considered as being informed by the latest clinical evidence available (5, 7).
- NICE CKD guidelines (NG203) currently recommend SGLT2 inhibitors in select CKD patients, who meet uACR thresholds and/or have T2DM. It is evident that the NG203 (Chronic kidney disease: assessment and management) guideline needs to be revised to incorporate a thorough and concise overview of all relevant recommendations on SGLT2 inhibitors in patients with CKD, with or without T2DM (7).
- Not all patients with CKD are prescribed ACE inhibitors, ARBs, and statins in UK clinical practice, and patients receiving individually optimised SoC inclusive of these treatments remain at residual risk of CKD disease progression and adverse outcomes (2).
- The recent 2023 UKKA guidelines recommend SGLT2 inhibitors to slow the rate of kidney function decline in patients with CKD with and without T2DM at broader ranges of eGFR and

lower uACR thresholds than earlier NICE guidelines, which is more reflective of evidence from the EMPA-KIDNEY ITT population than other comparator trials (5, 7, 30).

- Based on the existing evidence, empagliflozin should be positioned as a disease-modifying treatment option in combination with individually optimised SoC at the earliest opportunity in adult patients at risk of CKD disease progression.

B.1.3.1 Overview of CKD

CKD is a chronic progressive condition in which kidney function deteriorates over time, potentially leading to end-stage kidney disease

CKD is caused by abnormalities of kidney function or structure that are present for ≥3 months (7, 10, 31). This definition of CKD includes all individuals with markers of kidney damage or those with an eGFR < 60 mL/min/1.73m^2 on at least two separate occasions 90 days apart (with or without markers of kidney damage). Markers of kidney damage can include albuminuria, haematuria, and structural abnormalities detected by imaging, or a history of kidney transplantation (Table 3).

Table 3. **NICE criteria for ungraded CKD diagnosis**

	Criteria for CKD	Present for ≥3 months
1	Markers of kidney damage (one or more present)	• Albuminuria (AER ≥30 mg/24 hours; uACR ≥30 mg/g [≥3 mg/mmol]) • Urine sediment abnormalities • Electrolyte and other abnormalities due to tubular disorders • Abnormalities detected by histology • Structural abnormalities detected by imaging • History of kidney transplantation
OR		
2	Decreased eGFR	eGFR <60 mL/min/1.73m^2

Abbreviations: uACR, urine albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Source: NICE 2021 (7)

Structural and functional abnormalities of the kidney in CKD lead to progressive deterioration of renal function as measured by eGFR, eventually causing nephron loss and potentially leading to ESKD, also referred to as a kidney failure, necessitating RRT constituted by either dialysis or kidney transplant depending on disease severity (17, 18).

Disease severity in CKD is classified according to Kidney Disease Improving Global Outcomes (KDIGO) group recommendations, which incorporate eGFR and uACR categories into a two-dimensional framework to “stratify (CKD) risk, focus management priorities and guide referral to specialist care” (17). There are 6 eGFR categories ranging from normal to ESKD which are further subdivided by three albuminuria categories (Table 4). NICE CKD guidelines [NG203] highlight that the risk of adverse outcomes in CKD (e.g., all-cause mortality and cardiovascular [CV] events) elevates with increasing uACR and eGFR categories as summarised in Table 4.

Table 4. Classification of CKD based on eGFR and uACR categories

		uACR categories		
		A1 (<3 mg/mmol) Normal to mildly increased	**A2** (3 to 30 mg/mmol) Moderately increased	**A3** (>30 mg/mmol) Severely increased
eGFR categories	**G1:** normal and high (≥90 mL/min/1.73m^2)	Low risk*	Moderate risk	High risk
	G2: Mild reduction related to normal range for a young adult (60 to 89 mL/min/1.73m^2)	Low risk*	Moderate risk	High risk
	G3a: Mild to moderate reduction (45 to 59 mL/min/1.73m^2)	Moderate risk	High risk	Very high risk
	G3b: Moderate to severe reduction (30 to 44 mL/min/1.73m^2)	High risk	Very high risk	Very high risk
	G4: Severe reduction (15 to 29 mL/min/1.73m^2)	Very high risk	Very high risk	Very high risk
	G5: ESKD (<15 mL/min/1.73m^2)	Very high risk	Very high risk	Very high risk

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio
*No CKD if there are no other markers of kidney damage
Source: KDIGO 2012 clinical practice guidelines (10)

CKD has a heterogenous aetiology; however, a common pathophysiology is found across all causes of the condition

CKD results from various systemic conditions and primary kidney diseases, with T2DM and hypertension cited as the most common causes (19). Other less frequent causes include polycystic kidney disease (PKD), obstructive uropathy, and various glomerular nephrotic and nephritic syndromes (32)). While UK data on causation across the eGFR spectrum is limited, a 2020 analysis by UK Renal Registry (UKRR) in patients with eGFR <30 mL/min/1.73m^2 receiving RRT demonstrated that the most common identifiable causes were T2DM (30.5%), glomerulonephritis (12.3%) and hypertension (7.1%). T2DM was the most common cause of CKD in all age groups except 18-34, where glomerulonephritis was predominant (Table 5).

Table 5. UK Renal Registry (UKRR) CKD by aetiology in 2020

	Age groups							
CKD aetiology	**18-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**>85**	**All**
T2DM	19.5%	28.1%	31.0%	40.0%	32.4%	23.6%	14.7%	**30.5%**
Other	26.9%	17.9%	15.1%	16.8%	17.7%	20.0%	16.3%	**18.2%**
Uncertain aetiology	10.4%	13.1%	11.5%	11.0%	16.5%	21.3%	31.5%	**15.0%**
Glomerulonephritis	26.5%	15.3%	16.3%	11.1%	9.7%	8.1%	3.8%	**12.3%**
Hypertension	5.6%	7.9%	9.1%	6.4%	6.4%	7.2%	9.8%	**7.1%**
Polycystic Kidney Disease	2.8%	10.7%	11.6%	8.0%	5.3%	3.6%	2.2%	**6.7%**
Pyelonephritis	8.0%	5.0%	3.5%	3.7%	5.2%	7.1%	9.2%	**5.3%**
Renal Vascular Disease	0.4%	1.8%	1.9%	3.0%	6.9%	9.2%	12.5%	**4.9%**
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Abbreviations: CKD, chronic kidney disease; T2DM, Type 2 diabetes mellitus
Source: UK renal registry 24th annual report (33)

Irrespective of the origin of any renal injury, all CKD aetiologies follow a common pathophysiology characterised by progressive, and irreversible loss of nephrons (the core structural and functional units of the kidneys). Nephrons are composed of glomeruli that filter the blood, and tubules that return useful compounds into circulation and excrete waste products via urine. In CKD, nephrons undergo glomerular hypertension and hyperfiltration, triggering a proinflammatory, profibrotic cascade that causes interstitial scarring and nephron failure (34).

Post initial nephron failure, 'remnant' functional nephrons also experience glomerular hypertension in an effort to maintain homeostasis, which eventually leads to further nephron failure. Without intervention, this cycle can lead to ESKD where the kidneys are no longer able to perform an adequate level of glomerular filtration at which point RRT may be necessitated (35, 36).

CKD incidence and prevalence increases with age, with evidence of underdiagnosis in earlier disease stages

Estimates of the prevalence of CKD in the UK vary. Kidney Care UK (KCUK) have reported this as an estimated at 3.5 million (37), although a new report by Kidney Research UK (KRUK) suggests this could be much higher (38). It is projected that CKD will affect 14% of the UK population by 2025 (20). Furthermore, an increase of approximately 7% is expected in more advanced stages of CKD (3b-5) relative to the total CKD population (39). The NHS QoF 2021-2022 estimates the prevalence of CKD at stages G3a to G5 as 3.98% (1.9 million) amongst all adults aged ≥18 years in England (21). Health Survey for England (HSE) (2016) reported a higher prevalence of CKD at stages G3a to G5 of 7% in adults aged ≥35 years specifically (40). HSE (2016) further reported an estimated prevalence of CKD at stages G1 to G5 of 15% overall in this population (40). A 2020 English cohort study estimates a CKD prevalence of 18.2% across adults ≥60 years (41), and HSE 2016 also reported a 34% prevalence in adults aged ≥70 years (21).

Studies from 2020-2022, estimate that 44% of patients with CKD aged ≥60 years, and 48% of patients with CKD aged ≥18 years are undiagnosed in clinical practice respectively (41, 42).

Underdiagnosis is common in early CKD stages as patients are often asymptomatic. The diagnostic criterion for such patients is a raised uACR ≥3 mg/mmol or other markers of kidney damage; however, the National CKD Audit reports sub-optimal use of uACR testing among people at high risk of CKD (41, 43), limiting the potential to identify these patients early in clinical settings.

At a national level, an aging UK population is expected to contribute to increased CKD prevalence, while at an individual patient-level, a confluence of increasingly observed risk factors such as hyperglycaemia, hypertension, history of CVD, and obesity are also increasing the risk of developing CKD (44-46). However, there is promising but limited evidence demonstrating trends of improved management in some patient-level risk factors in UK clinical practice (20, 47).

B.1.3.2 Burden of disease in CKD

- CKD is associated with considerable comorbidities and complications that contribute to the disease burden. Patients with CKD are at a higher risk of experiencing adverse CV (e.g., HF, coronary artery disease, stroke, myocardial infraction [MI]) and non-CV events (e.g., anaemia, infections, and metabolic and bone mineral disorders [BMD]) as compared to non-CKD patients (22, 23).
- Patients with CKD demonstrate higher rates of hospitalisation as compared to patients without CKD (24). In the UK, patients with CKD have reported two-to-three-fold increased rates of emergency hospitalisation as compared to non-CKD patients, and a 2-fold higher risk of hospital readmission or death within 30 days of discharge across all disease stages (25).
- This burden of disease imposes substantial costs to the NHS, with RRT costs estimated to be £32,259 PPPY for dialysis and £27,033 for the initial cost of renal transplantation (20).
- A 2009-2010 study estimates direct healthcare costs for CKD at £1.45 billion per annum (half of which accruing to RRT), representing approximately 1.3% of the total NHS budget (26). This is supported by a recent report by KRUK which projects that NHS costs for CKD stages 1-5 (excluding RRT) will reach £1.95 billion by the end of 2023, representing 1% of the total NHS budget (38).
- CKD also impacts patients' QoL, with the extent of decrement varying by disease stage, treatment modality, and patients' comorbidity profile (27).
- Patients with CKD's risk of all-cause and CV mortality increases with eGFR decline and increasing albuminuria (28). This risk is evident in early stages of CKD and increases further as the disease progresses to later stages with particularly poor outcomes for patients with ESKD receiving RRT (29).

CKD is associated with a considerable number of comorbidities and complications which exert an increased disease burden as patients progress towards ESKD and require RRT

Patients with CKD are at higher risk of various complications including anaemia, infections, metabolic disorders (e.g., acidosis, hyperkalaemia) and BMD as compared to patients without CKD (22, 23). The Renal Risk in Derby (RRID) study reported that 19.9% of their cohort of Stage 3 patients with CKD had anaemia (48), the rates of which was reported to increase with advanced disease (49). Metabolic disorders such as hyperphosphatemia, hypocalcaemia, and secondary hyperthyroidism lead to an increased risk of fractures in patients with CKD (22, 23, 50). The RRID study reported that 19.9% of their cohort of Stage 3 CKD patients had anaemia (48), the rates of

which was reported to increase with advanced disease (49). Metabolic disorders such as hyperphosphatemia, hypocalcaemia, and secondary hyperthyroidism lead to an increased risk of bone fractures in patients with CKD (22, 50), with comorbidities further contributing to healthcare resource utilisation (HCRU) (24).

Once CKD has progressed to ESKD, RRT becomes the predominant treatment option (10). Since 1990, the global age-standardised incidence of patients requiring RRT has increased by 43.1% (dialysis) and 34.4% (transplant) (51). A patient-level microsimulation modelling study estimated a prevalence of 9.2 million people (diagnosed and estimated undiagnosed) with CKD by 2027 in UK and projected a 5% increase in costs for diagnosed CKD and RRT (52). The treatment of CKD and ESKD imposes substantial societal costs, which are highest for RRT, particularly in-hospital haemodialysis (HD) (53). In 2019, of the 57,510 ESKD patients receiving RRT in England, it was found that 32,367 (56.3%) of them received a kidney transplant, 20,759 (36.1%) received in-centre haemodialysis (ICHD), 3,175 (5.5%) received peritoneal dialysis (PD) and 1,209 (2.1%) home HD, further contributing to extensive HCRU and thus costs (29). In many western countries, at home HD, PD, and self-care dialysis are more cost-effective than in-hospital haemodialysis. However, in Europe, 89% of patients still underwent dialysis in secondary care settings in 2013, and 14% of UK patients received hospital PD (53).

A comprehensive analysis of the costs of dialysis undertaken in the UK in 2018 reported the annual direct cost per patient for home-based modalities to be £16,395 for continuous ambulatory peritoneal dialysis (CAPD), £20,295 for automated PD (APD), and £23,403 for home-based HD. The cost of dialysis was increased at £28,931 for satellite units and £32,678 for hospital units, including costs for transportation (25).Beyond the economic burden, patients with CKD undergoing RRT are also subjected to potential risks associated with treatment, which include haemolysis due to cannulas, air embolisms due to HD and continuous RRT, vascular access related infections, risk of severe blood loss, risk from fluid overload during APD, and risk of medicine-induced nephrotoxicity or systemic side effects caused by poor metabolite excretion resulting from reduced kidney function (54).

The 2023 KRUK report also highlights existing NHS resource constraints for RRT, whereby maximum capacity has likely been reached. This was compounded by a suspension of non-elective surgical care during COVID-19 in 2020, impacting kidney transplantation appointments and causing an estimated loss of 1,600 opportunities for kidney transplant surgeries. This led to concomitant increases in waiting lists and the proportion of patients receiving dialysis as a form of RRT (increased from 91.7% to 94.1%). Future growth in demand for RRT led by ongoing epidemiological trends in CKD has the potential to exacerbate current capacity constraints (38).

Patients with CKD are at a higher risk of all-cause mortality, poor CV outcomes, and CV death than the general population

Increased risk of all-cause mortality and CV mortality is evident from early-stage CKD and increases further as the disease progresses to later stages, with particularly poor mortality outcomes for patients with ESKD receiving RRT (28, 29). The RRID study reported an all-cause mortality rate of 41.2% by the end of the 5-year follow-up for Stage 3 CKD patients (55). UKRR (2019) reports a total death rate of 91 per 1,000 prevalent RRT patients (29). Further, DISCOVER CKD (2022), an international observational cohort study in patients with CKD reported an increased risk of all-cause mortality and CV mortality with decreasing eGFR levels and increasing uACR in English adults not receiving dialysis (Table 6) (28).

Table 6. **Mortality rate per 100 person-years among CKD patients by eGFR and uACR**

	uACR <3 mg/mmol	uACR 3 - <30 mg/mmol	uACR ≥30 mg/mmol
All-cause mortality			
eGFR 60 - 75	0.88 (0.82, 0.95)	1.87 (1.67, 2.10)	3.00 (2.31, 3.83)
eGFR 45 - <60	1.51 (1.40, 1.64)	3.05 (2.73, 3.41)	3.60 (2.73, 4.67)
eGFR 30 - <45	3.38 (3.01, 3.79)	5.63 (4.89, 6.46)	4.82 (3.43, 6.59)
eGFR 15 - <30	7.33 (5.69, 9.29)	9.65 (7.69, 11.96)	8.79 (5.84, 12.71)
eGFR 0 - <15	3.97 (0.82, 11.6)	10.28 (5.47, 17.57)	N/A
CV mortality			
eGFR 60 - 75	0.21 (0.18, 0.24)	0.51 (0.40, 0.63)	0.70 (0.39, 1.16)
eGFR 45 - <60	0.31 (0.26, 0.37)	0.60 (0.46, 0.77)	1.26 (0.77, 1.95)
eGFR 30 - <45	0.90 (0.71, 1.12)	1.16 (0.84, 1.57)	0.99 (0.43, 1.95)
eGFR 15 - <30	1.51 (0.82, 2.53)	1.51 (0.80, 2.58)	1.57 (0.51, 3.66)
eGFR 0 - <15	N/A	2.37 (0.49, 6.93)	N/A

Abbreviations: CKD, Chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; N/A, not applicable; uACR, urine albumin-creatinine ratio
Source: James et al. 2022 (28)

Patients with CKD also face increased risk of adverse CV events and outcomes including HF, coronary artery disease (CAD), peripheral vascular disease (PVD), stroke and MI (23, 28, 56), with DISCOVER CKD reporting on the increasing risk of stroke and MI in particular with higher uACR and lower eGFR categories (Table 7) (28).

Table 7. CV event rate per 100 person-years in CKD patients by eGFR & uACR

	uACR <3 mg/mmol	uACR 3-<30 mg/mmol	uACR ≥30 mg/mmol
MI			
eGFR 60 - 75	1.22 (1.15, 1.30)	1.79 (1.59, 2.01)	2.04 (1.47, 2.76)
eGFR 45 - <60	1.21 (1.11, 1.32)	1.57 (1.34, 1.84)	2.80 (2.01, 3.78)
eGFR 30 - <45	1.76 (1.50, 2.07)	1.79 (1.38, 2.29)	2.17 (1.26, 3.47)
eGFR 15 - <30	3.03 (1.99, 4.40)	2.93 (1.87, 4.35)	2.26 (0.91, 4.66)
eGFR 0 - <15	N/A	5.04 (1.85, 10.96)	N/A
Stroke			
eGFR 60 - 75	0.76 (0.70, 0.82)	1.05 (0.90, 1.23)	1.94 (1.39, 2.64)
eGFR 45 - <60	0.95 (0.86, 1.05)	1.29 (1.08, 1.53)	1.55 (1.00, 2.31)
eGFR 30 - <45	1.62 (1.36, 1.91)	1.79 (1.38, 2.29)	2.04 (1.16, 3.31)
eGFR 15 - <30	2.32 (1.44, 3.54)	1.78 (1, 2.94)	2.22 (0.89, 4.58)
eGFR 0 - <15	N/A	N/A	N/A

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; N/A, not applicable; uACR, urine albumin-creatinine ratio
Source: James et al. 2022 (28)

High CV and non-CV disease burden contributes to a higher rate of higher rate of all-cause hospitalisations (ACH) in CKD patients

Multimorbidity in CKD leads to complex treatment regimens. Progressive eGFR decline in CKD often becomes a limiting factor in the management of comorbidities, which increases patients' risk of hospitalisation compared to the general population. Iwagami et al. (2018) examined cause-specific hospitalisation rates for English CKD patients stages 3-5 from 2004 to 2014 to demonstrate a higher incidence rate of hospitalisation for patients with CKD compared to those without CKD (Table 8) (24). Hospitalisation for heart failure (HHF) demonstrated the largest difference with patients with CKD having a 9.7% hospitalisation incidence compared to 3.1% for patients without CKD.

Table 8. Incidence rate of cause-specific hospitalisations for patients with and without CKD

Cause of hospitalisation	Patients with CKD	Patients without CKD
HHF	9.7 (9.5 – 9.9)	3.1 (3.0 – 3.2)
Urinary tract infection	13.1 (12.9 – 13.3)	7.9 (7.7 – 8.1)
Pneumonia	12.6 (12.4 – 12.8)	8.2 (8.0 – 8.4)
Acute kidney injury	4.9 (4.7 – 5.0)	0.8 (0.8 – 0.9)
Myocardial infraction	6.9 (6.8 – 7.1)	3.8 (3.6 – 3.9)
Cerebral infraction	5.7 (5.6 – 5.8)	3.5 (3.4 – 3.6)
Gastrointestinal bleeding	5.1 (5.0 – 5.2)	3.2 (3.1 – 3.3)
Hip fracture	8.7 (8.6 – 8.9)	7.1 (7.0 – 7.3)
Venous thromboembolism	3.1 (3.0 – 3.2)	2.0 (1.9 – 2.1)
Intracranial bleeding	2.0 (1.9 – 2.1)	1.5 (1.4 – 1.6)

Abbreviations: CKD, chronic kidney disease; HHF, hospitalisation for heart failure
Source: Iwagami et al. 2018 (24).

In the UK, two-to-three-fold increased rates of emergency hospitalisation have been reported in patients with CKD as compared to those without the condition (25). CKD patients have almost a 2-fold higher risk of hospital readmission or death within 30 days of discharge across all disease

stages and approximately 28% of patients with CKD stages 4 and 5 are readmitted or die within 30 days of discharge (57). Similar results have been observed globally:

In the United States of America (US), ACH were found to be 4 times higher in CKD patients aged 18-64 years at any stage and 12 times higher in those with CKD Stage 4 or 5 compared to people without CKD (57). German adults with Stage 3 CKD demonstrated hospitalisation rates four times higher than those without CKD (58), and a Canadian study reported that more than 40% of patients with CKD aged >65 with unplanned hospitalisation die within 5 years regardless of admission cause (59). ACH has proven to be an indicator for long-term risk of death; thus, hospitalisations represent a substantial morbidity and mortality risk in CKD (59).

Increased HCRU and hospitalisations in CKD lead to a substantial economic burden on the NHS

CKD is a progressive disease that is associated with significant morbidity and increased risk of hospitalisations, which imposes a substantial economic burden on the healthcare system. A 2009-2010 estimate suggests that £1.45 billion was spent by the NHS on CKD, which comprised approximately 1.3% of the total NHS budget. A June 2023 report by KRUK projects that CKD stages 1-5 will cost the NHS £1.95 billion by the end of 2023 (excluding RRT). This alone represents approximately 1% of the total NHS budget, with 91% (£1.79 billion) of these costs attributable to CKD stages 3-5, and 9% (£167 million) attributable to CKD stages 1-2 (38).

Increased hospitalisations observed in CKD patients compared to the general population are a key driver of this economic burden (26). Morbidities can lead to a 3-fold surge in total cost of care as compared to CKD without additional conditions. At each stage of the disease, CKD in combination with comorbidities such as DM, CVD, and HF significantly amplify healthcare expenditures, with this effect steadily increasing as the disease progresses to later stages (60, 61). Hospitalisations are the key drivers for annual healthcare costs for CKD in the US and account for up to 65% of the total cost of CKD associated care (60, 61).

DISCOVER CKD assessed HCRU and costs stratified by CKD severity to report that hospitalisation rates were three times higher in the A3 uACR category than for A1. Hospitalisations increased to 889.7/1000 patient-years for those with stages 4 and 5 CKD (20). Mean annual per patient costs ranged from £4,966 (A1) to £9,196 (A3), and from £4,997 (G2) to £7,595 (G5) in the UK, establishing that the economic burden of healthcare in CKD is weighted towards a small proportion of patients with late-stage CKD, including those with kidney failure and/or albuminuria (21). DISCOVER CKD study further found that across all disease stages mean NHS healthcare costs PPPY were £5,401 for patients with CKD (21). Costs were found to increase as CKD stage increases, with G2A1 averaging £4,654 and G4A3 £11,419.

CKD progression to ESKD and RRT further increase the substantial economic burden on the NHS

Once patients with CKD progress to ESKD, RRT is the remaining treatment option (10) and although only a smaller proportion of patients advance to ESKD, RRT is associated with a substantial economic burden on the health system. In the US, dialysis and kidney transplants accounted for approximately $36 billion of total healthcare expenditure as per the US Renal Data System (USRDS) 2022 annual report. Per this report, PPPY inpatient and outpatient costs for patients with CKD were comparable at approximately $25,000 and $28,000 respectively, however dialysis contributed to the majority (92.7%) of total outpatient costs at $9.88 billion per year. Further, average PPPY costs for RRT were considerably higher, and estimated at $98,410 and $442,500 PPPY for dialysis and kidney transplants respectively (62).

Similarly, RRT is associated with a substantial economic burden on the NHS at £32,259 PPPY and £27,033 PPPY for dialysis and initial kidney transplant respectively (20). Of the £1.45 billion spent on treatment of CKD stages 3-5 in England in 2009-2010, more than 50% was spent on RRT, which was required for just 2% of the CKD population (26). KRUK (2023) further project that the cost of dialysis for people with ESKD will reach £1.05 billion (or 0.53% of the NHS budget), and that the cost of kidney transplants will reach £293 million by the end of 2023 (38). These estimates collectively demonstrate the need to prevent or delay CKD progression to reduce the economic burden on the NHS that is associated with later disease stages.

CKD is associated with a high symptomatic burden and decrements in health-related quality of life (HRQoL), particularly in later disease stages

CKD leads to decrements in patients' HRQoL that increase depending on disease stage, treatment modality, and patients' comorbidity profile (27). A study by Nguyen et. al (2018) used 2010 HSE data to show statistically significant decrements in health utility index of 0.11, 0.19 and 0.28 for patients with G2, G3a and G4/5 respectively, compared to patients with normal kidney function or at stage G1 (56). This is aligned with a 2020 systematic literature review (SLR) of HRQoL in CKD that reported a decline in UK-specific EQ-5D-3L-derived utilities of 0.85 at G2 to 0.73 at G5.

Nguyen et. al (2018) demonstrated that pain/discomfort and mobility were the HRQoL domains for which patients with CKD reported the most problems (56). This is supported by findings from a 2020 English prospective cohort study, where the EQ-5D-5L domains reported most common problems to be pain/discomfort, mobility, and usual activities (70.6%, 57.7%, and 46.2% of patients reporting any problem respectively). This study also found that higher comorbidity count and obesity are independently associated with patient-reported problems in these domains, demonstrating the importance of comorbidity management in improving the HRQoL of patients with CKD (55).

HRQoL is lowest for CKD patients requiring RRT, with utilities of 0.44 and 0.53 reported for patients on HD and PD respectively (63). Dialysis' detrimental impact on HRQoL has been attributed to the travel and dietary restrictions it imposes, as well as the copious amount of time patients need to spend in dialysis units. Such patients often require support with mobility and transportation, as well as with personal care, exerting a considerable burden on their carers and support networks (64). Kidney transplants have conversely been associated with positive effects on HRQoL (65).

CKD also impacts patients' and carers lived experiences, patients' perspective on their health, and their ability to perform normal activities of daily life

A 2022 survey conducted by the European Kidney Patients Federation (EKPF) on the impact of CKD on patient's lives revealed that 88% experienced some kind of life change due to their condition (66). Negative impacts reported included reduced energy for doing things they enjoyed earlier (42%), anxiety (34%), worry about losing their independence (33%), worry about the burden inflicted on friends/family (32%), feeling sick (27%) and being more irritable around friends/family (24%). Nearly 77% of survey respondents mentioned an impact of CKD on their work life and career, with 25% reporting reduced productivity, concern about their future earnings and loss of drive and ambition. The most common symptom experienced by patients was fatigue (62% of all respondents increasing to 75% by Stage 4 or 5). Additionally, more than half (55%) with severe CKD experienced at least five symptoms, reflecting the increased impact of the disease in advanced stages.

Overall, most patients (96%) had concerns about their future due to CKD; the most common being poor QoL (40%), fear of overall health getting worse (39%), and being a burden on their family/friends (37%). In the UK, 55% found it hard to cope emotionally with the impact of the disease and 63% had lower self-esteem, thus negatively impacting their relationships. Providing optimal care for both young and older patients with any chronic disease is challenging and in turn imposes substantial burden on their caregivers, especially immediate family (67, 68). Additionally, factors such as relationship between caregiver and patient; behavioural, and psychological symptoms displayed by the patient; patient's gender; and adverse events (AEs) impact caregiver burden (69).

B.1.3.3 Current clinical pathway of CKD in the UK

- Management of CKD in the NHS is informed by NICE clinical guidelines (NG203 and NG28) and NICE-accredited guidelines from the UKKA. Being the most recent, UKKA guidelines can be interpreted as being informed by the latest clinical evidence available (5, 7, 30).
- CKD screening is recommended in adults using eGFR and uACR if applicable risk factors exist, and annual eGFR monitoring is recommended for patients taking calcineurin inhibitors (e.g., ciclosporin), lithium, or on long-term anti-steroidal anti-inflammatory drugs (Nonsteroidal anti-inflammatory drugs [NSAIDs]) (7, 70).
- However, diagnosis typically occurs as an incidental finding in primary care during basic metabolic panels or routine eGFR and uACR testing as early CKD is often asymptomatic (7, 70).

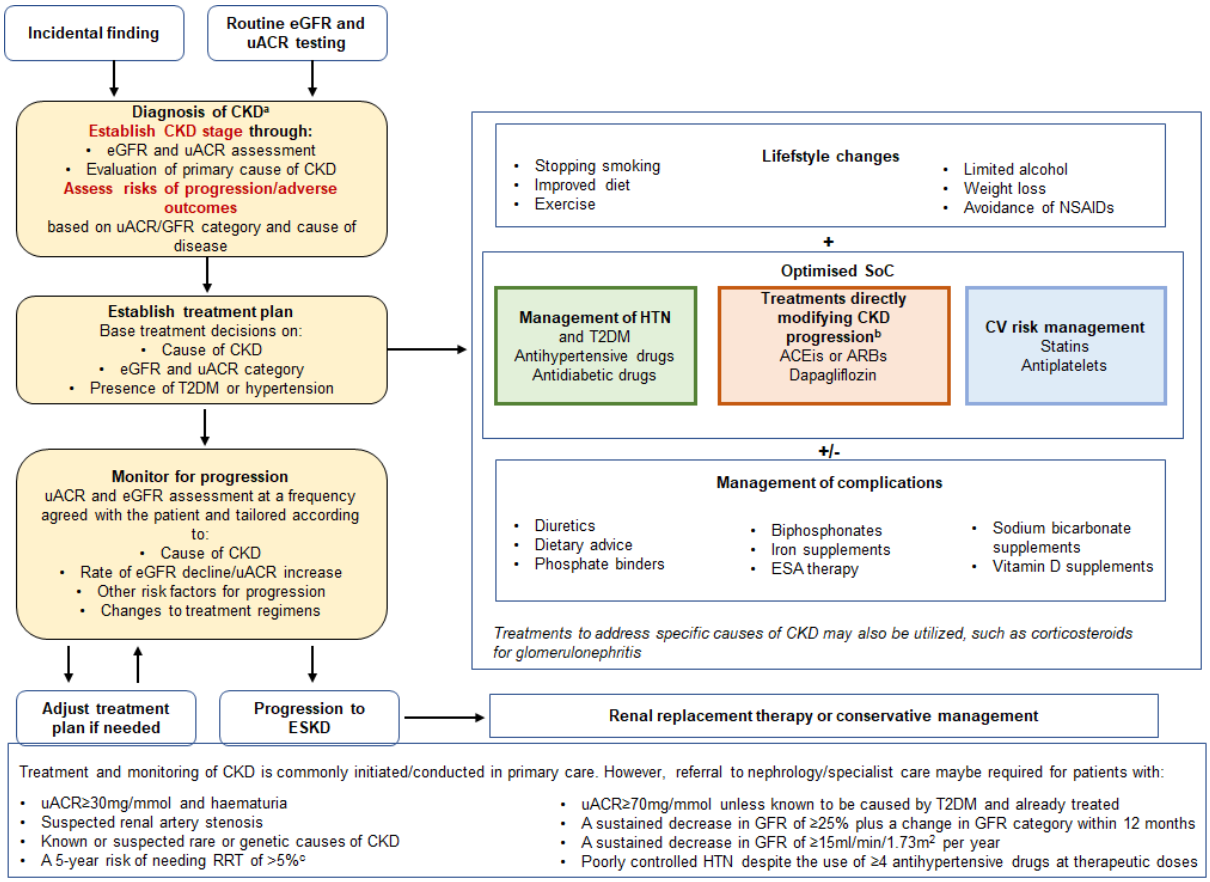
- The primary goal of CKD management is to prevent or delay progression to higher disease stages and ESKD, therefore reducing the risk of complications and adverse mortality outcomes (5, 7).
- Current established clinical practice in the NHS is individually optimised for each patient, wherein clinical management includes treatments directly modifying treatment progression such as renin-angiotensin-aldosterone system (RAAS) inhibitors and SGLT2 inhibitors, along with CVD risk management and comorbidity management, as well as management of CKD complications if required (5, 7, 30).
- NICE CKD guidelines (NG203) currently recommend SGLT2 inhibitors in selected CKD patients, who meet uACR thresholds and/or have T2DM. It is evident that the NG203 (Chronic kidney disease: assessment and management) guideline needs to be revised to incorporate a thorough and concise overview of all relevant recommendations on SGLT2 inhibitors in patients with CKD, with or without T2DM, and with or without albuminuria (7).
- If CKD progresses to stages 4 or 5 (7); assessments for RRT should be made at least 1 year before the patient reaches ESKD as per NICE guidelines NG107 (71).
- The 2023 UKKA guidelines make new recommendations for SGLT2 inhibitors to slow the rate of kidney function decline in CKD patients with and without T2DM at broader ranges of eGFR and lower uACR thresholds than existing guidelines, which is more reflective of evidence from the EMPA-KIDNEY ITT population than comparator trials (5, 7, 30).

Management of CKD in the NHS is informed by NICE clinical guidelines (Figure 2) and NICE-accredited guidelines from the UKKA. NICE Clinical Guideline 203 [NG203] for the assessment and management of people with or at risk of CKD was published in August 2021 (7), and an update of NICE Clinical Guideline 28 [NG28] was published in November 2021 which included recommendations for T2DM patients with comorbid CKD (5). UKKA guidelines for CKD management were published in May 2023. While these three guidelines were published within a 2-year period, they make differing recommendations for the role of SGLT2 inhibitors in CKD due to the fast-evolving publication and interpretation of clinical trial evidence for the drug class in this indication. As they are most recent, UKKA guidelines can be interpreted as being informed by the latest clinical evidence available.

CKD is commonly diagnosed as an incidental finding in primary care, and there is evidence of low adherence to uACR testing and monitoring guidance in UK clinical practice.

CKD screening is recommended in adults using eGFR and uACR if applicable risk factors are found, and annual eGFR monitoring is recommended for patients taking calcineurin inhibitors (e.g., ciclosporin), lithium, or on long-term anti-steroidal anti-inflammatory drugs (NSAIDs) (7, 70). However, diagnosis commonly occurs in primary care setting as an incidental finding during basic metabolic investigations or routine eGFR and uACR testing as early CKD is often asymptomatic Figure 2. Nearly 50-70% of CKD patients are diagnosed during screening for other conditions (31, 32, 70). The remaining 30-50% of CKD patients are then usually identified via specific CKD screening.

Figure 2. Current clinical pathway for CKD in the UK



Abbreviations: ACEis, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration; ESA, Erythropoiesis-stimulating agents; ESKD, end-stage kidney disease; HTN, hypertension; NSAIDs, Nonsteroidal anti-inflammatory drugs; RRT, Renal replacement therapy; SoC, standard of care; T2DM, Type 2 diabetes mellitus; uACR, urine albumin-to-creatinine ratio,

[a] Abnormalities of kidney function or structure present for more than three months, with implications for health. This includes all people with markers of kidney damage and those with an eGFR <60 mL/min/1.73m^2 on at least two occasions separated by a period of at least 90 days (with or without markers of kidney damage).

[b] The 2021 draft NICE guidelines for the treatment of CKD also recommend the use of SGLT2 inhibitors in patients with T2DM, if they meet the criteria in the relevant marketing authorisation.

[c] Measured using the 4-variable Kidney Failure Risk Equation.

Source: Adapted from DAPA appraisal [TA775] (6)

A CKD diagnosis is made if patients are found to have repeated measures of reduced eGFR <60 mL/min/1.73m^2 or increased uACR ≥3 mg/mmol at least 3 months apart (7). Further investigations may be performed to establish aetiology and KDIGO stage (10) and support individually optimised treatment plans to mitigate against the risk of adverse outcomes at each stage (7), including CT scans, renal biopsies, urea nitrogen tests, and Cystatin C (7, 10).

As referral criteria are strict, patients typically do not consult a specialist until their CKD has progressed to at least stage 3 (72). Scenarios where specialist referral is appropriate are a 5-year risk of needing RRT >5% (measured by the 4-variable ESKD Risk Equation); a uACR ≥70 mg/mmol (unless caused by DM and already treated), a uACR >30 mg/mmol with haematuria; a

sustained decrease in eGFR ≥25% and a change in eGFR category within 12 months; a sustained decrease in eGFR of ≥15 mL/min/1.73m^2 per year; poorly controlled hypertension; known or suspected rare or genetic cause of CKD; and suspected renal artery stenosis (7).

Post diagnosis, individualised annual monitoring plans are required to identify any further disease progression. NG203 suggests minimum number of annual eGFR and uACR tests dependent on KDIGO category based on KDIGO 2012 recommendations, with patients with more advanced CKD subject to more frequent monitoring based on risk (7, 10) (Table 9).

Table 9. Annual eGFR and uACR monitoring requirement for patients with or at risk of CKD

	A1	A2	A3
G1	0-1	1	1 or more
G2	0-1	0-1	0-1
G3a	1	1	2
G3b	1 to 2	2	2 or more
G4	2	2	3
G5	4	4 or more	4 or more

Abbreviation: CKD, chronic kidney disease; eGFR, estimated Glomerular filtration rate; uACR, urine albumin-to-creatinine ratio
Source: NG203 guidelines (7)

However, rates of uACR testing and monitoring are low in UK clinical practice: A 2023 Hospital Episode Statistics (HES) linked Clinical Practice Datalink (CPRD) Aurum observational study found only 45% of adults with CKD had a uACR measurement between January 2010 to December 2019. DISCOVER CKD further reported a low frequency of uACR testing in clinical practice with less than 10% of patients in the base cohort with 2 eGFR measures having a uACR measurement (28). Low rates of uACR testing contribute to most CKD diagnoses occurring at Stage 3 or above, as diagnosis of early disease is dependent on uACR while eGFR remains ≥60 mL/min/1.73m^2.

Treatment goals in CKD are to prevent or delay disease progression and reduce the risk of complications and AEs

The primary goal of CKD management is to prevent or delay progression to higher disease stages and ESKD, therefore reducing the risk of complications and adverse mortality outcomes (5, 7). UK clinical practice focusses on management of comorbidities including CVD (statins, anticoagulants, antiplatelet therapy), T2DM (antidiabetic medication), and hypertension (antihypertensive medication) leading to a complex treatment pathway with polypharmacy due to the need to meet multiple treatment goals. Disease-modifying therapy for CKD includes renin-angiotensin-aldosterone system (RAAS) inhibition (angiotensin-converting enzyme [ACE] inhibitors and angiotensin-receptor blockers [ARB]) and more recently SGLT2 inhibition as per NG203, NG28, and UKKA guidelines (Figure 2) (5, 7, 30).

SGLT2 inhibitors represent a significant advancement in disease-modifying treatment options for CKD patients, and 2023 UKKA guidelines reflect the latest clinical evidence

SGLT2 inhibitors are currently recommended as an adjunct to individually optimised SoC, in order to slow disease progression. Of note, NG203 (Chronic Kidney Disease: assessment and management) does not make direct recommendations on the use of SGLT2 inhibitors in patients with CKD, but instead directs readers to follow recommendations made in NG28 (Type 2 diabetes in adults: management) or TA775 (NICE technology appraisal guidance on dapagliflozin for treating chronic kidney disease). It is evident that the NG203 guidelines need to be revised to incorporate a thorough and concise overview of all relevant recommendations on SGLT2 inhibitors in patients with CKD, with or without T2D.

NG28 recommends that adults with T2D and CKD, who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), are offered an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if their uACR is over 30 mg/mmol and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds) (5). The guidelines also suggest that an SGLT2 inhibitor is considered for patients with both T2D and CKD (who are on an ARB or an ACE inhibitor at the highest tolerated dose), provided their uACR is between 3 and 30 mg/mmol (subject to meeting the criteria in the marketing authorisation).

TA775 recommends the SGLT2 inhibitor dapagliflozin (Forxiga®) as an option for treating CKD in adults if it is an add-on to optimised SoC including the highest tolerated licensed dose of ACE inhibitor or ARB, unless contraindicated, and people have an eGFR of 25 mL/min/1.73m^2 to 75 mL/min/1.73m^2 at the start of treatment and have T2D or have a uACR of 22.6 mg/mmol or more (6).

NG203, NG28 and TA775 do not recommend SGLT2 inhibitor use in CKD patients without either T2DM or albuminuria. However, the new UKKA Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease (published May 2023) makes recommendations to use SGLT2 inhibitors to slow the rate of kidney function decline in CKD patients with and without T2DM at broader ranges of uACR and eGFR (30).

In summary, the UKKA guidelines recommend SGLT2 inhibitors are initiated in CKD patients with/without T2D in the following scenarios:

- An eGFR 20-45 mL/min/1.73m^{2,} irrespective of albuminuria
- An eGFR >45 and uACR of ≥25 mg/mmol.

Furthermore, the guidelines suggest:

- SGLT2 inhibitors are initiated in patients with T2DM and eGFR >45–60 mL/min/1.73m^{2,} without albuminuria (uACR <25 mg/mmol)

- Clinicians consider SGLT2 initiation in patients with eGFR <20mL/min/1.73m^2 to slow progression of kidney disease.

The UKKA guidelines offer the following Quick Reference Guide for implementation in people with CKD with or without T2DM (Table 10).

Table 10. UKKA Quick Reference Guide for implementation in people with CKD with or without T2DM

SGLT-2 inhibition to reduce risk of kidney disease and cardiovascular outcomes*		Urinary Albumin-to-creatinine ratio (mg/mmol)	
		<25	≥25
eGFR (mL/min/1.73m^2)	≥60	†	Recommended
	≥45 to <60	Suggested (in type 2 diabetes)	Recommended
	≥20 to <45	Recommended	Recommended
	<20	Suggested	Suggested
	Dialysis	Not recommended ‡	Not recommended ‡

Abbreviations: eGFR, estimated glomerular filtration rate; SGLT2, sodium glucose co-transporter 2; UKKA, United Kingdom Kidney Association
*People with type 1 diabetes, polycystic kidney disease, or kidney transplant excluded from the definitive trials.
† In this guideline we do not make recommendations on the use of SGLT2 inhibition to reduce kidney disease progression for people with eGFR ≥60 mL/min/1.73m^2 and uACR <25 mg/mmol as this is outside the scope of this guideline. However, we support the use of SGLT2 inhibitors in this population for relevant indications, including treatment of people with heart failure and reduction of cardiovascular risk in people with T2D at high CV risk.
‡ Further research recommended in people with kidney replacement therapy to establish the role SGLT2 inhibition in these patients.
Source: UKKA Guideline 2023 (30)

UKKA guidelines reflect the latest clinical evidence for SGLT2 inhibitors in CKD, and data from both the pivotal EMPA-KIDNEY and DAPA-CKD trials were considered in their development. EMPA-KIDNEY incorporated a broader range of CKD patients as part of its inclusion criteria (eGFR ≥20 and <45mL/min/1.73m^2; or eGFR ≥45 and <90mL/min/1.73m^2 with uACR ≥22.6 mg/mmol) compared to DAPA-CKD (eGFR ≥25 and <75mL/min/1.73m^2 with uACR ≥22.6 to <565 mg/mmol). The recommendations made by UKKA are closely aligned with evidence of the efficacy of empagliflozin in the ITT population of EMPA-KIDNEY, indicating scope to prescribe empagliflozin in patients who would not be eligible for dapagliflozin but have residual risk of CKD disease progression.

RRT is required as a life-supporting treatment if CKD progresses to ESKD

A cohort of patients will still progress to ESKD despite individually optimised SoC and SGLT2 inhibition. If CKD disease cannot be managed appropriately and the disease progresses to stages 4 or 5 (usually regarded as pre-dialysis) (7); assessments for RRT to maintain normal homeostatic processes should begin before they reach Stage 5 or ESKD. NICE guidelines NG107 outline that assessments should be made at least 1 year before the patient reaches ESKD when RRT is likely to be needed (71). RRT options include HD, haemofiltration, haemodiafiltration, PD, and kidney

transplantation. Patients may also be given the choice of conservative management which may reflect patient preferences in cases where HRQoL or life expectancy are poor (7, 71).

B.1.3.4 Limitations of current pathway and unmet need

- There is no standard response criterion in CKD management and all CKD patients receiving individually optimised SoC maintain a residual risk of disease progression and adverse outcomes, irrespective of disease stage (2).
- ACE inhibitors and ARBs are not universally included in the SoC across all patients in UK clinical practice, and intolerability precludes prescription in some patients with CKD (5, 7, 30).
- Current NICE recommendations for SGLT2 inhibitors in the management of CKD exclude a broad range of CKD patients, including those without T2D or albuminuria, and/or with certain eGFR ranges (5, 7, 30).
- There is an unmet need for disease-modifying treatment options in CKD patients who remain at risk of disease progression, in particular those without access to SGLT2 inhibitors and those who cannot tolerate an ACE inhibitor or ARB.

Patients receiving individually optimised SoC including ACE inhibitors, ARBs and statins remain at residual risk of CKD disease progression and adverse outcomes

There is no standard response criterion in CKD management and all patients with CKD maintain a residual risk of disease progression and adverse outcomes irrespective of disease stage. This residual risk exists for patients receiving individually optimised SoC, as demonstrated in the EMPA-KIDNEY trial (which included patients receiving ACE inhibitors, ARBs and statins in both arms), where progression of CKD or death from CV causes occurred in 16.9% of patients in the placebo on top of SoC group (2).

There is evidence of lack of universal uptake of ACE inhibitors, ARBs, and statins in CKD patients in UK clinical practice

ACE inhibitors, ARBs and statins constitute part of SoC, with RAAS inhibitors classed as disease-modifying CKD treatment options as per TA775 (Figure 2) (6). However, DISCOVER CKD demonstrated that only 51.5% of patients with CKD were prescribed an ACE inhibitor or ARB in the UK CPRD cohort (28) due to issues with tolerability and contraindications (e.g., in patients at risk of hypotension or hyperkalaemia) (73), with Boehringer Ingelheim (BI) prescription data suggesting that [redacted] (74). Statins are recommended for reducing CV risk in patients with CKD who have a 10-year risk of developing CVD of ≥10%, and for secondary prevention in patients with CKD and established CVD (7, 75). However, DISCOVER CKD also reported only 52.9% of patients with CKD as receiving this drug class (28). As such, a significant proportion of patients with CKD are not receiving the SoC in UK clinical practice.

NG203 and TA775 restrict access to SGLT2 inhibitors for CKD patients with T2DM or albuminuria meaning a proportion do not have access to disease-modifying therapy

There is a substantial proportion of patients to whom SGLT2 inhibitors are currently not available. BI prescription data (Q1 2023) suggest [redacted] (74). This demonstrates that use of SGLT2 inhibitors is not yet well established in clinical practice, with scope to expand the use of this drug class in this indication to slow CKD disease progression.

Prior to EMPA-KIDNEY, SGLT2 inhibitor trials did not include a broad range of CKD patients (8, 9). Thus, based on available evidence, dapagliflozin is recommended for CKD patients with an eGFR between 25 to 75 mL/min/1.73m^2, with comorbid T2DM or a uACR ≥22.6 mg/mmol (6). Further, the CREDENCE trial restricted inclusion only to CKD patients with comorbid T2DM, uACR >30 mg/mmol and eGFR of 30 to <90 mL/min/1.73m^2. In contrast, EMPA-KIDNEY included patients with or without comorbid T2DM, eGFR of ≥20 to <45 mL/min1.73m^2, or eGFR of ≥45 to <90 mL/min/1.73m^2 and a uACR of ≥ 22.6 mg/mmol, representing an opportunity to extend SGLT2 inhibitors to a broader range of CKD patients not investigated in previous RCTs or covered by existing NICE recommendations.

The 2023 UKKA guidelines recommend SGLT2 inhibitor use in CKD patients with and without T2DM over a broader range of eGFR and lower uACR thresholds than NG203 and TA775, which is more reflective of evidence from the EMPA-KIDNEY ITT population than comparator trials. A NICE recommendation for empagliflozin in line with the ITT population will address an important unmet need for patients currently not able to access SGLT2 treatment for CKD and reflect UKKA guideline recommendations.

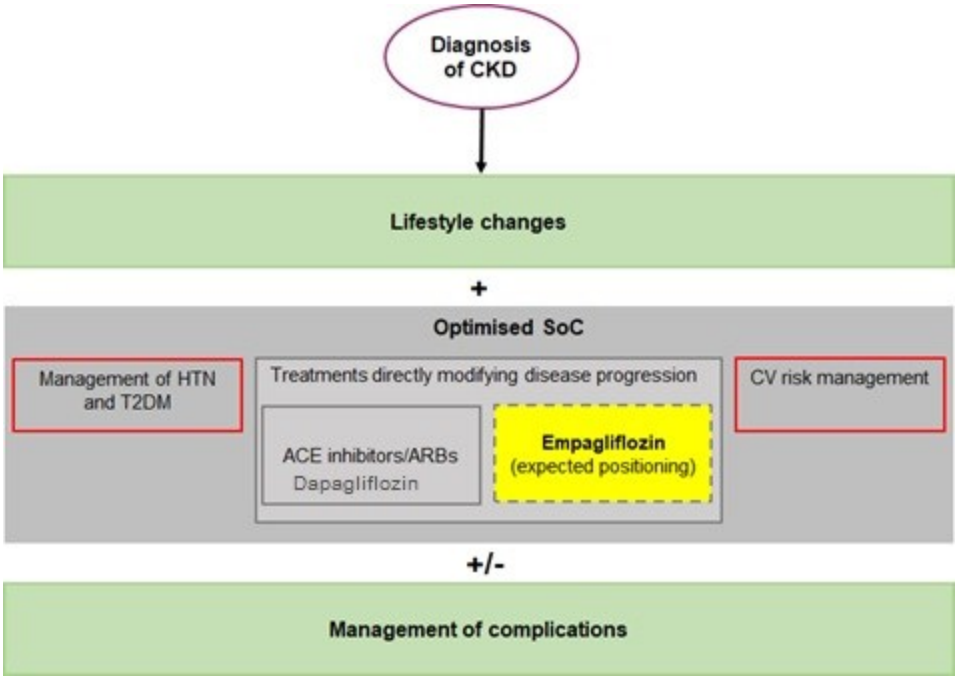
B.1.3.5 Expected positioning of empagliflozin in the UK treatment pathway

Empagliflozin should be positioned as a disease-modifying treatment option in combination with individually optimised SoC at the earliest opportunity in adult patients at risk of CKD disease progression (

Figure 3).

CKD is usually treated and monitored in primary care settings (7, 70, 76), however, empagliflozin should be made available in both primary and secondary care to ensure the broadest population of patients are able to gain access.

Figure 3. Expected positioning of empagliflozin in the UK treatment pathway



Abbreviations: ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blockers; CKD, chronic kidney disease; CV, cardiovascular; HTN, hypertension; SoC, standard of care; T2DM, Type 2 Diabetes mellitus
Source: Adapted from NICE guideline 2021 NG203 (7)

BI seek a recommendation for empagliflozin in adults with CKD in line with the pivotal EMPA-Kidney trial ITT population, plus a broader recommendation in CKD patients with comorbid T2DM, as an add-on to individually optimised standard care including ACE inhibitors or ARBs, unless these are contraindicated or not tolerated, and people have either, at the start of treatment:

- an eGFR of 20 mL/min/1.73m^2 up to 45 mL/min/1.73m^2 or
- an eGFR of 45 mL/min/1.73m^2 up to 90 mL/min/1.73m^2 and either:
    - a uACR of 22.6 mg/mmol or more or
    - T2DM.

A positive recommendation for empagliflozin in the above CKD population will provide additional options for patients and address an important unmet need for a disease-modifying option for CKD patients in England and Wales not currently covered by existing NICE recommendations.

B.1.4 Equality considerations

A positive recommendation for empagliflozin enabling broad access for patients across primary and secondary care settings and the multidisciplinary care team can help address inequalities in access to care for CKD patients, particularly in areas with limited presence of secondary and

specialist care facilities. A 2016 review outlined the pivotal role that primary care has in preventing the progression of disease and complications amongst CKD patients (48).

Principle 9 of NICE's Social Value judgements as part of its statement highlights the goal to reduce health inequalities across protected characteristics as well as considering those arising from socioeconomic factors (11). Socioeconomic disparities are associated with health inequalities in England, with more socially advantaged patients often receiving better access to secondary and specialist care in the NHS (12). There are demonstrable distributional health inequalities in terms of the risk and impact of CKD, with some groups more disadvantaged by the condition than others:

There is evidence of reduced access to dialysis services in rural areas, and people from areas with higher social deprivation are more likely to develop CKD, progress to more severe disease stages, and experience lower life expectancy with the condition compared to those from less socially deprived areas. Further, people from Black and South Asian backgrounds are three to five times more likely to require dialysis and on average wait between 168 to 262 days longer for kidney transplantation than those from a Caucasian background (77).

Resource constraints in a post-COVID-19 healthcare system may further exacerbate pre-existing inequalities in access to secondary and specialist care in the NHS. Secondary care in CKD is largely focussed on patients with ESKD, and barriers in ease and affordability of travel may further complicate access to these settings.

A NICE recommendation should allow broad access to empagliflozin for adults with CKD across primary and secondary care settings, as well as across the full multidisciplinary team as CKD patients may be seen by a variety of specialists in the NHS. Broad access is important for potentially improving the quality of care (thus reducing the burden of complications) and for alleviating any health inequalities in terms of access to nephroprotective treatments for CKD patients. Further, the availability of an additional SGLT2 inhibitor for patients with CKD could help to overcome potential supply issues that may limit access to treatments (78). Importantly, the availability of an additional SGLT2 inhibitor enables patient and physician choice.

B.2 Clinical effectiveness

- The EMPA-KIDNEY trial was designed to assess the effects of empagliflozin in a broad range of adult patients (n=6,609) with CKD at risk of disease progression, including patients without T2DM, and patients with varying levels of albuminuria.
- The pre-specified composite primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes, defined as:
  1. ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant,
  2. a sustained decrease in the eGFR to <10 mL/min/1.73m^2; a sustained decrease from baseline in the eGFR of at least 40%; or,
  3. death from renal causes.
- Key secondary outcomes were:
  - ACH (first and recurrent combined)
  - First occurrence of HHF or CV death, and
  - All-cause mortality.
- In March 2022, the Independent Data Monitoring Committee (DMC) recommended to stop the trial early due to positive efficacy after both pre-specified conditions were met.
- At median follow-up of 2.0 years (interquartile range, 1.5 to 2.4), empagliflozin significantly reduced the risk of kidney disease progression or CV death (primary outcome) compared to placebo (13.1% versus 16.9%, respectively; HR, 0.72; 95% confidence interval [CI], 0.64, 0.82; p<0.0001).
- The result of the primary outcome was consistent (interaction p-value >0.05) regardless of T2DM status at baseline, with the upper bound of the 95% CI for the HR <1.
- Secondary and tertiary outcomes were supportive of the treatment benefit observed in the primary outcome: compared to placebo, empagliflozin significantly reduced the risk of ACH (HR, 0.86; 95% CI, 0.78–0.95; p=0.003) (key secondary outcome), kidney disease progression (HR, 0.71; 95% CI, 0.62 to 0.81; p<0.0001) (tertiary outcome), and adjudicated CV death or ESKD (HR, 0.73; 95% CI, 0.59 to 0.89; p=0.0023) (tertiary outcome).
- There was a numerical but not statistically significant benefit in the key secondary outcomes all-cause mortality and HHF or CV death, and tertiary outcome CV death (p>0.05, in each).
- The further outcome analysis of the annual rate of change in eGFR (chronic slope) showed that the eGFR decline was lower for empagliflozin compared with placebo, with a between-group difference of 1.37 mL/min/1.73m^2 per year and a relative difference of 50%.
- Empagliflozin was generally well tolerated in patients with CKD, consistent with the known safety profile.
- The frequencies of patients with pre-specified non-serious adverse event (AE), AEs leading to treatment discontinuation, and SAEs were similar to placebo.

B.2.1 Identification and selection of relevant studies

A SLR was conducted to identify data on RCTs reporting on the efficacy and safety of potential comparators, namely SGLT2 inhibitors and finerenone for the treatment of adult patients with CKD/ DKD. The SLR was supplemented by a targeted literature review (TLR) to identify relevant observational studies that could supplement RCT evidence. The methods used to identify the relevant clinical evidence are described in Appendix D.

MEDLINE®, Embase® and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (via Ovid) were performed on 03 October 2022. This was supplemented with a desk search of conference proceedings from last 5 years (2019 to 2022 meetings). The TLR

searches were performed on the same date as SLR, using MEDLINE® and Embase® (via Ovid) as well as manual checking of bibliography lists of any relevant SLRs identified in the database search.

The eligible studies encompassed all RCTs evaluating efficacy of pharmacological interventions (SGLT2 inhibitors and finerenone) used in the treatment of adults (age ≥18 years) with CKD. The search strategy was designed to be broad and to encompass all interventions that currently comprise the SoC, as well as recently approved interventions and investigational agents for the management of CKD (eligibility criteria are shown in Table 8 and Table 9 of Appendix D). All studies meeting the pre-specified population, intervention, comparator, outcomes, and study (PICOS) eligibility criteria were retained. Data extraction was done in a pre-defined data extraction template (DET) in MS Excel® to capture the data elements of interest from each included study.

The SLR included three relevant trials of empagliflozin (EMPEROR-Reduced, EMPEROR-Preserved and EMPA-REG OUTCOME). The pivotal trial, EMPA-KIDNEY trial, compared oral empagliflozin 10mg OD on top of SoC versus matching placebo on top of SoC, in patients with established CKD. This is the primary source of clinical evidence in the economic model. At the time of performance, the EMPA-KIDNEY trial publication had not yet been published, thus information for EMPA-KIDNEY was taken from confidential clinical study reports. A full list of studies that were included and excluded during the SLR is provided in Table 10 and Table 11 of Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

As discussed in above Section B.2.1 Identification and selection of relevant studies, the SLR included four trials investigating the efficacy of empagliflozin in CKD (Table 11). The pivotal trial for empagliflozin in this indication is EMPA-KIDNEY, a phase III, randomised, double-blind, placebo-controlled trial that compared empagliflozin 10mg OD on top of SoC (n=3,304) to matched placebo on top of SoC (n=3,305) for the treatment of CKD in patients with and without comorbid T2DM (2, 79, 80). EMPA-KIDNEY is described in full in the following sections.

The EMPA-REG OUTCOME (81), EMPEROR-Reduced (82), and EMPEROR-Preserved (83) trials also evaluated the efficacy of empagliflozin; however in these trials, patients with CKD were subpopulations of the main population (Table 11**Error! Reference source not found.**) and included patients with uACR and eGFR values outside of the EMPA-KIDNEY eligibility criteria who were at less advanced stages of CKD, i.e. moderate to high risk according to KDIGO. Results of a supplementary efficacy analysis on a large population of patients from these trials complement the findings from the EMPA-KIDNEY trial (predominantly in patients at very high risk according to KDIGO) by providing evidence in renal endpoints and support the generalisability of the EMPA-KIDNEY results to a broad population of patients at various stages of CKD. Thus, these trials

provide additional information and evidence relevant to the decision problem. For the full supplementary analysis, refer to Appendix M.

Despite the usefulness of these trials in demonstrating efficacy in the broad CKD population, the primary objectives of these trials were not directly relevant to the original decision problem, therefore were not included in economic model. The pivotal trial, EMPA-KIDNEY, was the main source of clinical efficacy evidence in the cost-utility model described in Section **Error! Reference source not found.**.

Table 11. Clinical effectiveness evidence

Study	EMPA-KIDNEY (NCT03594110) (2, 79, 80)	EMPA-REG OUTCOME NCT01131676 (81)	EMPEROR-Reduced NCT03057977 (82)	EMPEROR-Preserved NCT03057951 (83)
Study design	Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment	Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment	Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment	Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment
Population	Patients with evidence of CKD at risk of kidney disease progression, with or without diagnosed DM (see Section B.2.3.2 Eligibility criteria for study participants).	Patients With T2DM and high CV risk	Patients with chronic HF and reduced EF defined as LVEF ≤40%	Patients with chronic HF and LVEF >40%
Intervention(s)	Empagliflozin per oral 10 mg OD in addition to SoC (which could include treatment with RAS-inhibitors, diuretics, and beta-blockers)	Empagliflozin per oral 10 mg or 25 mg OD in addition to SoC (which could include treatment with glucose-lowering therapies, RAS-inhibitors, and beta-blockers)	Empagliflozin per oral 10 mg OD in addition to SoC (which could include treatment with diuretics, RAS-inhibitors, ARN-inhibitors, beta-blockers, and MRAs)	Empagliflozin per oral 10 mg OD in addition to SoC (which could include treatment with diuretics, RAS-inhibitors, ARN-inhibitors, beta-blockers, and MRAs)
Comparator(s)	Placebo plus SoC	Placebo plus SoC	Placebo plus SoC	Placebo plus SoC
Study relevant for this appraisal & reason	Yes, meets the PICO criteria as defined in the decision problem	Meets PICO criteria as defined in the decision problem for a subpopulation of the trial: the trial did not specify CKD as an inclusion criterion	Meets PICO criteria as defined in the decision problem for a subpopulation of the trial: the trial did not specify CKD as an inclusion criterion	Meets PICO criteria as defined in the decision problem for a subpopulation of the trial: the trial did not specify CKD as an inclusion criterion
Indicate if study supports application for marketing authorisation	Yes	Yes, provides supplementary evidence for CKD population outside of EMPA-KIDNEY	No	No
Indicate if study used in the economic model	Yes	No	No	No

Study	EMPA-KIDNEY (NCT03594110) (2, 79, 80)	EMPA-REG OUTCOME NCT01131676 (81)	EMPEROR-Reduced NCT03057977 (82)	EMPEROR-Preserved NCT03057951 (83)
Reported outcomes specified in the decision problem (Outcomes incorporated in the model are marked in bold)	• Time to the first occurrence of a composite of kidney disease progression or CV death • Time to adjudicated death from any cause • Time to the first occurrence of HHF or CV death • Time to occurrence of ACH (first and recurrent combined) • Time to the first occurrence of kidney disease progression • Time to adjudicated CV death • Time to first occurrence of adjudicated CV death or ESKD • Annual rate of change in eGFR • **Adverse effects of treatment** • **Health-related quality of life measured by EQ-5D-5L**	• Composite renal outcomes (eGFR decline, ESKD, or renal death) and (eGFR decline, ESKD, or CV or renal death) • ESKD • HHF • CV death • HHF or CV death • 3-point MACE (CV death, MI, or stroke) • ACH • All-cause mortality	• Composite renal outcomes (eGFR decline, ESKD, or renal death) and (eGFR decline, ESKD, or CV or renal death) • ESKD • HHF • CV death • HHF or CV death • ACH	• Composite renal outcomes (eGFR decline, ESKD, or renal death) and (eGFR decline, ESKD, or CV or renal death) • ESRD • HHF • CV death • HHF or CV death
All other reported outcomes	• Time to renal outcomes • **eGFR changes over time** • **uACR changes over time** • Progression in albuminuria • Time to adjudicated death by category of cause • Time to first occurrence of CV death or ESKD • Time to first occurrence of a major CV event	N/A	N/A	N/A

Study	EMPA-KIDNEY (NCT03594110) (2, 79, 80)	EMPA-REG OUTCOME NCT01131676 (81)	EMPEROR-Reduced NCT03057977 (82)	EMPEROR-Preserved NCT03057951 (83)
	• Time to occurrence of adjudicated HHF • Time to new onset of DM • Time to first occurrence of self-reported gout • HbA1c changes over time			

Abbreviations: ACH, all-cause hospitalisations; ARN, angiotensin receptor-neprilysin; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; EQ-5D, EuroQol- 5 Dimension; HbA1c, glycated haemoglobin, HF, heart failure; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infraction; MRA, aldosterone receptor antagonist; N/A, not applicable; OD, once daily; PICO, patient intervention comparator outcome; RAS, renin-angiotensin system; SoC, standard of care; T2DM, type 2 diabetes mellitus; uACR, urine albumin-creatinine ratio.

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

The EMPA-KIDNEY trial investigated the effect of empagliflozin 10mg oral OD on top of SoC versus matching placebo on top of SoC on the combined risk of kidney disease progression and CV death in patients with CKD. The rationale for testing empagliflozin in the full range of people at risk of CKD progression was based on findings from the EMPA-REG OUTCOME trial (84) and other clinical and experimental data, which showed SGLT2 inhibitors induce glycosuria and lower BP and albuminuria (85-87). Empagliflozin had also been shown to have haemodynamic effects in the kidney in the absence of elevated blood glucose i.e., in people without DM (88). In summary, it was hypothesised that empagliflozin may have beneficial effects on kidney disease progression and CV risk among those with CKD, irrespective of the presence of DM. Thus, the EMPA-KIDNEY trial aimed to include large numbers of patients without DM, patients with an eGFR <30mL/min/1.73m^2, and patients with low levels of proteinuria (measured by the uACR) to assess the safety and efficacy of empagliflozin in a broad range of people with CKD with and without DM (2).

The enrolled patients were broadly representative of the population of patients with CKD who are at risk for disease progression (2). The applicability of the trial results to NHS clinical practice is discussed further in Section B.2.5.1 Applicability to clinical practice.

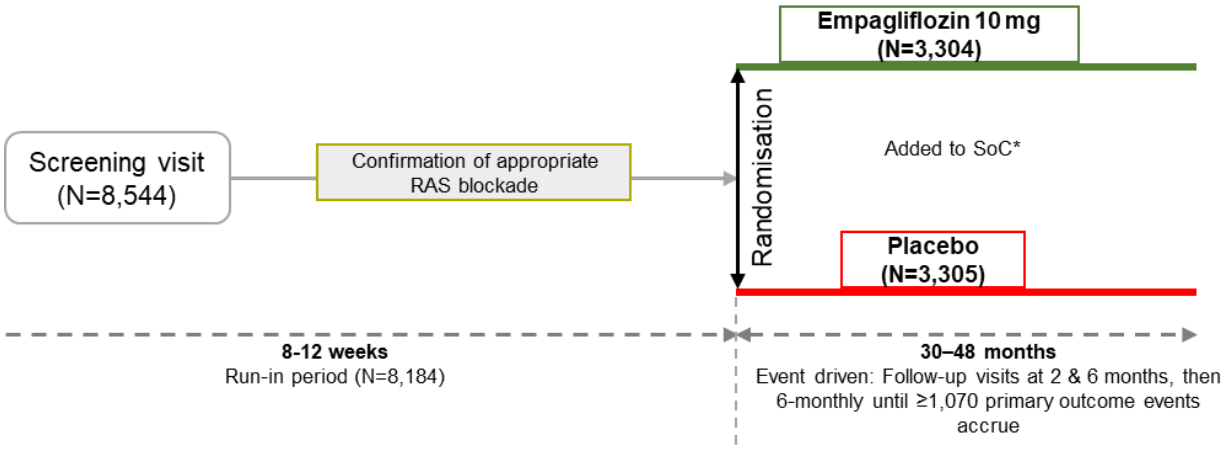
B.2.3.1 EMPA-KIDNEY trial design

EMPA-KIDNEY was a large, international, multicentre, phase III, double-blinded, randomised placebo-controlled trial conducted between February 2019 and July 2022 assessing the effect empagliflozin on top of addition to SoC on the progression of kidney disease and CVD in a wide range of patients with CKD with or without DM (2). Patients were allocated using a minimised randomisation algorithm to receive either oral empagliflozin 10 mg OD or matching placebo in a 1:1 ratio. The algorithm helped ensure balance between the treatment groups with respect to the following prognostic variables: age, sex, prior DM, eGFR and uACR (both based on local laboratory results at screening) (79).

In total, 8,544 potentially eligible patients were screened. Post screening, 8,184 patients entered an 8-12 week ‘Run-in’ period prior to randomisation, during which they received single-blind placebo tablets. This was to ensure that only those patients likely to continue taking study treatment for an extended period were randomised and provided investigators with an opportunity to review and approve the participation of each participant to ensure they were on appropriate background therapy (including RAAS blockade). In total 6,609 patients were ultimately randomised to

empagliflozin 10 mg OD (n=3,304) or matching placebo (n=3,305). See Figure 4 for schematic depiction of the trial design and Figure 5 for a CONSORT diagram illustrating the patient flow (2).

Figure 4. The EMPA-KIDNEY trial design



Abbreviations: RAS, Renin-angiotensin system; SoC, Standard of care
*Guideline directed medical therapy.
Source: Adapted from EMPA-KIDNEY Clinical trial report (CTR) (79)

The pre-specified composite primary outcome was the first occurrence of progression of kidney disease or death from CV causes. Progression of kidney disease was defined as:

1. ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant,
2. a sustained decrease in the eGFR to <10 mL/min/1.73m^2, a sustained decrease from baseline in the eGFR of at least 40%, or
3. death from renal causes.

Key secondary outcomes were:

- ACH (first and recurrent combined),
- First occurrence of HHF or CV death, and
- All-cause mortality (2).

A formal interim analysis to decide whether to stop the trial for benefit was planned to be made after 150 ESKD events (chronic dialysis, transplant) had occurred, by which time it was expected that approximately 60% of all first primary outcomes had occurred. At the time of the interim analysis, 624 (58% of 1070) primary outcome events had occurred (interim database lock 22nd Feb 2022) and two conditions were required to be met:

- Hazard ratio for the primary outcome of <0.778 with a two-sided p-value of <0.0017 and
- Hazard ratio for the outcome of ESKD (chronic dialysis, transplant) or CV death (other secondary outcome) of <0.778 with a two-sided p-value of <0.05.

Furthermore, in March 2022, the Independent DMC recommended to stop the trial early due to positive efficacy after both of these pre-specified conditions were met (79).

B.2.3.2 Eligibility criteria for study participants

Key inclusion and exclusion criteria of EMPA-KIDNEY are listed in Table 12. Eligible participants were adult CKD patients with or without comorbid DM. The number of patients with or without DM (of any type) was intended to be at least one-third of each, and the number of patients with an eGFR ≥45 mL/min/1.73m^2 was limited to about one-third. All patients were required to provide written informed consent (79).

Table 12. Inclusion and exclusion criteria of the EMPA-KIDNEY trial

Inclusion criteria	• Males and females aged ≥18 years, or 'full age' as required by local regulation (e.g., 20 years in Japan) • Evidence of CKD at risk of kidney disease progression, defined on the basis of local laboratory results recorded ≥3 months before and at the time of the screening visit, and required that: CKD-EPI eGFR ≥20 and <45 mL/min/1.73m^2; or CKD-EPI eGFR ≥45 and <90 mL/min/1.73m^2 with uACR ≥200 mg/g (22.6 mg/mmol) (A2-A3) (or protein: creatinine ratio ≥300 mg/g [30 mg/mmol]) • A local investigator judging that the participants neither required empagliflozin (or any other SGLT2 or dual SGLT1/2 inhibitor), nor that such treatment was inappropriate • Patients treated with clinically appropriate doses of a RAS inhibitor with either ACE inhibitors or ARB, unless treatment was either not tolerated or indicated
Exclusion criteria	• Receiving a SGLT2 or dual SGLT1/2 inhibitor at the time of study or, receiving dual RAS-inhibition (two of ACE inhibitors, ARB, or DRI treatment) • T2DM and prior atherosclerotic cardiovascular disease† with an eGFR>60 mL/min/1.73m^2 at screening • T1DM‡ • Undergoing maintenance dialysis, functioning kidney transplant, or scheduled living donor transplant* • Polycystic kidney disease or Previous or scheduled bariatric surgery or ketoacidosis in the past 5 years • Symptomatic hypotension*, or systolic blood pressure <90 or >180 mmHg, or ALT or AST >3x ULN at screening • Hypersensitivity to empagliflozin or another SGLT2 inhibitor • Intravenous immunosuppression therapy in the previous 3 months; or anyone currently on >45 mg prednisolone (or equivalent)* • Use of an investigational medicinal product in the 30 days prior to screening visit • Poorly compliant with clinic visits or prescribed medication* • Medical history that might limit individual's ability to take trial treatments for the duration of the study (e.g., severe respiratory disease; history of cancer or evidence of spread within last 4 years, other than non-melanoma skin cancer; or recent history of alcohol or substance misuse)* • Current pregnancy, lactation, or women of childbearing potential, unless using highly effective contraception • Additionally, individuals were excluded at the randomisation visit of the participant if they did not adhere to run-in treatment, were no longer willing to be randomised and followed for at least 3 years, were considered by a local investigator not to be suitable for randomisation, or experienced ketoacidosis, heart attack, stroke, or hospitalisation for heart failure, or hospitalisation for urinary tract infection or acute kidney injury during run-in

Abbreviations: ACE, Angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin receptor-II blocker; AST, aspartate transaminase; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiological collaboration; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; SGLT, sodium-glucose cotransporter; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; uACR, urine albumin-to-creatinine ratio, ULN, upper limit of normal.

*Based on self-reports at screening and randomisation visits.

†Myocardial infarction, angina, stroke, or peripheral arterial disease (including lower limb amputation)

‡ As of January 2020, the protocol was amended to allow currently enrolled patients with T1D to continue in the study and limit screening of new patients with T1D due to a sponsor decision. At that time, the Data Monitoring Committee (DMC) did not report any safety concerns in patients with T1D.

Source: EMPA-KIDNEY Collaborative Group 2022 (1)

B.2.3.3 Settings and locations where data were collected

EMPA-KIDNEY was a multicentre study conducted in 241 centres in eight countries across North America, Europe, and Asia (2). Of the 6,609 randomised patients, 2,648 (40%) were from Europe; 1,717 (26%) from North America, 1,632 (25%) from China and Malaysia, and 612 (9%) from Japan (79).

B.2.3.4 Trial drugs and concomitant medications

Study interventions are summarised in Table 13. Disallowed concomitant medications included any SGLT2 inhibitors or combined sodium-glucose cotransporter 1 (SGLT1) and 2 inhibitors, except the blinded trial medication. Women of childbearing potential had to agree to use highly effective contraception throughout the trial and for 7 days after the end of the trial (79).

Table 13. The EMPA-KIDNEY trial drugs

Drug	Dose	Frequency of administration	Route of administration	Duration
Empagliflozin, film coated tablet	10 mg	Once daily	Oral	Until the necessary number of events were observed to evaluate efficacy for the primary composite outcome
Placebo matching empagliflozin, film coated tablet	-			

Source: The EMPA-KIDNEY Collaborative Group (2)

B.2.3.5 Pre-specified primary and secondary outcomes of EMPA-KIDNEY

The primary and secondary outcomes of the EMPA-KIDNEY trial are shown in Table 14 below.

Table 14. Pre-specified primary and secondary outcomes

Primary outcome	Definition
Progression of kidney disease or death from CV causes	A composite of time to the first occurrence of progression of kidney disease (ESKD*, a sustained decrease in the eGFR to <10 mL/min/1.73m^2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomisation); or CV death ('as adjudicated')
Key secondary outcomes	**Definition**
Death from any cause	Time to death from any cause ('as adjudicated')
HHF or death from CV causes	Time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated')
Hospitalisation for any cause	Time to occurrences of ACH (first and recurrent combined)
Other secondary outcomes	**Definition**
Progression of kidney disease	Time to the first occurrence of kidney disease progression
Death from CV causes	Time to CV death ('as adjudicated')
Composite of ESKD or death from CV causes	Time to first occurrence of CV death ('as adjudicated') or ESKD

Further outcomes	Definition
Annual rate of change in eGFR	Annual rate of change in eGFR
HRQoL[#]	EQ-5D values and EQ-VAS over time, as measured by the health-related quality of life EuroQol 5 dimensions 5 levels questionnaire
Safety	Only pre-specified non-serious AEs were collected along with all SAEs. The pre-specified non-serious AEs were AEs leading to study drug discontinuation, bone fracture, severe hypoglycaemia, gout, symptomatic dehydration, AEs of special interest (ketoacidosis, lower limb amputation, and liver injury), and AEs that could lead to amputation. Adjudicated AEs, specific AEs and a number of trial-specific safety outcomes were analysed.

Abbreviations: ACE, all-cause hospitalisations; AE, adverse events; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analogue scores; HHF, hospitalisation for heart failure; HRQoL, health-related quality of life; SAE, serious adverse event

*ESKD - defined as the initiation of maintenance dialysis or receipt of a kidney transplant

[#]The HRQoL results are presented in Appendix N

Source: The EMPA-KIDNEY Collaborative Group 2023 (2); EMPA-KIDNEY CTR (79)

Central, blinded adjudication was performed by trained clinicians based at the Central Coordinating Office, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) at the University of Oxford for death events and events initially reported as HHF, myocardial infarction, stroke, liver injury, ketoacidosis, lower limb amputation, acute kidney injury (AKI), and genital infections. Only events that have been confirmed or not refuted by adjudication were included in the relevant analyses (79).

B.2.3.6 Pre-specified subgroup analyses

The subgroups of key interest were DM status, baseline eGFR, and baseline uACR. Furthermore, the primary outcome was subject to subgroup analyses for age, sex, region, ethnicity, baseline blood pressure, baseline body mass index (BMI), history of prior disease (including CVD), cause of CKD, baseline laboratory values, and medication use at randomisation (2).

B.2.3.7 Demographics and baseline characteristics

Patients in the empagliflozin and placebo groups were well balanced with respect to demographic and clinical characteristics at baseline (Table 15). The patient population broadly represented those with CKD who are at risk for disease progression. Approximately two-thirds of the patients (66.8%) were men, 54.6% of the patients were ≥65 years old, including 23.0% of patients ≥75 years old. The majority of patients had a baseline eGFR equivalent to Stage 3 CKD (≥30 to <60 mL/min/1.73m^2; 44.3% and 13.4% had an eGFR of ≥30 to <45 and ≥45 to <60 mL/min/1.73m^2 respectively), followed by Stage 4 (34.5%; eGFR <30 mL/min/1.73m^2). Mean eGFR at baseline was 37.37 ± 14.48 mL/min/1.73m^2 for the empagliflozin group and 37.26 ± 14.42 mL/min/1.73m^2 for the placebo group. A marginal majority of patients in both the groups (approximately 52% in each) had macroalbuminuria. Median uACR at baseline was 329.35 mg/g (37.22 mg/mmol);

330.58 mg/g (37.36 mg/mmol) for the empagliflozin group and 327.26 mg/g (36.98 mg/mmol) for the placebo group (2, 79).

The majority (54.0%) of patients were non-diabetic while, 44.4% had comorbid T2DM (empagliflozin: 44.5%, placebo: 44.4%) achieving the protocol requirement of including at least one-third with DM and one-third without DM. Over a quarter of patients had comorbid CVD (empagliflozin: 26.1%, placebo: 27.4%) and over 10% had comorbid myocardial infarction (10.6%, in each empagliflozin and placebo groups). The use of concomitant medications was generally well balanced across the treatment groups. The most common non-study medication of interest at baseline was RAS-inhibitors (empagliflozin: 85.7%, placebo: 84.6%) (2, 79).

Table 15. Demographic and baseline characteristics of randomised patients in the EMPA-KIDNEY trial

Baseline characteristic*	Empagliflozin 10 mg	Placebo
Number of subjects, N	3,304	3,305
Age (years), mean (SD)	63.9 (13.9)	63.8 (13.9)
Female sex, N (%)	1,097 (33.2)	1,095 (33.1)
Race, N (%)†		
White	1,939 (58.7)	1,920 (58.1)
Black	128 (3.9)	134 (4.1)
Asian	1,194 (36.1)	1,199 (36.3)
Multiple	14 (0.4)	7 (0.2)
Other	29 (0.9)	45 (1.4)
Body mass index¶ (kg/m^2), mean (SD)	29.7 (6.7)	29.8 (6.8)
Blood pressure (mm Hg)		
Systolic	136.4 (18.1)	136.7 (18.4)
Diastolic	78.1 (11.7)	78.1 (11.9)
History of DM, N (%)‡		
Yes	1,525 (46.2)	1,515 (45.8)
No	1,779 (53.8)	1,790 (54.2)
DM type, no./total no. (%)		
Type 1	34/1,525 (2.2)	34/1,515 (2.2)
Type 2	1,470/1,525 (96.4)	1,466/1,515 (96.8)
Other or unknown	21/1,525 (1.4)	15/1,515 (1.0)
History of cardiovascular disease, N (%)§		
Yes	861 (26.1)	904 (27.4)
No	2,443 (73.9)	2,401 (72.6)
eGFR‖		
Mean – mL/min/1.73m^2 (SD)	37.4 (14.5)	37.3 (14.4)
Distribution, N (%)		
<30 mL/min/1.73m^2	1,131 (34.2)	1,151 (34.8)
≥30 to <45 mL/min/1.73m^2	1,467 (44.4)	1,461 (44.2)
≥45 mL/min/1.73m^2	706 (21.4)	693 (21.0)
Urinary albumin-to-creatinine ratio**		
Geometric mean (95% CI)	219 (205-234)	226 (211-242)
Median (IQR)	331 (46-1061)	327 (54-1074)
Distribution, N (%)		
<30	665 (20.1)	663 (20.1)
≥30 to ≤300	927 (28.1)	937 (28.4)
>300	1,712 (51.8)	1,705 (51.6)

Baseline characteristic*	Empagliflozin 10 mg	Placebo
Median NT-proBNP (IQR)- ng/litre	162 (70-421)	159 (68-417)
Baseline medications, N (%)		
Renin-angiotensin system inhibitor	2,831 (85.7)	2,797 (84.6)
Any diuretic	1,362 (41.2)	1,453 (44.0)
Any lipid-lowering medication	2,190 (66.3)	2,188 (66.2)
Cause of kidney disease, N (%)		
Diabetic kidney disease	1,032 (31.2)	1,025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; no/N, number; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; SD, standard deviation.

*Percentages may not total 100 because of rounding.

† Race was reported by the patients. The "other" category indicates that the race was not specified, or the patient preferred not to answer.

¶ The body mass index is the weight in kilograms divided by the square of the height in metres.

‡ History of DM was defined as a patient-reported history of DM of any type, use of glucose-lowering medication, or a glycated haemoglobin level of at least 48 mmol per mole (6.5%) at the randomisation visit.

§ History of cardiovascular disease was defined as a patient-reported history of myocardial infarction, heart failure, stroke, transient ischaemic attack, or peripheral arterial disease.

‖ The values represent the measurement recorded at the randomisation visit or the most recent local laboratory result recorded before randomisation.

** For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams and creatinine was measured in grams.

Source: The EMPA-KIDNEY Collaborative Group 2023 (2).

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

The statistical analysis methods and definitions of study groups used in the pivotal EMPA-KIDNEY trial are described in Table 16.

B.2.4.1 Statistical methods and analysis sets

Table 16. Summary of statistical analysis in the EMPA-KIDNEY trial

Study name (number)	EMPA-KIDNEY (NCT03594110)
Research hypothesis	For each outcome, evidence of a treatment effect was evaluated with a 2-sided test based on the following hypotheses: • Null hypothesis: There is no difference between the effect of placebo and the effect of empagliflozin in terms of the outcome in question. • Alternative hypothesis: There is a difference between the effect of placebo and the effect of empagliflozin in terms of the outcome in question.

Analysis sets	• **Screened Set (SCR):** all patients screened for the trial and who provided informed consent (n=8,266).
	• **Randomised set (RS):** all randomised patients, whether treated or not (n=6,609).
	  ○ OC-AD: Observed case including data after treatment discontinuation
	  ○ OC-OT: Observed case on treatment.

Study name (number)	EMPA-KIDNEY (NCT03594110)
	• **Treated set (TS):** all patients who were dispensed randomised trial medication. All randomised patients were dispensed study medication and therefore included in the TS (n=6,609). Efficacy analyses were based on the RS of patients using all available data from the follow-up period (OC-AD), thus following the ITT analysis approach. Data occurring after the final follow-up visit were not considered.
Hypothesis testing	• Formal hypothesis testing was performed for the primary efficacy outcome. If the primary efficacy outcome was statistically significant, the formal hypothesis testing of the key secondary outcomes was to be performed via the Hochberg procedure to control the familywise error rate. • The information fraction used in the α-spending functions for the primary and key secondary outcomes was based on the number of primary outcome events observed at the time of the interim analysis, as a proportion of the anticipated number at the scheduled end of the trial. As such an information fraction of 58% (624/1070) was used. This led to a 2-sided α - spending level of 0.0017 for the primary efficacy outcome. • Formal statistical testing of the key secondary outcomes was performed starting with a 2-sided α-spending level of 0.0290 and preserving the overall type I error rate for the trial at 2-sided α of 0.05.
Statistical analysis for primary outcome	• Assessment of primary outcome involved an ITT comparison among all randomised patients using a Cox proportional hazards regression model. The model was adjusted for the variables used in the minimisation algorithm (age, sex, DM status, eGFR, uACR and region) to estimate the HR ratio associated with allocation to empagliflozin versus placebo (with the Wald chi-square statistic used to both test significance and generate an asymptotic 95% CI). An HR below one favoured empagliflozin. Ties were handled using Breslow's method. • For the analysis of the primary outcome, the Hwang-Shih-DeCani α-spending function with parameter γ=-8 was used to account for multiplicity. The α-levels were adjusted according to the actual proportion of primary outcome events observed at the interim. • Kaplan-Meier curves were produced to summarise the primary outcome data. The number of events in each of the individual components that contribute to the overall number of primary composite events were summarised descriptively. • EMPA-KIDNEY trial was statistically powered to demonstrate efficacy for the primary composite endpoint in the overall population.
Statistical analysis for key and other secondary outcomes	• As statistical significance was observed for the primary outcome, the key secondary outcomes were formally analysed via the Hochberg 'step-up' procedure to control the familywise error rate. • For the analysis, the Hwang-Shih-DeCani α-spending function with parameter γ=0 was used to account for multiplicity. The error rates were adjusted according to the actual proportion of primary outcome events observed at the interim. • The estimand for key secondary outcome 'time to first occurrence of HHF or CV death' was the HR of the time to first occurrence of HHF or CV death in the target population, for patients randomised to empagliflozin relative to those randomised to placebo, ignoring any non-fatal intercurrent events and in the hypothetical absence of death from any cause not included in the outcome. • The estimand for key secondary outcome 'time to occurrences of ACH (first and recurrent)' was the HR of the time to occurrences of ACH in the target population, for patients randomised to empagliflozin relative to those randomised to placebo, ignoring any non-hospitalisation non-fatal intercurrent events and in the hypothetical absence of death from any cause. ACH were analysed using a joint frailty model that accounts for the dependence between

Study name (number)	EMPA-KIDNEY (NCT03594110)
	recurrent hospitalisations and all-cause death through a participant-specific frailty term. • The estimand for key secondary outcome 'time to death from any cause' is the HR of the time to first occurrence of death from any cause in the target population, for patients randomised to empagliflozin relative to those randomised to placebo, ignoring any non-fatal intercurrent events. • The other secondary outcomes were analysed using the same methodology as for the primary outcome. No formal hypothesis testing or adjustment for multiple testing was performed for these outcomes, the analyses were considered as supportive to the main analyses. • The trial might not have been sufficiently powered for secondary or tertiary CV outcomes because: – The study was stopped early based on positive efficacy – The median follow-up time was approximately 2.0 years. – The EMPA-KIDNEY population had a lower absolute risk of kidney disease progression and CV events and mortality due to enrolling more patients without DM (54%), only 27% had CV disease at baseline with <10% with HF and 48% had a uACR <300 mg/g (30 mg/mmol). All these conditions (severe albuminuria, T2DM, CV disease and HF) are independent risk factors for CV events and mortality. Therefore, the occurrence of these events was likely to be low since the population does not have risk factors for those events occurring.
Statistical analysis of further outcomes	The main analyses of annual rate of change in eGFR used all available centrally assessed eGFR measurements for the period of interest, except for the exclusion of any eGFR data collected after an ESKD event. The shared parameter model was used to calculate the annual rate of change in eGFR, separately for the periods from: • Baseline to the final follow-up visit (i.e., the total slope) • From the 2-month visit to the final follow-up visit (i.e., the chronic slope)
Statistical analysis of safety outcomes	• The time to first occurrence of the trial-specific AE outcomes was analysed using the same methodology as for the primary efficacy outcome. • The main analysis of these outcomes was based on the RS OC-AD. Additional analyses on the TS OC-OT were also performed. • Pre-specified non-serious AEs included AEs leading to study treatment discontinuation, bone fractures, severe hypoglycaemia, gout, symptomatic dehydration, AESIs (ketoacidosis, LLA, and liver injury), and AEs that could lead to amputation.
Sample size & power calculation	• EMPA-KIDNEY was an event-driven trial • The trial was planned to randomise approximately 6000 patients from about 200-250 sites and continue until a minimum of 1070 primary outcome events occurred. This would provide an overall power of 90% at p=0.05 (2-sided) to detect an 18% relative reduction in the primary outcome (time to kidney disease progression or CV death).
Data management, patient withdrawals	**Handling of missing data** • For time to event outcomes, patients who were event-free but had dropped out of the trial prematurely, were to be censored. • For outcomes analysed by MMRM, missing data were handled via the methodology of MMRMs. • eGFR was estimated from creatinine measured in the central laboratory wherever possible. However, where a central laboratory eGFR measurement was expected but missing, the local blood creatinine measurement closest to the ideal follow-up day within the scheduled follow-up visit period (if one exists) was used to estimate the local eGFR instead. **Premature discontinuation of trial medication**

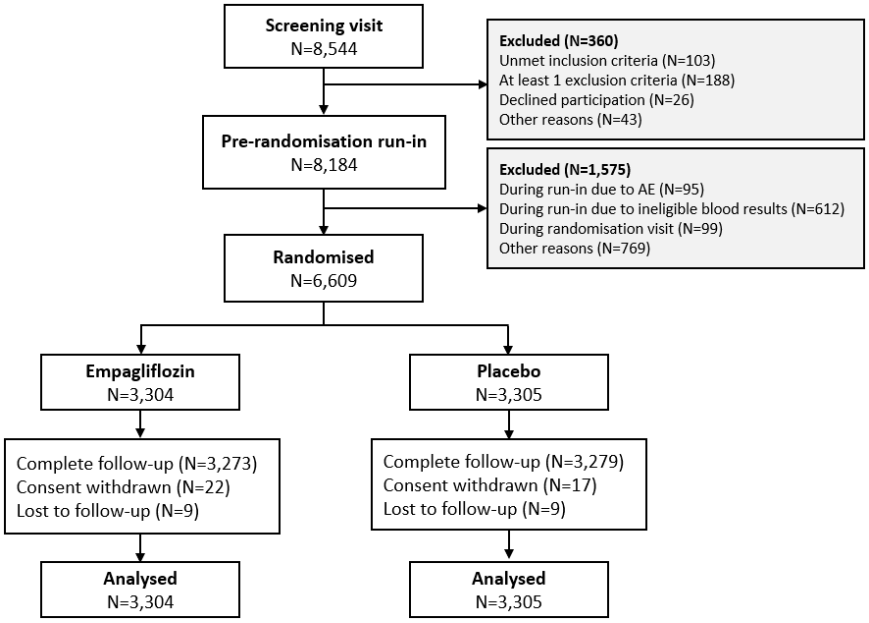
Study name (number)	EMPA-KIDNEY (NCT03594110)
	• Follow-up information were collected from all trial patients, irrespective of whether they continued to take study treatment, usually at routine follow-up clinic visits, unless they withdrew consent. • All efforts were made to continue to follow-up such patients, and those being followed by telephone or other remote method were encouraged to provide blood samples for central analysis at relevant time points. • If AEs occurred that were believed to be due to empagliflozin, including significant elevation of liver transaminases, the study treatments could be temporarily or permanently discontinued. **Withdrawal of informed consent** • Participants were free to withdraw consent for some or all aspects of the trial at any time. • The decision to withdraw ideally was to be put in writing and a copy maintained at the LCC (with key data items being recorded on the trial computer-based system). The written information was to specify which aspect(s) of the trial consent was being withdrawn.

Abbreviations: ACH, all-cause hospitalisations; AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; HF, heart failure; HR, hazard ratio; ITT, intention to treat; LCC, Local clinical centre; LLA, lower limb amputation; MMRM, mixed model repeated measure analysis; OS-OT, observed case on treatment; OC-AD, random-set observed case including data after treatment discontinuation; OC-OT, treated set observed case on treatment; uACR, urine albumin-to-creatinine ratio
Source: EMPA-KIDNEY CTR 2022 (79)

B.2.4.2 Participant flow in the relevant randomised controlled trials

A total of 8,544 potential participants attended a screening visit; 8,184 patients (95.8%) entered the pre-randomisation run-in phase, and 6,609 underwent randomisation (2). Of the 6,609 randomised patients (3,304 and 3,305 patients to empagliflozin and placebo arms, respectively), 6,568 patients (99.4%) completed the trial, including 315 patients who died (79). Of the 6,609 patients treated with study medication, 1,603 patients prematurely discontinued treatment (24.3%, including patients who died). The most common reasons for premature discontinuation of study medication were AEs (7.3%) and unknown, i.e., largely consisting of patients who provided no early treatment discontinuation reason but attended the final follow-up with a treatment stop date >1 day prior to the visit date (9.6%). Participant flow in the EMPA-KIDNEY trial is shown in Figure 5 (79).

Figure 5. CONSORT diagram of patient flow in each stage of the EMPA-KIDNEY trial



Abbreviation: AE, adverse event
Note: Complete follow-up defined as death before April 01, 2022 (start of final follow-up window) or completed final follow-up with last known alive after April 01, 2022
Source: Adapted from the EMPA-KIDNEY Collaborative Group 2022 (2)

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the critical appraisal of EMPA-KIDNEY, a parallel group RCT, is shown in Table 17. The complete critical appraisal is provided in Appendix D.

Table 17. Results of the critical appraisal of EMPA-KIDNEY trial

	EMPA-KIDNEY (NCT03594110)
Was randomisation carried out appropriately?	Yes. Randomisation was in 1:1 ratio using a minimised randomisation algorithm that helps to ensure balance between the treatment groups with respect to the prognostic variables
Was the concealment of treatment allocation adequate?	Yes.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and patient characteristics were well balanced between the two treatment groups at baseline, and randomisation.
Were the care providers, participants, and outcome assessors blind to the treatment allocation?	Yes. This was a double-blind study. Central Coordinating Office (CCO) based at Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) in Oxford provided adjudication in a manner blinded to the treatment assignment.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No. Proportion of patients who discontinued study treatment was low and well balanced between the two treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes specified in the study protocol were reported in the clinical study report.

	EMPA-KIDNEY (NCT03594110)
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed in the randomised set.

B.2.5.1 Applicability to clinical practice

EMPA-KIDNEY is the largest phase III trial investigating SGLT2 inhibitors in CKD so far and had broad eligibility criteria encompassing adult patients with CKD previously underrepresented in other SGLT2 inhibitor trials. Prior SGLT2 inhibitor trials have excluded the broad range of CKD patients, particularly those with lower eGFR and uACR (8, 9), whereas in contrast, EMPA-KIDNEY included patients with or without comorbid T2DM, eGFR of ≥20 to <45 mL/min1.73m^2, or eGFR of ≥45 to <90 mL/min/1.73m^2 and a uACR of ≥200mg/g (22.6 mg/mmol) (2).

In EMPA-KIDNEY, SoC was more aligned to clinical practice than other SGLT2 inhibitor trials in CKD. Physicians were responsible for ensuring individually optimised SoC was in place for each participant, including management of CV risk factors and other existing comorbidities (e.g., hypertension, T2DM etc.), and to ensure appropriate RAAS-inhibition was in place (i.e., ACE inhibitor or ARB), unless such treatment was either not tolerated or not indicated, making EMPA-KIDNEY's results applicable to patients with CKD seen in clinical settings.

As reported in section B.1.3.4, approximately 52–[redacted] of CKD patients in the NHS receive an ACE inhibitor or ARB. On the contrary, all or most patients in prior SGLT2 inhibitor CKD trials to date have received an ACE inhibitor or ARB (100% in CREDENCE and 97% in DAPA-CKD) (8, 9, 89). As a result, at approximately 85%, the rate of ACE inhibitor or ARB use in EMPA-KIDNEY is more representative of UK clinical practice than SoC in other SGLT2 inhibitor trials (2). EMPA-KIDNEY also included patients with a broad range of underlying causes of CKD, which reasonably correspond to causes of CKD as reported in the UKRR (amongst patients with eGFR <30 mL/min/1.73m^2 receiving RRT) (Table 18).

Further, clinical expert opinion concluded that whilst there are inherent differences between the EMPA-KIDNEY population and the real-world NHS CKD population, the patient population in EMPA-KIDNEY is similar to those seen in NHS clinical practice, and the results of the trial are generalisable to the UK clinical setting (Appendix O). Of note, the target CKD population in this submission is patients who meet the EMPA-KIDNEY renal inclusion criteria.

In summary, the EMPA-KIDNEY trial represents a highly relevant extension of the evidence of SGLT2 inhibition across a broad range of CKD patients, representative of those seen in NHS clinical practice.

Table 18: Causes of CKD in EMPA-KIDNEY vs UKKR report

Cause of kidney disease	EMPA-KIDNEY (placebo)	UK Renal Registry
DKD	31.0%	30.5%

Hypertensive or renovascular disease	22.4%	7.1%
Glomerular disease	24.7%	12.3%
Other	12.7%	18.2%
Unknown	9.2%	15.0%
PKD	NR	6.7%
Pyelonephritis	NR	5.3%
Renal Vascular Disease	NR	4.9%

Abbreviations: DKD, diabetic kidney disease; PKD, polycystic kidney disease
Sources: UK renal registry 24th annual report (33), EMPA-Kidney Collaborative Group (2022) (2)

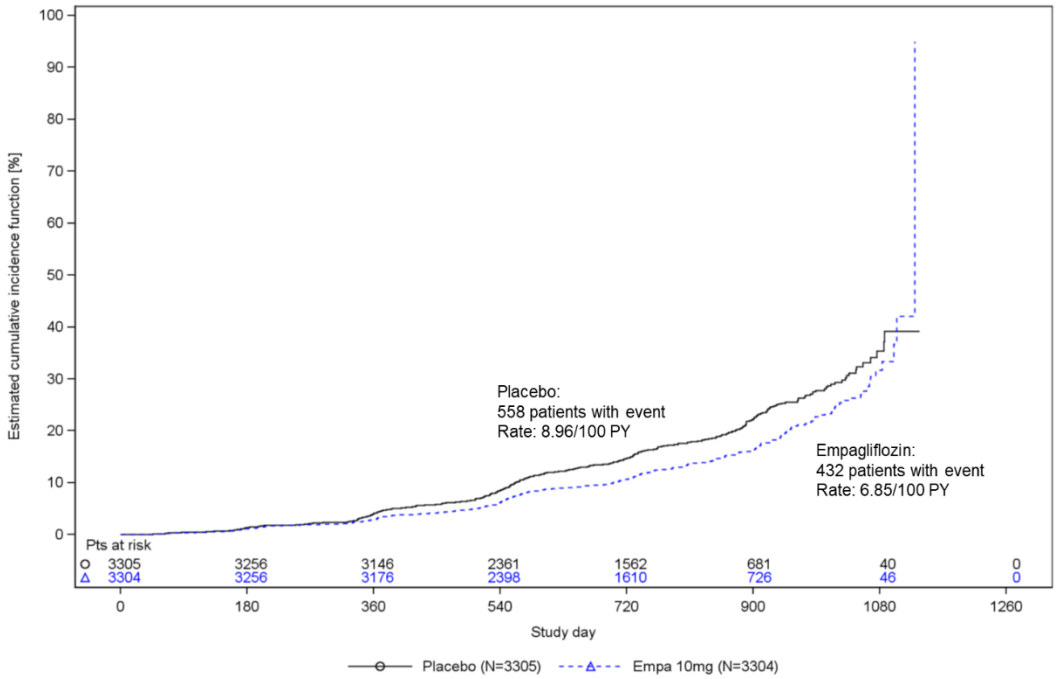
B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Primary outcome: kidney disease progression or CV death

Empagliflozin significantly reduced the relative risk of the primary outcome by 28% compared with placebo (Absolute Risk Reduction [ARR] 3.6%)

Empagliflozin significantly reduced the risk of progression of kidney disease or death from CV causes, which occurred in 432 patients (13.1%) of the empagliflozin group and 558 patients (16.9%) of the placebo group (HR 0.72; 95% CI 0.64 to 0.82; p<0.001). Due to the pragmatic design and limited follow-up visits, the first clear evidence of separation of the estimated cumulative incidence of kidney disease progression or CV death between empagliflozin and placebo became evident approximately 1 year after randomisation, however may have been sooner if data were collected at earlier visits, and continued to separate throughout the 2½ years of follow-up time until the number of patients at risk became too low to provide stable estimates (Figure 6) (2).

Figure 6. Time to the first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function (considering non-CV/renal death as a competing risk) – RS

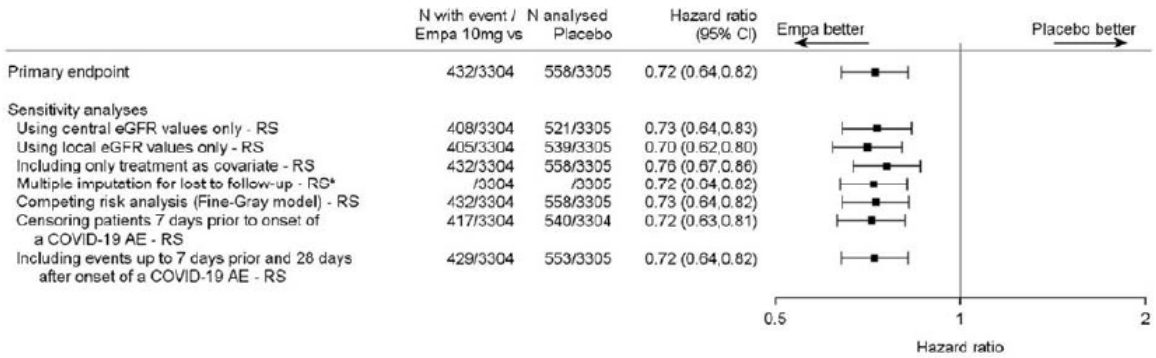


Abbreviations: CV, cardiovascular; PY, patient year; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, Figure 11.1.1.1: 1 and Table 11.1.1.1: 1 (79)

Results of the individual components of the primary outcome, kidney disease progression and CV death, are detailed in Section B.2.6.3 Tertiary/exploratory outcomes below.

The results of the sensitivity analyses were consistent (i.e., the HR and CIs were similar) with the results of the primary analysis (Figure 7). There was no meaningful effect on the primary analysis results with respect to the presence of COVID-19 AEs.

Figure 7. Sensitivity analyses of the time to the first event of kidney disease progression or adjudicated CV death – RS



Abbreviations: AE, adverse event; CI, confidence interval; eGFR, estimated glomerular filtration rate; RS, randomised set.
*There is no single definition of number of patients with an event as each imputation can produce a different number of events.
Source: EMPA-KIDNEY CTR 2022, Figure 11.1.1.2: 1 (79)

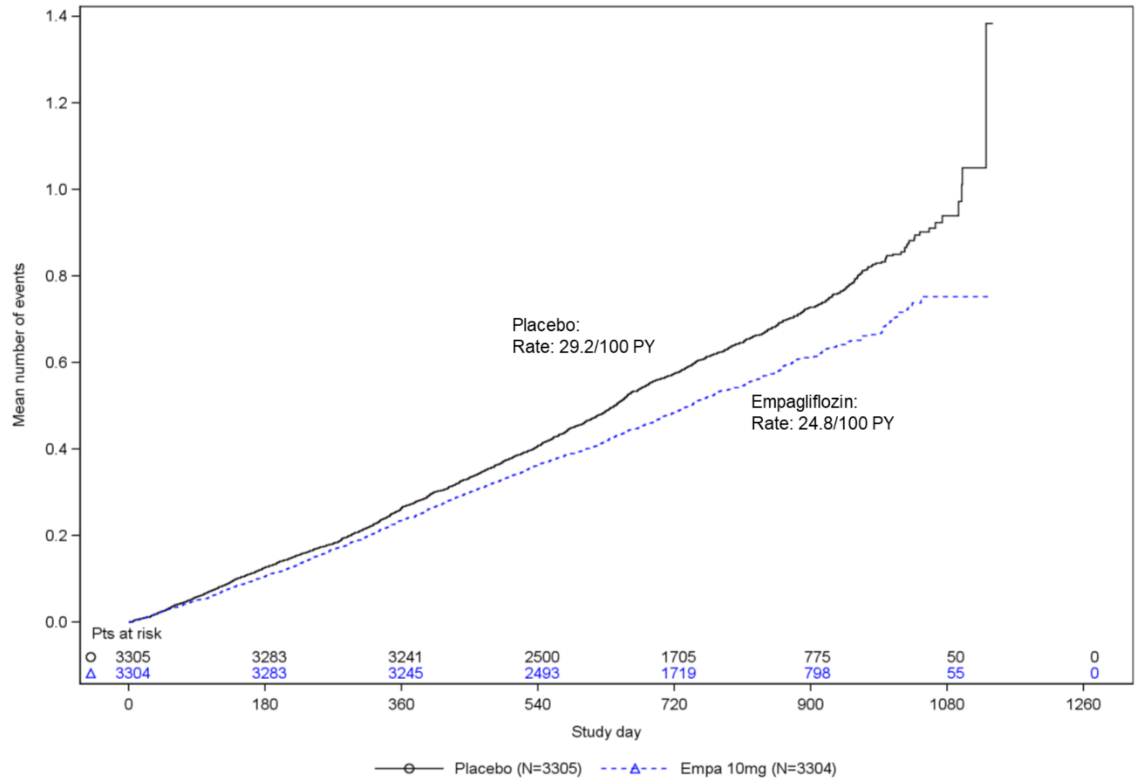
B.2.6.2 Key secondary outcomes

B.2.6.2.1 Time to occurrence of ACH (first and recurrent combined)

Empagliflozin significantly reduced the risk of ACH (first and recurrent combined), including those attributable to renal and CV reasons, compared with placebo

The rate of first and subsequent hospitalisations from any cause was lower in the empagliflozin group than in the placebo group (24.8 vs. 29.2 hospitalisations per 100 patient-years; HR 0.86; 95% CI, 0.78 to 0.95; p=0.0025). The total number of hospitalisation events (first and recurrent) was also lower in the empagliflozin group than in the placebo group (1,611 vs. 1,895). The mean cumulative incidence of ACH in the empagliflozin and placebo groups started to diverge shortly after randomisation and continued to separate over time (Figure 8) (79).

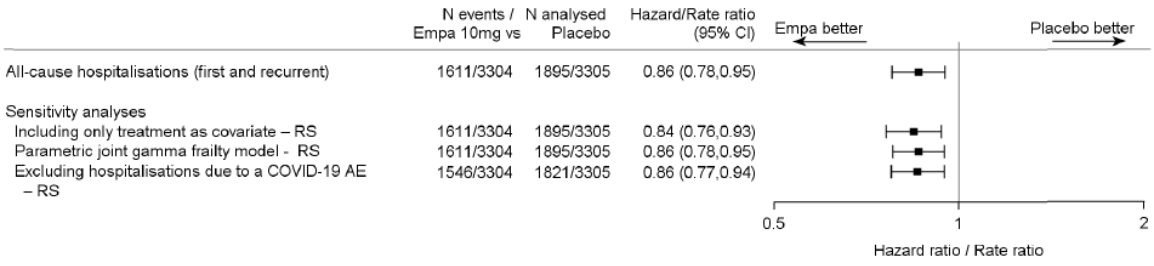
Figure 8. Time to events of ACH, mean cumulative function – RS



Abbreviations: ACH, all-cause hospitalisations; PY, patient year; RS, randomised set.
Source: The EMPA-KIDNEY Collaborative Group 2023 (2); EMPA-KIDNEY CTR 2022, Figure 11.1.2.3: 1 (79)

The results of the sensitivity analyses were consistent with the overall results (Figure 9).

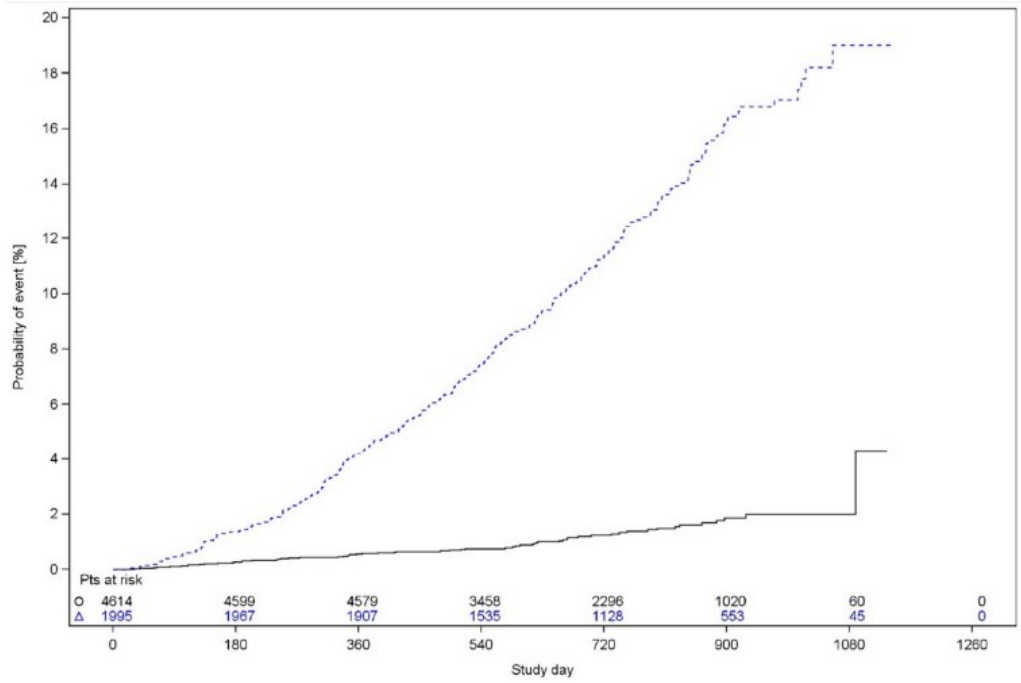
Figure 9. Sensitivity analyses of time to ACH and adjudicated death – RS



Abbreviations: ACH, all-cause hospitalisations; AE, adverse event; CI, confidence interval; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, 11.1.2.3: 2 (79)

To further explore the impact of hospitalisation, post hoc analysis of survival time from first hospitalisation in EMPA-KIDNEY was performed. The analysis showed that mortality rate in patients with at least one hospitalisation accounted to 25% over the remaining trial duration period. The risk of death was almost ten times higher in patients with hospitalisations compared to those without hospitalisations (HR 9.53; 95% CI 7.18, 12.64; p <0.0001) (Figure 10).

Figure 10: Time to death comparing patients with and without hospitalisations – RS



Abbreviations: RS, randomised set.

Source: Data on File. Boehringer Ingelheim Ltd. (90)

The reasons for hospitalisations were analysed using AEs leading to hospitalisations per system organ class. AEs leading to hospitalisations were reported most frequently in the system organ classes of infections and infestations, surgical and medical procedures, cardiac disorders, renal and urinary disorders, and investigations, all of which comprised approximately two-thirds of all hospitalisations. Renal and cardiovascular reasons for hospitalisations were analysed based on the respective the system organ classes and additionally based on a user-defined list of renal and cardiovascular AEs leading to hospitalisations. In all analyses, the total number of renal/CV hospitalisations and the proportion of patients with events were lower in the empagliflozin group than in the placebo group. The HR is generally consistent across all analyses.

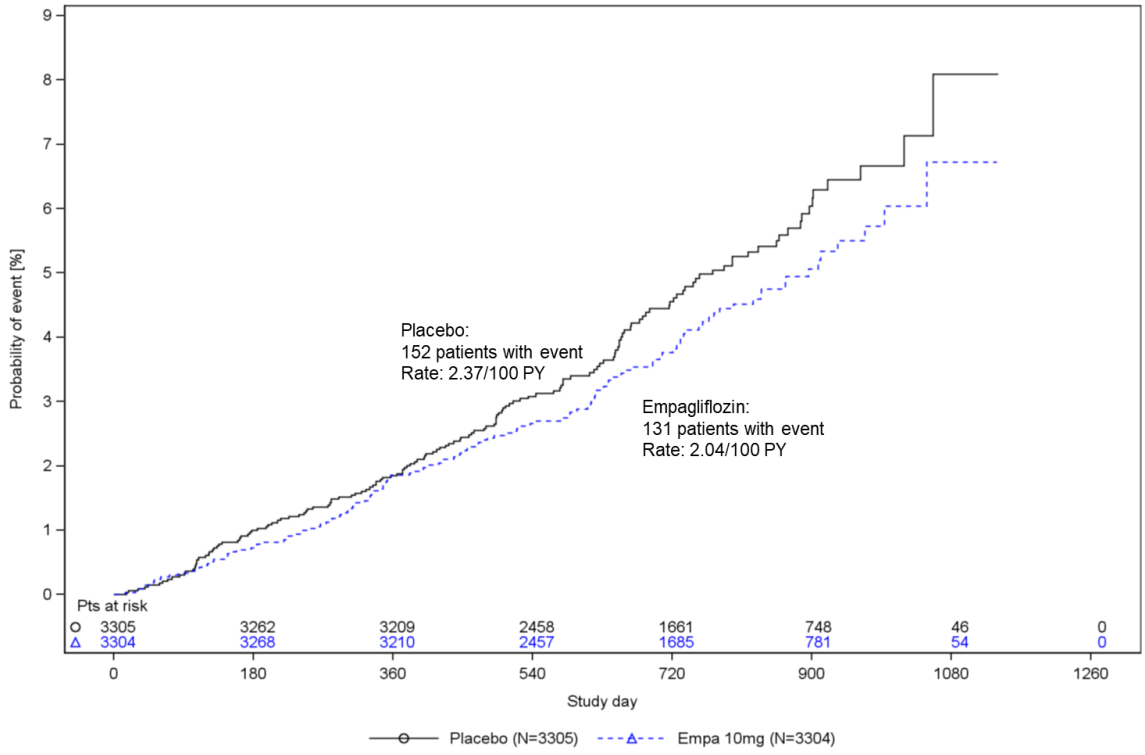
B.2.6.2.2 Time to first occurrence of HHF or CV death

There was a numerical reduction in the risk of HHF or CV death

There were 131 (4.0%) and 152 (4.6%) patients with any event of this composite outcome in the empagliflozin and placebo groups, respectively; however, the reduction in the risk of HHF or CV death with empagliflozin as compared with placebo did not reach statistical significance (HR, 0.84; 95% CI, 0.67 to 1.07; p=0.1530). This was due to sample power: the trial had a lower absolute risk of CV events and mortality as the enrolled patients were less likely to have these events (>50% patients did not have baseline DM or severe albuminuria and >70% did not have baseline CV

disease) (for details see Section B.2.4.1 Statistical methods and analysis sets). The cumulative incidence of HHF or CV death between empagliflozin and placebo is displayed in Figure 11 (79).

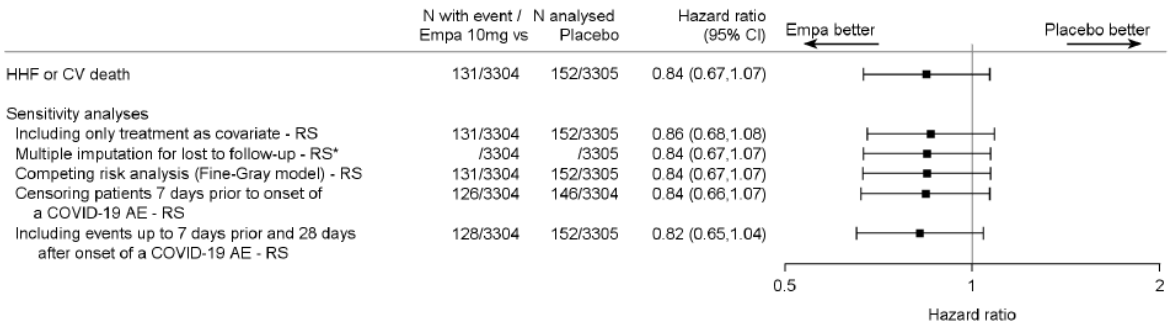
Figure 11. Time to the first event of adjudicated HHF or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as a competing risk) – RS



PY, patient year; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, Figure 11.1.2.2: 1 and Table 11.1.2.2: 1 (79)

The results of sensitivity analyses were consistent with the overall results (Figure 12).

Figure 12. Forest plot of sensitivity analyses of time to the first event of adjudicated HHF or adjudicated CV death – RS



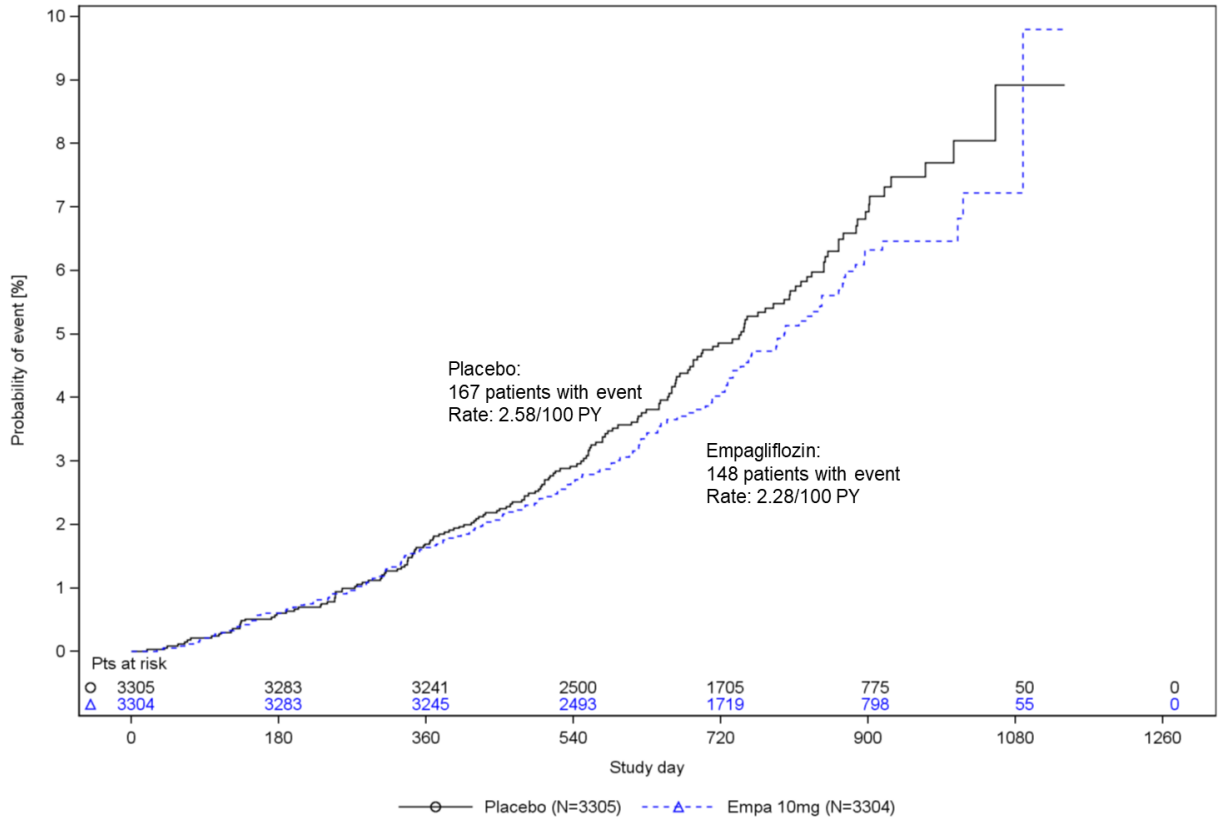
Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; RS, randomised set.
Events confirmed or unrefuted by adjudication are considered as an outcome event
*There is no single definition of number of patients with an event because each imputation can produce a different number of events
Source: EMPA-KIDNEY CTR 2022, Figure 15.2.2.1.2: 1 (79)

B.2.6.2.3 Time to adjudicated death from any cause

There was a numerical reduction in all-cause mortality for empagliflozin vs. placebo

There were 148 (4.5%) deaths in the empagliflozin group and 167 (5.1%) deaths in the placebo group. However, the reduction in the risk of all-cause death with empagliflozin treatment as compared with placebo did not reach statistical significance (HR 0.87; 95% CI, 0.70 to 1.08; p=0.2137). Historically, it is very difficult to demonstrate all-cause mortality in randomised clinical trials as it can take a long observation time, or a very high-risk population, to achieve enough events to reach statistical significance. Here, a nominal p-value of 0.2137 and a nominal relative risk reduction of 13% trending in the direction of reduced risk in those randomised to empagliflozin versus placebo is observed, which can be explained by a lower than anticipated rate of all-cause death due to the enrolled population, too few events, and too little time, overall contributing to having limited power. The hazard ratios were consistent with the totality of evidence for empagliflozin. The Kaplan-Meier estimates of all-cause death between empagliflozin and placebo is displayed in Figure 13 (79).

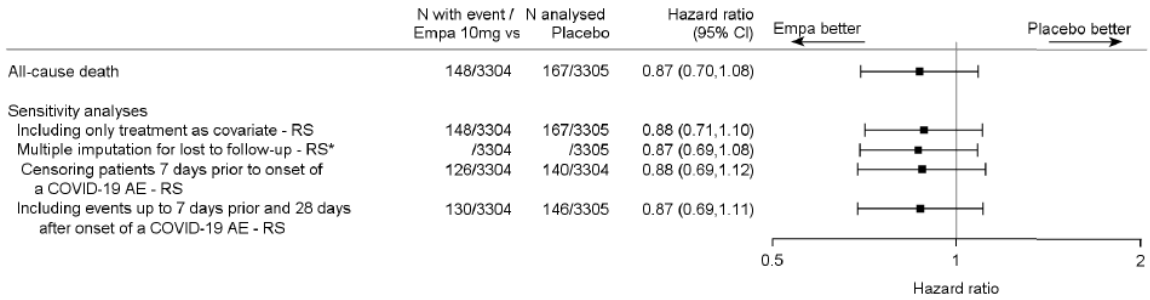
Figure 13. Time to adjudicated death from any cause, Kaplan-Meier estimate – RS



Abbreviations: PY, patient-year; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, Figure 11.1.2.1: 1 and Table 11.1.2.1: 1 (79)

The results of sensitivity analyses were consistent with the overall results (Figure 14).

Figure 14. Forest plot of sensitivity analyses of time to adjudicated death from any cause – RS



Abbreviations: AE, adverse event; CI, confidence interval; RS, randomised set.
Events confirmed or unrefuted by adjudication are considered as an outcome event.
*There is no single definition of number of patients with an event because each imputation can produce a different number of events
Source: EMPA-KIDNEY CTR 2022, Figure 15.2.2.3.2: 1 (79)

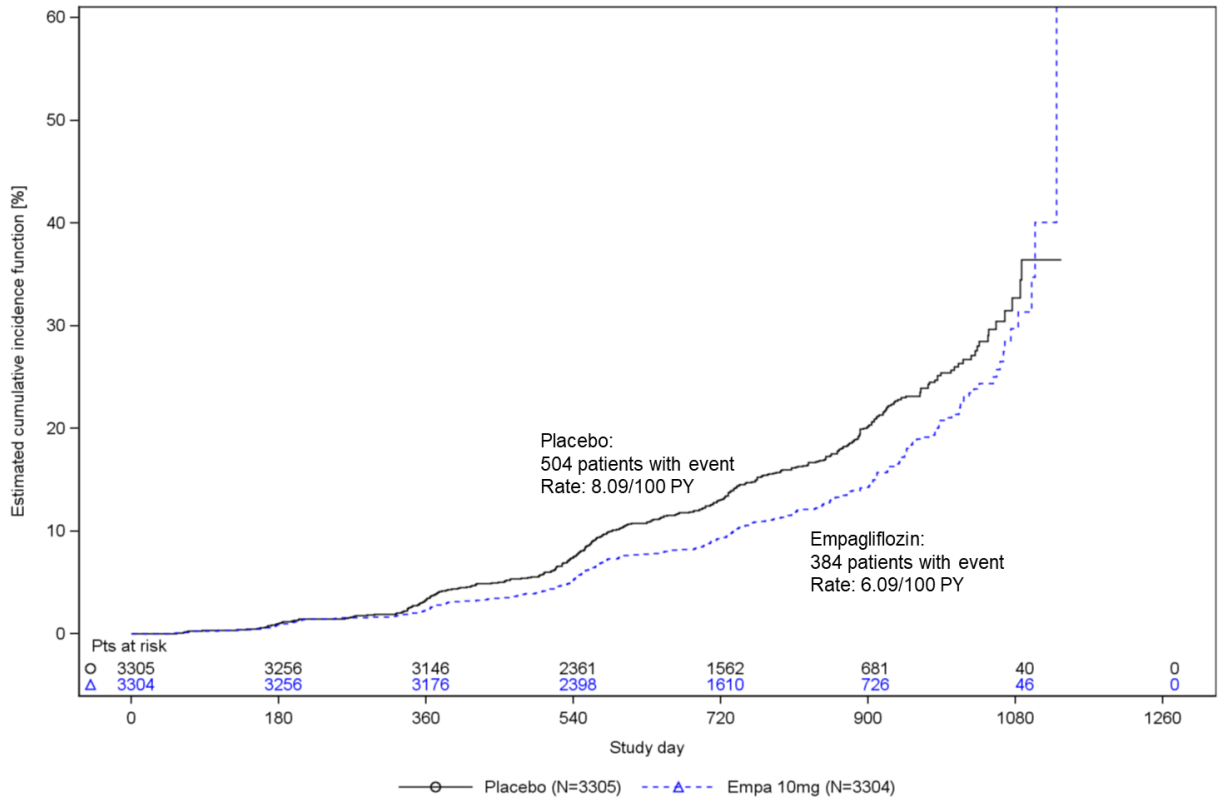
B.2.6.3 Tertiary/exploratory outcomes

B.2.6.3.1 Time to first occurrence of kidney disease progression

Empagliflozin significantly reduced the risk of kidney disease progression compared with placebo

Kidney disease progression occurred in 384 patients (11.6%) in the empagliflozin group and 504 patients (15.2%) in placebo group; the risk of kidney disease progression was significantly lower with empagliflozin treatment vs. placebo (HR, 0.71; 95% CI, 0.62 to 0.81; p<0.0001). The separation of the cumulative incidence of kidney disease progression became evident approximately 1 year after randomisation and continued over time until the number of patients at risk became too low to provide stable estimates (Figure 15) (2).

Figure 15. Time to the first event of kidney disease progression, estimated cumulative incidence function (considering non-renal death as a competing risk) – RS



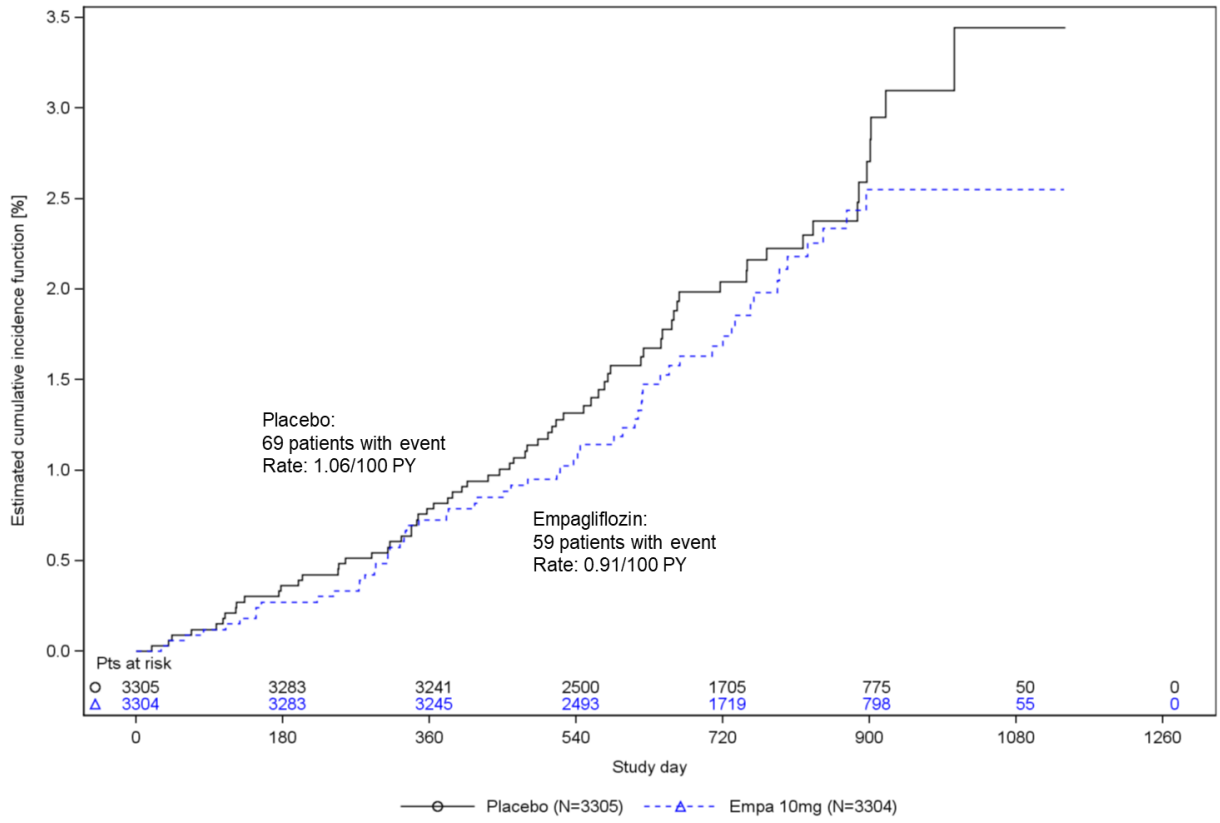
Abbreviations: CI, confidence interval; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, Figure 15.2.1.1: 1 and Table 11.1.2.4: 1 (79)

B.2.6.3.2 Time to adjudicated CV death

There was a numerical reduction in time to adjudicated CV death for empagliflozin vs. placebo

Adjudicated CV death occurred in 59 patients (1.8%) in the empagliflozin group and 69 (2.1%) patients in the placebo group. There was no statistically significant treatment difference between empagliflozin and placebo (HR, 0.84; 95% CI, 0.60 to 1.19; p=0.3366). This was due to sample power: the trial was under powered to detect a difference in CV death and mortality between arms as the enrolled patients were less likely to have these events (>50% patients did not have baseline DM or severe albuminuria and >70% did not have baseline CV disease) (for details see Section B.2.4.1 Statistical methods and analysis sets), The cumulative incidence of adjudicated CV death is displayed in Figure 16.

Figure 16. Estimated cumulative incidence function for time to adjudicated CV death (non-CV death as competing risk)-RS



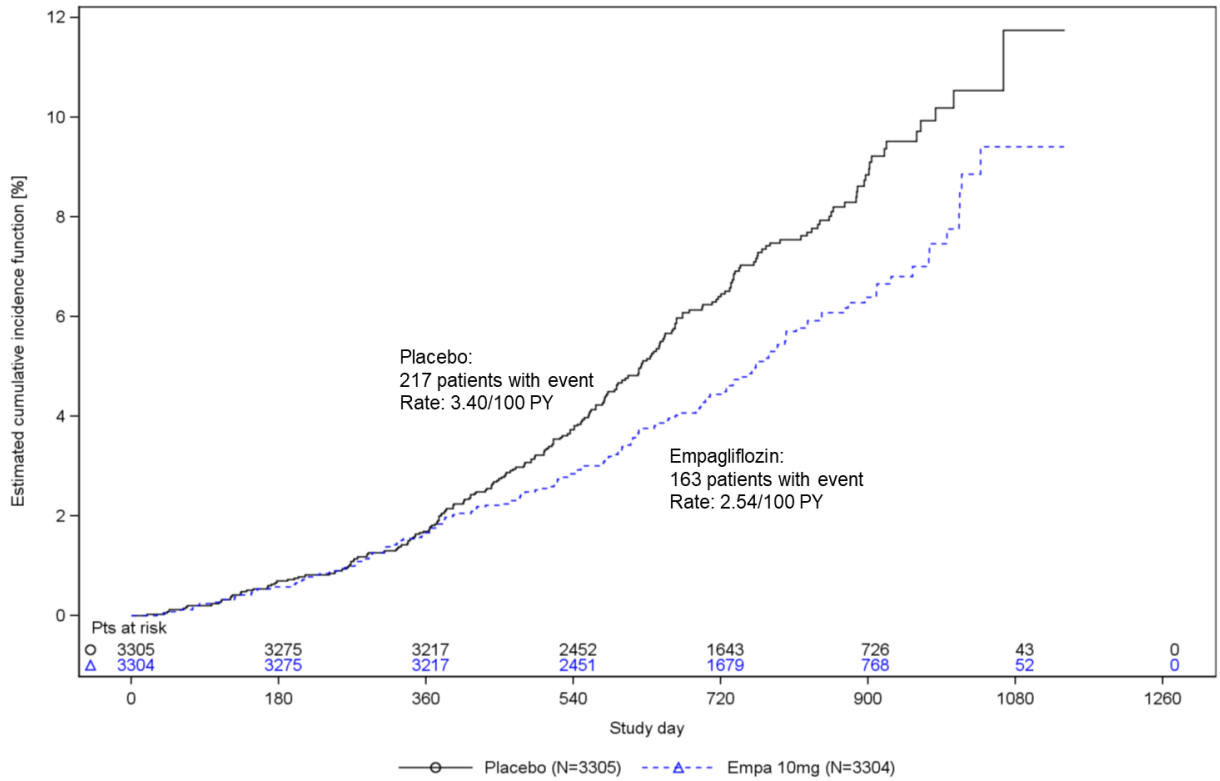
Abbreviations: CI, confidence interval; CV, cardiovascular; RS, randomised set.
Note - Death from cardiovascular causes occurred in 59 patients (1.8%) in the empagliflozin group and 69 patients (2.1%) in the placebo group.
Source: EMPA-KIDNEY CTR 2022, Figure 15.2.3.2: 1 and Table 11.1.2.5: 1 (79)

B.2.6.3.3 Time to first occurrence of adjudicated CV death or ESKD

Empagliflozin significantly reduced the risk of adjudicated CV death or ESKD compared with placebo

CV death or ESKD occurred in 163 (4.9%) patients in the empagliflozin group and 217 (6.6%) patients in placebo group. The risk of CV death or ESKD was significantly reduced with empagliflozin treatment vs. placebo (HR, 0.73; 95% CI, 0.59 to 0.89; p=0.0023). The separation of the estimated cumulative incidence of CV death or ESKD between empagliflozin and placebo became evident approximately 1 year after randomisation and continued over time until the number of patients at risk became too low to provide stable estimates (Figure 17) (79).

Figure 17. Time to adjudicated CV death or ESKD, estimated cumulative incidence function (considering non-CV death as a competing risk) – RS



Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; RS, randomised set.
Source: EMPA-KIDNEY CTR 2022, Figure 11.1.2.6: 1 and Table 11.1.2.6: 1 (79)

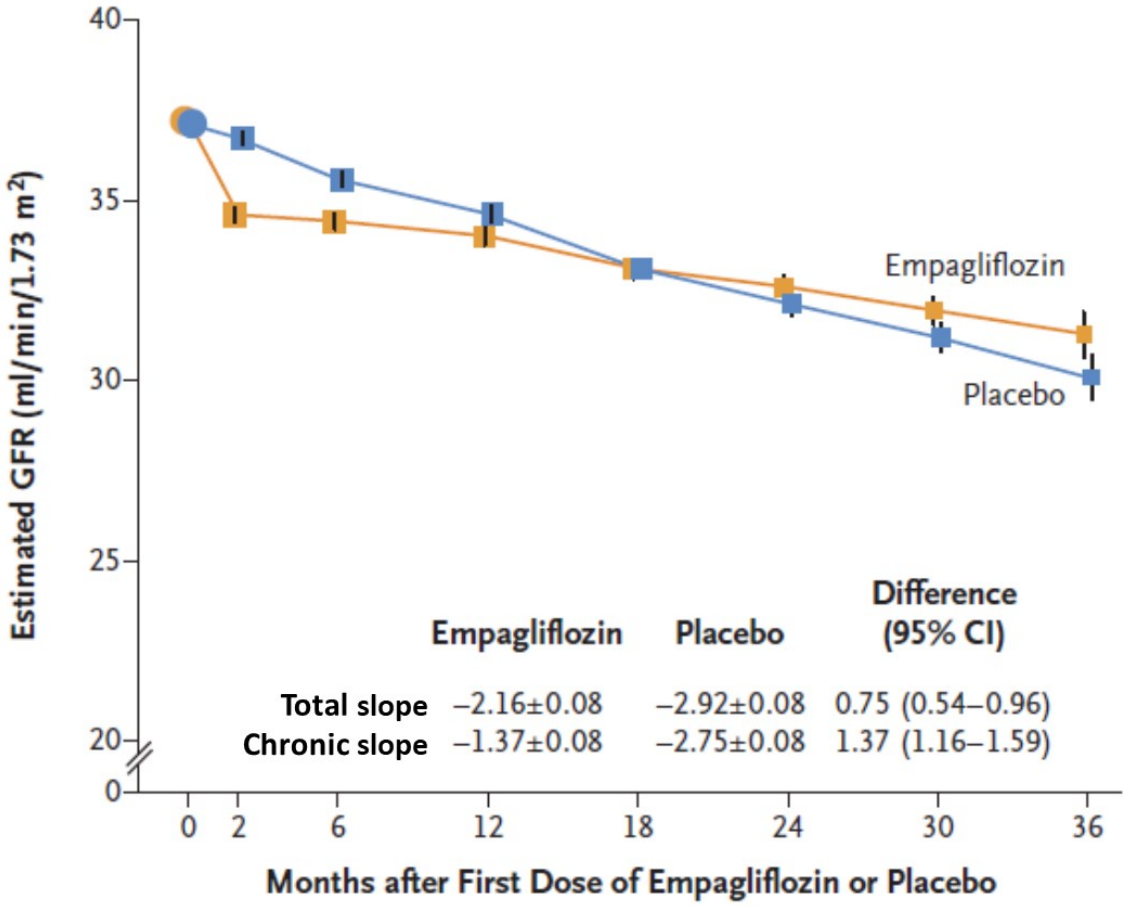
B.2.6.4 Further outcomes

B.2.6.4.1 Annual rate of change in eGFR

The eGFR decline was lower for the empagliflozin group compared with placebo group

An expected acute decrease in the eGFR was seen in the empagliflozin group at the start of the trial regimen due to haemodynamic effects; however, the rate of annual decline slowed after the initial decrease. When the results are fitted on a slope analysis, on average patients in EMPA-KIDNEY progressed at a rate of 2.75 mL/min/1.73m^2 per year. Overall, the between-group difference in the eGFR slope from randomisation to the final follow-up visit was 0.75 mL/min/1.73m^2 (95% CI, 0.54 to 0.96; p<0.0001) per year, favouring empagliflozin. With respect to the decline in eGFR from 2 months to the time of the final follow-up visit, there was a between-group difference of 1.37 mL/min/1.73m^2 (95% CI, 1.16 to 1.59; p<0.0001) per year and relative difference to placebo of -50% (95% CI -0.56%, -0.44%; p<0.0001) (Figure 18) (2).

Figure 18. Change from Baseline in the eGFR



Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
The values shown as "Total slope" represent the mean (±SE) changes from randomisation to the final follow-up visit. The values shown as "chronic slope" represent the mean (±SE) changes from 2 months after the first dose of empagliflozin or placebo to the final follow-up visit.
Source: Adapted from The EMPA-KIDNEY Collaborative Group 2023 (79)

B.2.7 Subgroup analysis

The pre-specified subgroups of key interest at baseline for the efficacy outcomes were:

- DM status (present/absent),
- eGFR (<30 mL/min/1.73m^2, ≥30 to <45 mL/min/1.73m^2, ≥45 mL/min/1.73m^2), and
- uACR (<30 mg/g [3 mg/mmol], ≥30 to ≤300 mg/g [3 to 30 mg/mmol], >300 mg/g [30 mg/mmol]).

HRs and CIs were estimated with the use of Cox proportional hazards regression models, with adjustment for age, sex, history of DM, eGFR, uACR (with albumin measured in milligrams and creatinine measured in grams), and geographic region.

The pre-specified subgroup for people with DM was requested by NICE in the final scope; this was a pre-specified subgroup of key interest in the EMPA-KIDNEY trial. The final scope additionally requested subgroup analyses for people with CVD and people with other causes of CKD

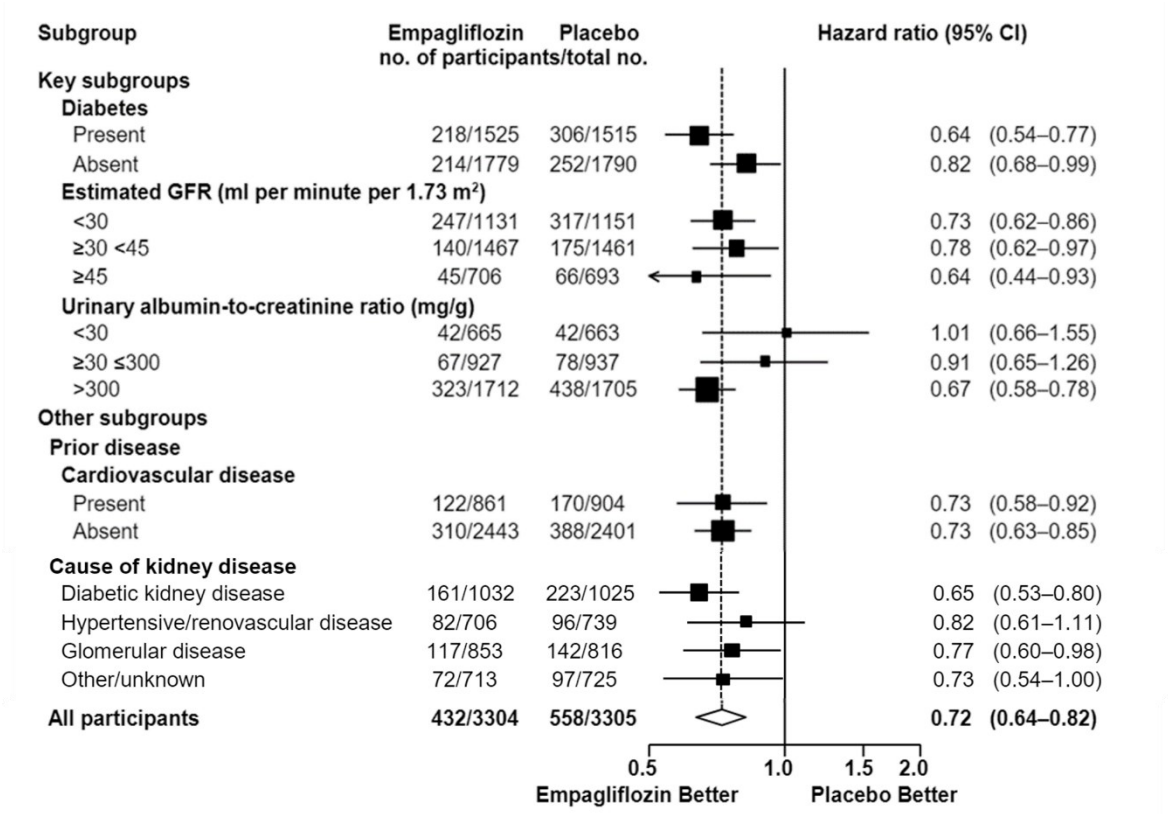
(interpreted to mean people without a history of DM and CVD) if evidence allows. 'People with CVD' was a prespecified subgroup in EMPA-KIDNEY; 'people without DM and without CVD' was not. Cause of CKD was a prespecified subgroup analysis, which includes patients with 'other/unknown' causes, however this is not mutually exclusive with CVD or T2D. The heterogenous nature of CKD should be noted; of patients with diabetes enrolled in EMPA-KIDNEY, one third of them had a primary cause of kidney disease other than diabetes (e.g., glomerular and hypertensive/renovascular).

Available results for the requested subgroups, plus the two other pre-specified subgroups of key interest, are detailed below.

The results of the subgroup analyses of the primary outcome for baseline DM status and baseline eGFR were consistent (interaction p-values >0.05), with the upper bound of the 95% CI for the HR for each subgroup <1. There was some evidence that the proportional risk reduction may have been larger among patients with higher uACR.

Figure 19 shows the HRs for the primary outcome in pre-specified subgroups of key interest, defined according to baseline characteristics, and the additional pre-specified subgroup of people with CVD and causes of CKD (2). Additional results of prespecified subgroups of key interest for primary and key secondary endpoints can be found in Appendix E.

Figure 19. Forest plot for pre-specified subgroup analyses of time to the first event of kidney disease progression or adjudicated CV death



Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.
Source: Adapted from the EMPA-KIDNEY Collaborative Group 2023 (79)

B.2.8 Meta-analysis

Pairwise meta-analysis was not feasible for this submission as there are no head-to-head trials comparing empagliflozin to the comparators in the NICE scope, specifically dapagliflozin. Indirect treatment comparison (ITC) via network meta-analysis (NMA) has therefore been performed. Please see Section B.2.9 Indirect and mixed treatment comparisons and Appendix D for details.

B.2.9 Indirect and mixed treatment comparisons

- There were differences in trial design, studied population and endpoint definition that did not allow a meaningful direct comparison of empagliflozin vs. dapagliflozin based on CKD trials. Therefore, ITC (NMA) based on an expanded evidence network including patients with prevalent CKD from multiple trials was performed to examine the relative efficacy of empagliflozin to potential comparators for the treatment of patients with CKD/DKD.
- Thirteen RCTs assessing safety and efficacy of empagliflozin, canagliflozin, dapagliflozin and finerenone in a mix of CKD or DKD populations were selected for inclusion in the NMA. These included studies where CKD/DKD diagnosis was a primary inclusion criterion, as well as studies in T2DM or HF patients with subgroup analyses of CKD/DKD patients.
- Where more than one study was available to assess a treatment effect of a given comparator, assessments of heterogeneity were undertaken prior to conducting the NMA. The majority of the tests for heterogeneity yielded non-significant results.
- All analyses were conducted in a Bayesian framework applying a fixed effects (FE) model in case of non-heterogeneity. The model parameters were estimated using a Markov Chain Monte Carlo (MCMC) algorithm implemented in the Just Another Gibbs Sampler (JAGS) software package.
- The efficacy of interventions did not differ meaningfully for most outcomes. The SGLT2 inhibitors had better efficacy than finerenone for most included outcomes but the difference was non-significant.
- Based on NMA results, the economic assessment assumes equivalence of treatment effects between empagliflozin and the comparator dapagliflozin. This is further supported by an independent source, reporting similar treatment benefits and safety across SGLT2 inhibitors with their use for modifying risk of kidney disease progression and AKI not only in patients with T2DM at high CV risk but also in patients with CKD or HF irrespective of diabetes status, primary kidney disease, or kidney function (91).
- For the full SLR report and NMA feasibility assessment, refer to Appendix D. For the full results of the NMA, refer to Appendix N.

B.2.9.1 Objective of the indirect comparison

The primary objective of the NMA was to examine the relative efficacy of empagliflozin to comparators for the treatment of patients with CKD/DKD, with or without other comorbidities such as T2DM or HF. The secondary objective was to assess the appropriateness of the NMA to inform the economic model for the assessment of the cost-effectiveness of empagliflozin relative to comparators in CKD/DKD. Dapagliflozin is the comparator identified in the NICE Scope, however canagliflozin and finerenone were also included in the NMA and are therefore reported here.

B.2.9.2 Evidence base and comparators

A clinical SLR and TLR was conducted to identify all the relevant RCTs and observational studies, respectively, related to the treatment of CKD/DKD (Section B.2.9.5 Results and Appendix D). From the evidence base identified in the SLR, studies were selected for inclusion in a feasibility assessment for the NMA according to a narrower set of criteria that included only Phase III (or II/III) studies evaluating approved doses of included treatments, and studies of duration of >52 weeks.

Thirteen RCTs conducted in a mix of CKD or DKD populations were selected for inclusion in the NMA; these 13 trials studied the efficacy and safety of empagliflozin, canagliflozin, dapagliflozin and finerenone. Five RCTs (CREDENCE (9), DAPA-CKD (8), EMPA-KIDNEY (79), FIDELIO-DKD (92) and FIGARO-DKD (93)) included CKD or DKD patients as the target population. Five RCTs (CANVAS program [CANVAS (94), CANVAS-R (95)], DECLARE-TIMI 58 (96), Dekkers 2018 (97), EMPA-REG OUTCOME (98), MB102029 (99)) included patients with T2DM, some of whom had CKD or DKD. The final three RCTs included patients with HF, some of whom had CKD or DKD (DAPA-HF (100), EMPEROR-Reduced (101), EMPEROR-Preserved (102)). Please see Table 20 for further details on the characteristics of included trials.

B.2.9.3 NMA framework

An anchored Bayesian NMA was chosen for this analysis, rather than a matching adjusted indirect comparison (MAIC), due to inherent differences in the trials of EMPA-KIDNEY and DAPA-CKD. Key differences between the two trials are summarised in Table 19 below.

Table 19 Summary of key differences in baseline characteristics between EMPA-KIDNEY and DAPA-CKD trials

	EMPA-KIDNEY	DAPA-CKD
SGLT2 inhibitor	**Empagliflozin**	**Dapagliflozin**
No. of patients (n)	6,609	4,304
T2DM, %	44	68
History of CV disease	27	37
eGFR, mL/min/1.73m^2, mean ± SD	37.4±14.8	43.1±12.4
uACR, mg/g, median (IQR)	329.35 (48.53, 1068.93)	949 (477-1885)
uACR category, mg/g, %□		
<30, %	20.1	0
≥30 to <300, %	28.2	10
≥300, %	51.7	90

Abbreviations: CV, cardiovascular disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; T2DM, type-2 diabetes mellitus; uACR, urine albumin-to-creatinine ratio.
Sources: The EMPA-KIDNEY Collaborative Group 2023 (79), Heerspink 2020 (8)

A MAIC weights the patients in the index trial so that the means of the baseline characteristics in the index trial match the means of the same characteristics in the comparator trial; the population of interest for this ITC is that of the EMPA-KIDNEY population, which is broader than several comparator trials. The subset of EMPA-KIDNEY patients who met DAPA-CKD renal inclusion criteria differs largely from the DAPA-CKD ITT population, thus absolute risk of outcomes in these two trials is not purely determined by CKD status. Other confounders must be present, but these are largely unknown and thus cannot be adjusted for in the analysis.

Patient identifiable data (PID) for comparator trials is unavailable to match to the DAPA-CKD trial population to that of the EMPA-KIDNEY trial; it is only possible to match EMPA-KIDNEY data to the population of comparator trials. Furthermore, a MAIC can only match on observed and reported characteristics, so cannot account for all possible sources of heterogeneity.

Bayesian NMA preserves randomisation and therefore controls for reported and unreported sources of heterogeneity; thus, effect modifiers are the only concern, not prognostic factors. A MAIC is more sensitive to differences in prognostic factors, and there are differences in baseline eGFR between EMPA-KIDNEY and DAPA-CKD. An anchored NMA was selected as there is a connected network of interventions with a common comparator, and the use of NMA preserves randomisation by using relative versus absolute effects.

Moreover, MAIC ignores correlations between covariates, which may affect the performance of the method if correlations differ between studies. In this case, the correlation of covariates within DAPA-CKD were not known, so it was not possible to assess how they may differ from that of EMPA-KIDNEY.

All analyses were therefore conducted in a Bayesian framework, applying both a FE and random effects (RE) model, with the former being preferred in the absence of heterogeneity. For binomial outcomes, the NMA was performed on the proportion of patients experiencing each outcome of interest. A regression model with binomial likelihood and the logit link function was used. For rate outcomes, the NMA was performed using count data and the number of person-years at risk. A Poisson likelihood and log link was used. The model parameters were estimated using a MCMC algorithm implemented in the JAGS software package. All analyses were performed using R version 4.0.5 and JAGS version 4.3.0.

B.2.9.4 Assessment of heterogeneity

The evidence base included both studies with CKD/DKD as a primary inclusion criterion as well as broader studies in T2DM or HF patients with a reported subgroup of CKD/DKD patients. Across the 13 trials, various definitions for the target population were used: KDIGO risk score of High or Very High, CKD Stage 3 or higher (according to the National Kidney Foundation [NKF] definition), or eGFR <60 mL/min/1.73m^2 were considered eligible groups of patients for this analysis. It should be noted that the KDIGO definition classifies patients according to both eGFR and albuminuria, while the NKF definition uses only eGFR levels; use of NKF CKD Stage 3+ excludes patients with normal to mildly decreased eGFR despite severely increased albuminuria.

In addition to differing definitions of CKD, the included studies showed differences with respect to a number of other factors other than CKD. CREDENCE, FIDELIO-DKD and FIGARO-DKD enrolled only patients with CKD and T2DM; EMPA-KIDNEY and DAPA-CKD enrolled CKD patents with and without T2DM. CANVAS, CANVAS-R, DECLARE-TIMI 58, Dekkers 2018 analysed published studies of T2DM patients; DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced enrolled patients with HF. Two studies, FIDELIO-DKD and EMPA-KIDNEY were explicitly designed to include CKD patients under-represented in prior SGLT2 inhibitors trials. In particular, EMPA-KIDNEY recruited a high percentage (54%) of patients without T2DM, with eGFR

<45 mL/min/1.73m^2 (78%), and with uACR <300 mg/g [30 mg/mmol] (48%); FIDELIO-DKD enrolled patients at lower eGFR levels (maximum of 60 mL/min/1.73m^2 for uACR 30 to 300 mg/g [3 to 30 mg/mmol] and maximum 75 mL/min/1.73m^2 for patients with uACR 300-5000 mg/g [30 to 565 mg/mmol]).

Patient populations in the included studies were broadly similar in terms of distribution of age, sex, and BMI. The proportion of Asian patients varied widely among studies; EMPA-KIDNEY included the largest percentage of Asian patients (36.2%). Distributions of eGFR and uACR at baseline varied widely, however, driven by differing inclusion criteria and different CKD/DKD subgroup definitions with respect to these measures; these measures are known prognostic factors so differences in these values are likely to affect renal outcomes. Studies also differed notably in the proportion of patients with history of CVD; in particular, EMPA-KIDNEY and the CANVAS program included lower proportions of patients with CVD (22.4% and 26.8% respectively), compared to CREDENCE, FIDELIO-DKD, and EMPA-REG OUTCOME (50.4%, 54.1%, and 100% respectively).

Assessments of heterogeneity were undertaken prior to conducting the NMA. All but one test for heterogeneity yielded non-significant results; however, estimates of relative treatment effects may still be affected by known differences between trials. As with any NMA, the validity of the estimates of relative efficacy depends on the comparability of the trials included in the analysis. As no closed loops exist in the network of evidence, it was not possible to evaluate inconsistency.

B.2.9.5 Results

A summary of characteristics of included trials is presented in Table 20Table 20. The following efficacy outcomes were assessed in the NMA: composite renal outcomes, progression to ESKD/ESRD, HHF, CV death, a composite of HHF or CV death, 3P-MACE+, all-cause mortality, and ACH. The composite renal outcomes were defined as follows: 1.) eGFR decline, ESKD, or renal death or 2.) eGFR decline, ESKD, or CV or renal death; for both composite outcomes eGFR decline thresholds of 40%, 50%, and 57% were considered. Further details on outcome definitions can be found in Appendix D.

Significant heterogeneity was only observed for the comparison between dapagliflozin and placebo for the outcome “3P-MACE+ and 3P-MACE” (see Appendix N for details). All other comparisons showed non-significant results for heterogeneity. Generally, the efficacy of the interventions did not differ meaningfully for most outcomes. Empagliflozin was associated with a lower rate of ACH admissions than finerenone (OR 0.92 [0.85-1.00]) and dapagliflozin was associated with a lower rate of HHF than finerenone (OR 0.64 [0.41-0.98]). No other statistical differences were found between interventions. However, the SGLT2 inhibitors showed numerically better efficacy than

finerenone for most included outcomes, with generally similar SGLT2 inhibitor treatment effects. Detailed results for each outcome are presented in Appendix N.

Table 20. Summary of the trials used to conduct the indirect treatment comparison

Trial name	Intervention	N	Blinding	Disease area	Population eligible for SLR/NMA[a]	Definition of CKD/DKD	eGFR inclusion criteria	uACR inclusion criteria
CANVAS program (CANVAS **(94)**) and CANVAS-R **(95)**	Canagliflozin 100 mg or 300 mg	1,110	Double-blind	T2DM, HbA1c ≥7.0 and ≤10.5%, elevated risk of CVD	Subgroup: • KDIGO high risk • KDIGO very high risk • eGFR <60 mL/min/1.73m^2 • uACR >300 mg/g (30 mg/mmol)	-	≥30 mL/min/1.73m^2	For CANVAS-R: Documented micro- or macroalbuminuria or documented HDL-C of <1 mmol/L (<39 mg/dL)
	Placebo	929						
CREDENCE (9)	Canagliflozin 100 mg	2,202	Double-blind	T2DM and CKD	Whole population	Documented micro- or macroalbuminuria or documented HDL-C of <1 mmol/L (<39 mg/dL)	30 to <90 mL/min/1.73m^2	uACR, >300 to 5000, mg/g (30 to 565 mg/mmol)
	Placebo	2,199						
DAPA-CKD (8)	Dapagliflozin 10 mg	2,152	Double-blind	CKD with or without T2DM	Whole population	eGFR 25 to 75 mL/min/1.73 m^2 and uACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)	25 to 75 mL/min/1.73m^2	uACR of 200 to 5000 mg/g (22.6 to 565 mg/mmol)
	Placebo	2,152						
DAPA-HF (100)	Dapagliflozin 10 mg or placebo	1,926	Double-blind	HF and LVEF ≤40%	Subgroup: eGFR <60 mL/min/1.73m^2	-	≥30 mL/min/1.73m^2	-
DECLARE-TIMI 58 (96)	Dapagliflozin 10 mg	8,582	Double-blind	T2DM	Subgroup: • eGFR <60 mL/min/1.73m^2 • uACR >300 mg/g (30 mg/mmol)	-	-	Creatinine clearance of ≥60 mL/min*
	Placebo	8,578						

Trial name	Intervention	N	Blinding	Disease area	Population eligible for SLR/NMA[a]	Definition of CKD/DKD	eGFR inclusion criteria	uACR inclusion criteria
Dekkers, 2018 (97)	Dapagliflozin 10 mg	93	Double-blind	T2DM and impaired kidney function	Subgroup: eGFR ≥12 to <45 mL/min/1.73m^2 (Pooled from 11 trials)	-	≥12 to <45 mL/min/1.73m^2	-
	Dapagliflozin 5 mg	58						
	Placebo	69						
MB102029 (99)	Dapagliflozin 10 mg	85	Double-blind	T2DM, HbA1c ≥7.0 and ≤11%	Subgroup: Moderate renal impairment	eGFR ≥30 to <60 mL/min/1.73m^2	≥30 to <60 mL/min/1.73m^2	-
	Dapagliflozin 5 mg	83						
	Placebo	84						
EMPA-KIDNEY (79)	Empagliflozin 10 mg	3,304	Double-blind	CKD with or without DM	Whole population	eGFR ≥20 but <45 mL/min/1.73m^2 or an eGFR ≥45 but <90 mL/min/1.73m^2 with a uACR ≥200 mg/g (22.6 mg/mmol)	eGFR ≥20 but <45 mL/min/1.73m^2 or an eGFR ≥45 but <90 mL/min/1.73m^2 with a uACR ≥200 mg/g (22.6 mg/mmol)	uACR ≥200 mg/g (22.6 mg/mmol)
	Placebo	3,305						
EMPA-REG OUTCOME (98)	Empagliflozin 10 mg or 25 mg	1,498	Double-blind	T2DM, drug naïve, high CV risk	Subgroup: • KDIGO high risk • KDIGO very high risk • eGFR <60 mL/min/1.73m^2 • uACR >300 mg/g (30 mg/mmol)	-	≥30 mL/min/1.73m^2	-
	Placebo	752						

Trial name	Intervention	N	Blinding	Disease area	Population eligible for SLR/NMA[a]	Definition of CKD/DKD	eGFR inclusion criteria	uACR inclusion criteria
EMPEROR-Preserved (102)	Empagliflozin 10 mg or placebo	5,988	Double-blind	Chronic heart failure	Subgroup: • KDIGO high risk • KDIGO very high risk • eGFR <60 mL/min/1.73m^2 • uACR >300 mg/g (30 mg/mmol)	-	≥20 mL/min/1.73m^2	-
EMPEROR-Reduced (101)	Empagliflozin 10 mg	981	Double-blind	HF, LVEF ≤40%, and elevated NT-proBNP	Subgroup: • KDIGO high risk • KDIGO very high risk • eGFR <60 mL/min/1.73m^2 • uACR >300 mg/g (30 mg/mmol)	eGFR <60 mL/min/1.73m^2 or uACR >300 mg/g (30 mg/mmol)	-	-
	Placebo	997						
FIDELIO-DKD (92)	Finerenone 10 or 20 mg	2,833	Double-blind	T2DM and DKD	Whole population	• uACR 30 to <300 mg/g (3 to 30 mg/mmol), eGFR 25 to <60 mL/min/1.73 m^2, and a history of diabetic retinopathy or	• 25 to <60 mL/min/1.73 m^2 paired with albuminuria 1 or • 25 to <75 mL/min/1.73 m^2 paired with albuminuria 2	1. Persistent, moderately elevated albuminuria uACR 30 to <300 mg/g [3 to <30 mg/mmol] (paired with eGFR 1.) 2. Persistent, severely elevated albuminuria uACR, 300 to 5000 mg/g [30 to 565

Trial name	Intervention	N	Blinding	Disease area	Population eligible for SLR/NMA[a]	Definition of CKD/DKD	eGFR inclusion criteria	uACR inclusion criteria
	Placebo	2,841				• uACR 300 to 5000 mg/g [30 to 565 mg/mmol] and eGFR 25 to <75 mL/min/1.73 m^2 Patients were required to have a serum potassium level of 4.8 mmol per litre or less.		mg/mmol] (paired with eGFR 2.)
FIGARO-DKD (93)	Finerenone 10 mg or 20 mg	3,686	Double-blind	T2DM and DKD	Whole population	• Moderately elevated albuminuria and eGFR 25 to 90 mL/min/1.73m^2 or • Persistent, severely elevated albuminuria and eGFR ≥60 mL/min/1.73 m^2	≥25 to <90 mL/min/1.73m^2	Persistent high albuminuria (uACR>30 [3 mg/mmol] but <300 mg/g [30 mg/mmol] and eGFR >25 but <90 mL/min/1.73m^2) or Persistent very high albuminuria (uACR >300 mg/g [30 mg/mmol] and eGFR >90 mL/min/1.73m^2)
	Placebo	3,666						

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; g, gram; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; m, metre; mg, milligram; min, minute; mL, millilitre; mmol, millimole; NT-proBNP, N-terminal pro b-type natriuretic peptide; SGLT2-i, sodium-glucose cotransporter two inhibitor; T2DM, type 2 diabetes mellitus; uACR, urine albumin-to-creatinine ratio.

[a]The broadest subgroup(s) meeting inclusion criteria are listed here. Trials may report data for additional subgroups (e.g., eGFR <45 mL/min/1.73m^2 or eGFR <60 mL/min/1.73m^2 and uACR >300 mg/g [30 mg/mmol])

*Creatinine clearance <60mL/min based on Cockroft-Gault equation listed as exclusion criteria.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

There are several limitations to this evidence base in terms of suitability for an NMA. Firstly, the definition of CKD varied across included studies, both in terms of study inclusion criteria and reported subgroups of T2DM or HF trials. In terms of composite renal event, differences in use of eGFR reduction thresholds between studies prevented indirect comparisons of all four interventions in a single network for this outcome. Additionally, estimation of relative treatment effects for ACH was limited by a lack of reported data for canagliflozin and dapagliflozin. Finally, the follow-up time of reported outcomes differed across studies; while the NMA assumes that event rates of each outcome are constant over time.

B.2.9.7 Conclusion

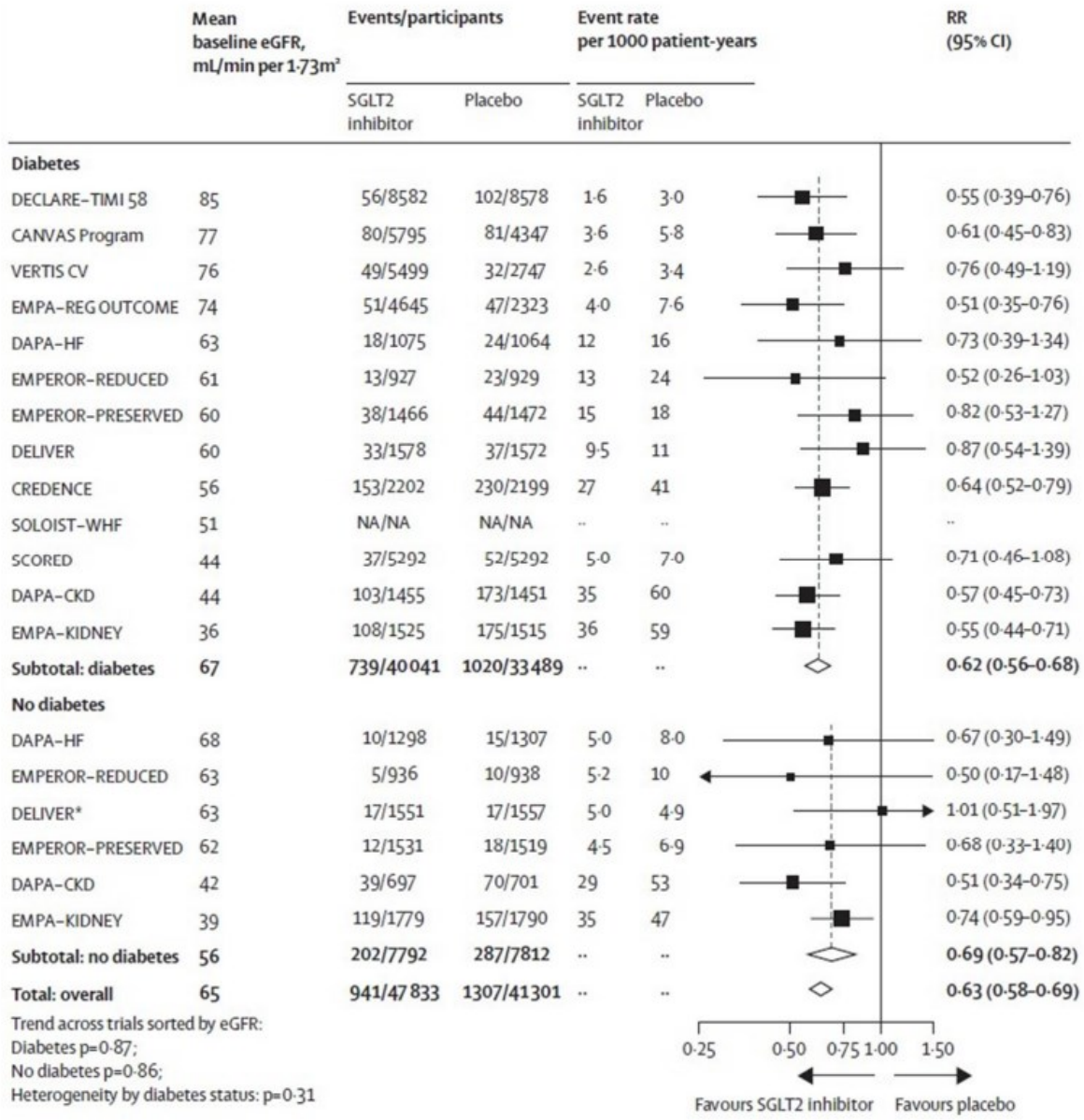
Despite the uncertainties, the strengths of this analysis include the derivation of an evidence base from an SLR. Furthermore, the evidence base available for the NMA consisted of a connected network of placebo controlled RCTs, allowing for an anchored indirect comparison of the interventions of interest.

In summary, the efficacy of the interventions included in the NMA network did not differ meaningfully for most outcomes. Compared to finerenone, empagliflozin was associated with a significantly lower rate of ACH admissions and dapagliflozin was associated with a significantly lower rate of HHF. No other statistical differences were found between interventions. Results suggested the SGLT2 inhibitors had better efficacy than finerenone for most included outcomes, but the difference was non-significant. Moreover, clinical expert opinion supports the conclusion that there is no difference in treatment effect between empagliflozin and dapagliflozin in similar eligible populations (see Appendix O).

Since there are no meaningful differences observed for most of the outcomes, the economic assessment versus dapagliflozin assumes equivalence of treatment effects between empagliflozin and SGLT2 comparators, thus justifying the decision to perform a cost-comparison analysis for empagliflozin versus dapagliflozin in this appraisal. This is further supported by the entirety of the evidence which has been generated over the years for SGLT2 inhibitors that supports a consistent kidney protective effect across several compounds and in various disease populations and clinical CKD phenotypes. A recent meta-analysis systematically investigated outcomes from 13 trials with SGLT2 inhibitors, which included patients with DM (n = 74,804) and without DM (n = 15,605); trial-level mean baseline eGFR ranged from 37 mL/min/1.73m^2 to 85 mL/min/1.73m^2 (91). Overall, SGLT2 inhibitors reduced the risk of kidney disease progression by 37% (RR 0.63, 95% CI 0.58, 0.69), with similar effects in patients with DM (RR 0.62, 95% CI 0.56,0.68) and without DM (RR 0.69, 95% CI 0.57, 0.82), (heterogeneity by DM status p = 0.31) and consistency across baseline eGFR levels (Figure 20). Likewise, consistent treatment effects on kidney disease

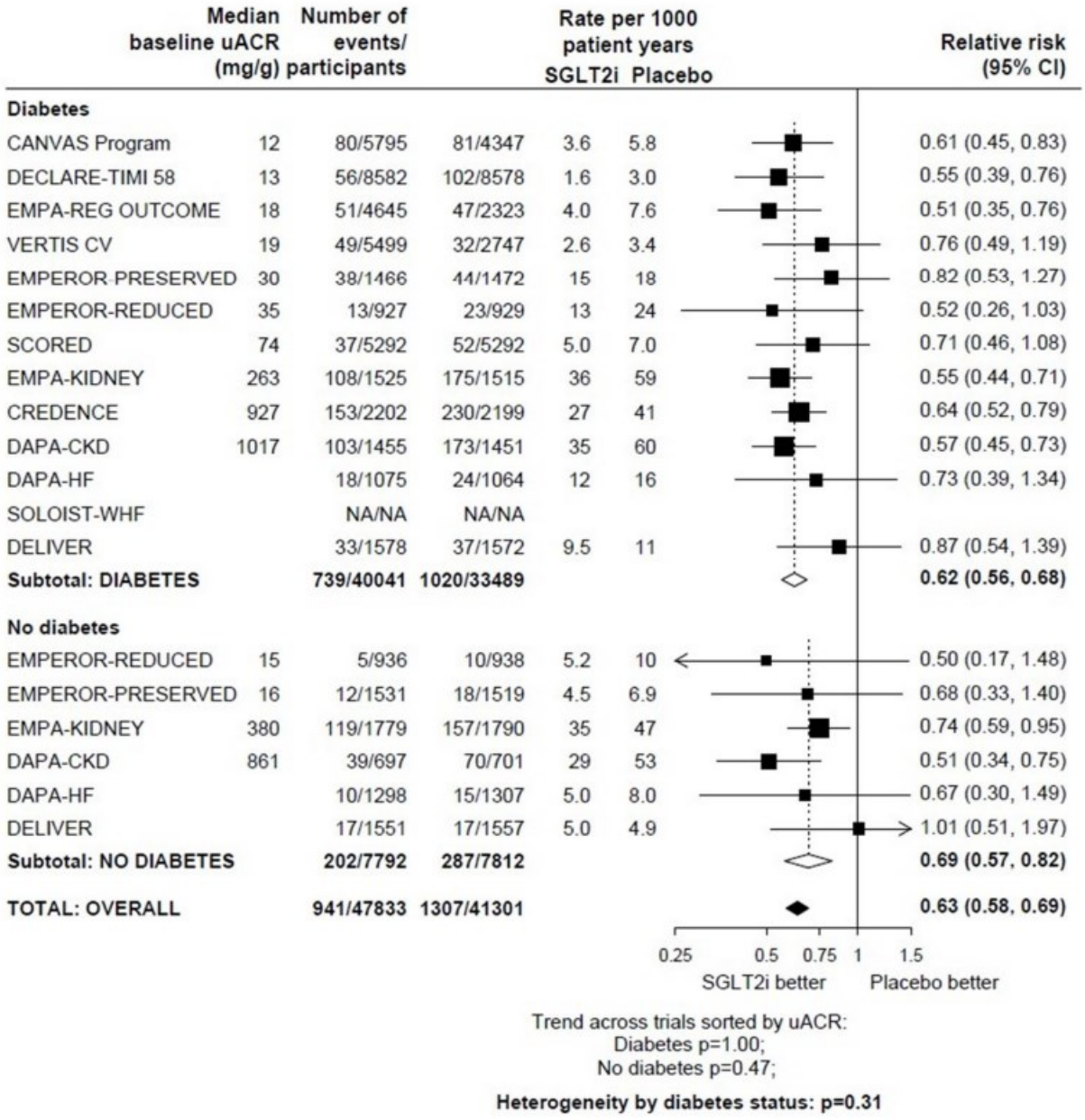
progression were observed in both DM and non-DM patients across a broad range of baseline uACR values (Figure 21).

Figure 20. Effect of SGLT2 inhibitors on kidney disease progression by DM status and eGFR



Abbreviations: CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SGLT2, Sodium-glucose transporter 2; RR, relative ratio
Kidney disease progression was defined as a sustained decrease in eGFR (≥50%) from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure in all presented trials.
*One participant without diabetes in DELIVER was missing a baseline creatinine measurement and was excluded.
Source: Herrington et al. (91)

Figure 21. Effect of SGLT2 inhibitors on kidney disease progression by DM status and uACR



Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT2, Sodium-glucose transporter 2; RR, relative ratio; uACR, urine albumin to creatinine ratio.

Kidney disease progression was defined as a sustained decrease in eGFR (≥50%) from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure in all presented trials.
Source: Herrington et al. (91)

B.2.10 Adverse reactions

For the full adverse reactions results of the trial, refer to Appendix F. Median exposure to study medication was approximately 22 months in both treatment groups, with 91% of patients treated for at least 1 year. Safety was assessed descriptively based on AE, adverse events of special interest (AESI), and specific AEs (2).

Empagliflozin and placebo groups had similar frequencies of patients with reported SAEs and pre-specified non-serious AEs (Table 21). The frequency of patients reported with AEs leading to discontinuation of study medication was also similar between treatment groups. The frequency of patients with investigator-defined drug-related AEs was low. The frequency of patients with SAEs overall was comparable between both groups. The frequency of patients with fatal AEs was similar in both groups (79).

Table 21. Overall summary of AE - TS

Category of AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients in the TS, N (%)	3,304 (100.0)	3,305 (100.0)
Patients with any pre-specified non-serious AE	1,447 (43.8)	1,520 (46.0)
Investigator-defined drug-related AE	79 (2.4)	60 (1.8)
AE leading to discontinuation of study medication	232 (7.0)	241 (7.3)
Patients with SAE		
Resulting in death	88 (2.7)	93 (2.8)
Life threatening	36 (1.1)	33 (1.0)
Persistent or significant disability/incapacity	14 (0.4)	17 (0.5)
Requires or prolongs hospitalisation	852 (25.8)	937 (28.4)
Congenital anomaly or birth defect	0	1 (<0.1)
Other medically important serious event[a]	308 (9.3)	315 (9.5)

Abbreviations: AE, adverse event; SAE, serious adverse event; TS, treated set.
Note: Percentages calculated using total number of patients per treatment as the denominator. A patient may be counted in more than one seriousness criterion.
[a]Other medically important serious events were important medical events in the opinion of a responsible local investigator (i.e., not life threatening or resulting in hospitalisation, but could jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).
Source: EMPA-KIDNEY CTR 2022, Table 15.3.1.2.1: 1 (79).

The frequencies of SAEs in each system organ class were similar in the empagliflozin and placebo groups. The most frequently reported SAEs and pre-specified non-serious AEs were in the system organ class metabolism and nutrition disorders, followed by infections and infestations, investigations, and renal and urinary disorders. On the PT level, the most frequently reported SAEs and pre-specified non-serious AEs were gout, AKI, and coronavirus infection (Table 22). All other SAE were reported in less than 3.0% of patients per treatment group (79).

Table 22. Serious and pre-specified non-serious AE with frequency >2% - TS

MedDRA system organ class MedDRA PT	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients	3,304 (100.0)	3,305 (100.0)
Total with serious and pre-specified non-serious AE	1,447 (43.8)	1,520 (46.0)
Metabolism and nutrition disorders	416 (12.6)	445 (13.5)
Gout	231 (7.0)	266 (8.0)
Dehydration	72 (2.2)	65 (2.0)
Hypoglycaemia	68 (2.1)	67 (2.0)
Infections and infestations	355 (10.7)	324 (9.8)
Coronavirus infection	98 (3.0)	107 (3.2)
Investigations	177 (5.4)	199 (6.0)

MedDRA system organ class MedDRA PT	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Blood potassium increased	76 (2.3)	87 (2.6)
Renal and urinary disorders	158 (4.8)	182 (5.5)
Acute kidney injury	93 (2.8)	117 (3.5)
With investigator-defined drug-related AE	79 (2.4)	60 (1.8)

Abbreviations: AE, adverse event; MedDRA, Medical dictionary for regulatory activities; MedDRA PT, Medical dictionary for regulatory activities preferred term; SAE, serious adverse event; TS, treated set.
Source: EMPA-kidney CTR 2022, Table 12.1.2.1: 1 and Table 15.3.1.2.1: 4 (79).

AESIs were pre-specified in the protocol as liver injury, ketoacidosis, and AE leading to lower limb amputation. Specific AE were defined as severe hypoglycaemia, urinary tract infection, genital infection, bone fracture, urinary tract malignancy, volume depletion, AKI, gout, hyperkalaemia, and COVID-19 events (Table 23). The overall frequencies for liver injury, serious urinary tract infection, serious genital infection, severe hypoglycaemia, and urinary tract malignancy were comparable in the empagliflozin and placebo groups. Ketoacidosis and lower limb amputations occurred in higher number of patients in the empagliflozin group than in the placebo group. Otherwise within the individual categories of AESIs and specific AEs, generally similar proportions of patients in both treatment groups had serious AEs. Few AEs in any category of AESIs or specific AEs led to treatment discontinuation. Safety results in the subgroup of patients with a baseline eGFR <20 mL/min/1.73m^2 were consistent with the overall AE profile in the trial (79).

Table 23. Summary of AESI and specific AE – TS

Category of AESI and specific AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients	3,304 (100.0)	3,305 (100.0)
AESI		
Liver injury (adjudicated)	13 (0.4)	12 (0.4)
Serious	5 (0.2)	7 (0.2)
Up to 30 days after treatment discontinuation	13 (0.4)	12 (0.4)
Ketoacidosis (adjudicated)	6 (0.2)	1 (<0.1)
Serious	6 (0.2)	1 (<0.1)
Leading to discontinuation	0	0
Lower limb amputation (adjudicated)	26 (0.8)	14 (0.4)
Leading to discontinuation	1 (<0.1)	1 (<0.1)
Up to final follow-up visit	28 (0.8)	19 (0.6)
Specific AE		
Severe hypoglycaemic events (narrow SMQ)	74 (2.2)	72 (2.2)
Serious	13 (0.4)	14 (0.4)
Leading to discontinuation	1 (<0.1)	2 (0.1)
Serious urinary tract infection (narrow sub-BIcMQ)	42 (1.3)	47 (1.4)
Leading to discontinuation	3 (0.1)	5 (0.2)
Serious genital infection (adjudicated)	1 (<0.1)	0
Bone fracture events (user-defined)	121 (3.7)	106 (3.2)
Serious	106 (3.2)	49 (1.5)
Leading to discontinuation	1 (<0.1)	2 (0.1)
Bone fracture events (narrow BIcMQ) up to trial completion	136 (4.1)	123 (3.7)
Urinary tract malignancy up to trial completion (broad sub-BIcMQ)	19 (0.6)	15 (0.5)
Volume depletion (narrow sub-BIcMQ)	98 (3.0)	90 (2.7)

Category of AESI and specific AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Hypotension (narrow sub-BIcMQ, a subset of volume depletion)	22 (0.7)	22 (0.7)
Serious	46 (1.4)	41 (1.2)
Leading to discontinuation	2 (0.1)	1 (<0.1)
Symptomatic dehydration (user-defined)	80 (2.4)	70 (2.1)
Serious acute kidney injury (adjudicated)	93 (2.8)	117 (3.5)
Gout (user-defined)	270 (8.2)	303 (9.2)
Serious	8 (0.2)	7 (0.2)
Leading to discontinuation	1 (<0.1)	0
Serious hyperkalaemia (user-defined)	85 (2.6)	96 (2.9)
Leading to discontinuation	2 (0.1)	2 (0.1)
COVID-19 events	104 (3.1)	110 (3.3)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BIcMQ, Boehringer Ingelheim customised MedDRA query; TS, treated set; SMQ, standardised MedDRA query; BIcMQ, Boehringer Ingelheim customised MedDRA query adjudication of events stopped at final follow-up period; any residual effect period afterwards was not considered for these events.
Source: EMPA-KIDNEY CTR 2022, Synopsis Table 4; Table 12.1.3.2.7: 1 and Table 12.1.3.2.10: 1 (79).

The adverse event profile for empagliflozin is further similar to that other SGLT2 inhibitors, which has been shown by the above-mentioned meta-analysis published by Herrington et al. (2022) (109, (91).

B.2.11 Ongoing studies

There are no ongoing studies of empagliflozin relevant for this appraisal.

B.2.12 Interpretation of clinical effectiveness and safety evidence

In the EMPA-KIDNEY trial, treatment with empagliflozin 10 mg OD as an add-on to SoC in patients with CKD demonstrated superiority compared to placebo for the primary outcome, time to the first occurrence of kidney disease progression or CV death. The trial also demonstrated superiority of empagliflozin over placebo for the key secondary outcome of time to ACH. The reduction in risk of all-cause death and HHF or CV death was not statistically significant with empagliflozin treatment as compared with placebo; however, it should be noted these key secondary outcomes were based on a relatively small number of patients with events. The results of all sensitivity analyses were consistent with the results of the primary analysis (i.e., the HR was numerically similar).

For the primary outcome, treatment with empagliflozin lead to a clinically and statistically significant reduction in risk of kidney disease progression or CV death by 28% compared with placebo added to SoC. The treatment effect of empagliflozin became apparent approximately 1 year after randomisation and was maintained over time. The results of the primary outcome were consistent across the pre-specified key subgroups of DM status and baseline eGFR categories as well as other subgroups such as patients with and without CVD (the upper bound of the 95% CI for the HR for each subgroup <1).

Treatment with empagliflozin significantly reduced the risk of ACH by 14% compared with placebo. The treatment effect of empagliflozin was observed shortly after randomisation and maintained throughout the trial. Risk reduction for the time to first occurrence of kidney disease progression and the time to first occurrence of ESKD or CV death were of similar magnitude to that of the primary outcome. Few adjudicated CV deaths occurred in both treatment groups; the treatment difference was not statistically significant because of the low number of events.

Overall, empagliflozin was well tolerated in CKD patients and had similar frequencies of patients with reported SAE and pre-specified non-serious AE as placebo. The overall frequencies of AESI and specific AE such as liver injury, serious urinary tract infection, serious genital infection, severe hypoglycaemia, and urinary tract malignancy were also comparable in the empagliflozin and placebo groups. The frequency of patients reported with AE leading to discontinuation of study medication was also similar between treatment groups.

In addition to direct evidence, the relative efficacy of empagliflozin versus competing interventions for the treatment of patients with CKD was assessed in an ITC (NMA). The NMA results showed that the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin show consistent benefit for the treatment of CKD/DKD and may offer benefit over finerenone, though study heterogeneity from differing inclusion criteria prevents statistical differentiation between these interventions. Our findings are further supported by the meta-analysis published by Herrington et al. (2022) (109, (91), which showed consistent benefits and safety of SGLT2 inhibitors in modifying risk of kidney disease progression and acute kidney injury, not only in patients with type 2 diabetes at high cardiovascular risk, but also in patients with chronic kidney disease or heart failure irrespective of diabetes status, primary kidney disease, or kidney function. Together, our findings combined with those of independent sources support the assumption of equivalence of treatment effects between empagliflozin and the comparator dapagliflozin in the economic assessment (see section **Error! Reference source not found.**).

In conclusion, data presented in this section demonstrate that compared to placebo, empagliflozin 10mg led to a significant reduction in risk of progression of kidney disease or death from CV causes as well as a significant reduction in ACH amongst a broad range of patients with CKD who were at risk for disease progression. The data therefore supports addition of empagliflozin to the guideline directed medical therapy for patients with CKD.

B.3 Cost-effectiveness

- A de novo Markov state patient-level microsimulation model was developed in Microsoft Excel® to estimate the cost-effectiveness of oral empagliflozin 10 mg OD on top of individually optimised SoC versus placebo on top of SoC for the treatment of adult patients with CKD.
- The model is structured around a set of 18 mutually exclusive and collectively exhaustive KDIGO health states defined by eGFR and uACR chosen to represent the natural history of CKD and economically important events in the disease progression. Death was an absorbing state in the model.
- Bootstrapping/sampling was used to randomly select individual patients entering the model based on a combination of eGFR and uACR states, baseline demographic characteristics and comorbidities representative of the ITT population of the EMPA-KIDNEY trial.
- Patients' disease progression through KDIGO health states was modelled through annual transition probabilities derived from eGFR slopes and uACR changes over time. Treatment specific transition probabilities were applied while patients were alive and remained on treatment (i.e., up until treatment discontinuation).
- No treatment effect was assumed after treatment discontinuation, following which disease progression (through KDIGO health states) is modelled using observational data reported in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) or Chronic Renal Insufficiency Cohort Study (CRIC) registries.
- Patients entering the model were at risk of common CKD complications including CVD, hypertension, infections, BMD, anaemia, DM, and AKI among others. Individual risk of experiencing each complication was determined by risk equations that incorporated predictor variables including eGFR and uACR, or probabilities sourced from published literature.
- The model incorporates costs involved in the management of CKD and associated complications, over time. Costs were obtained primarily through a structured literature search (Appendix I) and are assigned for the specific health state/ complication/ event in each cycle of the model engine.
- Health state utility values and clinical event disutility values were obtained through a structured literature review and prior NICE technology appraisals (TAs), and relevant health care state utilities from EMPA-KIDNEY trial were utilised in the scenario analysis.
- The cost-effectiveness analysis was consistent with the NICE reference case and performed from an NHS and PSS perspective. Costs and benefits were discounted at a rate of 3.5%.
- A time horizon of 50 years was adopted to reflect a lifetime analysis in older and younger individuals (mean age of the full ITT cohort was 63.8 years).
- In the deterministic base-case economic analysis, treatment with empagliflozin, compared with placebo, as an add-on therapy to SoC was dominant, with an incremental cost-effectiveness ratio (ICER) of -£6,431.37/quality-adjusted life year (QALY) gained and a net health benefit (NHB) of 1.12 at the £20,000 willingness to pay (WTP) threshold. Results of the cost comparison versus dapagliflozin resulted in no difference in costs associated with SGLT2 treatment acquisition and its management.
- The probabilistic ICER was also dominant (-£5,998.34/QALY gained) and highly comparable with the deterministic ICER, with 99% probability of cost-effectiveness at a WTP threshold of £4,000.
- The key drivers of the deterministic sensitivity analysis were the age limit for patients being eligible for RRT (80 years limit in the base-case), and health state utilities for patients in G+15_A-300.
- The scenario analyses also demonstrated that ICER remained dominant in all cases.
- In summary, the cost-utility analysis demonstrated oral empagliflozin 10 mg OD is a highly cost-effective treatment option for CKD.

B.3.1 Published cost-effectiveness studies

An SLR of published UK full economic evaluations assessing the cost-effectiveness of CKD treatments was conducted in October 2022. Full details of the SLR search strategy, study selection process, results and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing studies that were included and excluded at each stage are presented in Appendix G. MEDLINE® (Ovid SP®), EMBASE® (Ovid SP®) and EconLit® (Ovid SP®) were searched in addition to hand searching of conference proceedings and health technology assessment (HTA) websites. Eligible records for inclusion were those reporting novel economic evaluations of the cost-effectiveness of CKD treatments.

In total, 2,462 unique records were identified in the SLR database searches. 2,315 records were excluded following title and abstract review. 125 records were excluded following full text review, and 22 remaining records were found to meet the eligibility criteria. Hand searching found an additional 4,583 records, of which 4,570 records were excluded following review, meaning 13 records were ultimately included from hand-search results. A total of 35 publications reporting on 33 unique economic evaluations were ultimately included in the SLR as relevant to UK clinical practice.

B.3.1.1 Summary of published cost-effectiveness studies

The summary of the cost-effectiveness studies meeting inclusion and exclusion criteria for the SLR is presented in Table 7 and 8 of Appendix G. Of the 33 unique UK economic evaluations in CKD identified through the searches, three were patient-level simulation models (103-105), twenty-three were Markov models (106-127), one was a pathway model (128), one was a proportional hazards risk prediction model (129), and five did not report the model type (130-133). Three of these evaluations assessed the SGLT2 inhibitors dapagliflozin (DAPA) (6, 122) and canagliflozin (131). The strengths and limitations of the published CKD models including the NICE committee critiques of those submitted for Single Technology Appraisal (DAPA-CKD model) were reviewed to inform the eventual structure of the model for empagliflozin in CKD (130-133).

In the dapagliflozin CKD model (TA775) (6), a Markov model was chosen to synthesise the economic evidence submitted for the economic assessment. The following critiques were received from the NICE external assessment group (EAG) in relation to this model choice:

1. Some of the estimated transition probabilities applied in the DAPA-CKD model did not appear to be clinically plausible. For example, the same transition probabilities were used for subgroups of patients without albuminuria, patients with DM and patients without DM. It is unlikely to be appropriate since CKD progression would be different for all these subgroups

2. The DAPA-CKD model estimated state specific mortality risks using a “mean of covariates” approach. The EAG considered that this reflected a misinterpretation of the outputs of the multivariable survival model, which had been shown to lead to bias when estimating survival distributions
3. The EAG believed that resolving the poor model fit may require a different modelling approach (e.g., a time-homogeneous multi-state model which jointly estimates all transition probabilities between model states using a single dataset) and that it might be possible to achieve a better model fit to OS using an alternative modelling approach

B.3.2 Economic analysis

To address the limitations of published models and those critiqued by previous NICE committees appraising dapagliflozin (6, 122), a de novo Markov state patient-level microsimulation model was developed in Microsoft Excel® to assess the cost-effectiveness of empagliflozin in patients with CKD. A microsimulation approach was selected over a cohort-level method for the following reasons:

- Microsimulation methodology offers advantages over a cohort-level model, including the flexibility to randomly allocate baseline characteristics and risk factors, and to track individual disease histories over time. This approach was deemed necessary to reliably model a broad range of progression paths across CKD patients with different eGFR and uACR levels (103-105)
- A microsimulation approach offers an advantage in cases where state transition probabilities depend on baseline characteristics and past medical history (e.g., time since disease onset, the occurrence of previous events, or time-varying response to treatment), in addition to time-dependent risk factors such as eGFR and uACR. This approach also enables modelling of the occurrence of complications based on established risk equations or probabilities linked to eGFR and uACR, which are particularly relevant in CKD (134)
- A microsimulation model also helps in modelling of multiple complications and comorbidities independently which allows to capture the burden of CKD patients in a more aligned way to the routine clinical care practice
- Microsimulation approaches also facilitate transition probabilities that are a function of any number of attributes and offer flexibility to capture a greater scope of outputs since the model can return estimates of the entire distribution of events, rather than just expected values (135)
- Microsimulation approaches further facilitate flexibility in allowing random allocation of baseline characteristics to important sources of heterogeneity, allowing for continuous, dynamic risk factors that can be modified over time and their ability to track individual disease histories over time (46)

- In the empagliflozin microsimulation model, mortality risk was predicted based on UK National life tables and evidence identified through literature searches (specifically, CVD mortality risk equations [e.g., CKD-PC registries]) and all-cause mortality reported on patients receiving RRT (UKRR registries). Also, a patient-level microsimulation model utilises individual patient characteristics (including age, eGFR and uACR) to determine mortality risk. This patient-level approach negates the need for a "mean of covariates" approach and hence the associated bias
- In the empagliflozin microsimulation model, treatment effects are applied directly on the progression of eGFR and uACR (to capture benefit derived from slowing disease progression). Additionally, treatment effect was also applied on HHF and AKI to allow capturing of treatment benefit on these outcomes beyond the benefit derived from slowing disease progression. No treatment effect on mortality is applied, eliminating risk of double counting
- The appropriateness of patient-level microsimulation methodology for modelling CKD is supported by published literature identified in the cost-effectiveness SLR (103-105), as well as further literature published since SLR completion (46, 135).
- NICE Scientific Advice was also obtained on the appropriateness of the microsimulation model presented in this submission. This concluded that the structure of the model and approach to modelling CKD disease progression and management were broadly appropriate, and that the model's internal validity was high. Recommendations resulting from NICE Scientific Advice were applied to the final empagliflozin microsimulation model (136).

These factors collectively contribute to why a microsimulation approach was deemed necessary and appropriate to reliably model the progression of complex and multi-morbid CKD patients as seen in the broad, heterogenous CKD population included in the pivotal EMPA-KIDNEY trial. An extensive internal and external validation of the model was carried out prior to conducting the cost-utility analysis, with internal model validation performed by comparing outcomes observed in source studies used in the derivation of risk equations and studies and cohorts not directly used in the development of risk equations being utilised for external validation (section B.3.14).

B.3.2.1 Patient population

The base-case analysis evaluated the cost-effectiveness of empagliflozin 10mg oral OD on top of individually optimised SoC in adult patients with CKD, in line with the final NICE scope of this appraisal. The baseline characteristics of the patients were derived from the ITT population of the EMPA-KIDNEY trial (see section **Error! Reference source not found.**). Truncation of minimum and maximum baseline values was applied in cases of extreme values, as per Appendix P. In line with the EMPA-KIDNEY trial, three patient populations were considered: all CKD patients, CKD patients with DM and CKD patients without DM. The patient population derived from the trial was

broadly representative of the CKD population in UK clinical practice (see section B.2.5.1 Applicability to clinical practice).

B.3.2.2 Model structure

The model is structured around a set of 18 mutually exclusive and collectively exhaustive KDIGO health states chosen to represent the natural history of CKD and economically important events in the disease progression. KDIGO stages are also in line with disease severity classification in NG203 and KDIGO guidelines (7, 10). Patients may progress through the 18 health states, which are based on a combination of eGFR and uACR values (Table 24).

Table 24. KDIGO classification health states incorporated in the model

Health state	KDIGO classification	eGFR thresholds (mL/min/1.73m^2)	uACR level (mg/mmol)
G+90_A-30	G1 * A1	Above 90	Lower than 3
G+90_A-300	G1 * A2	Above 90	3-30 mg/mmol
G+90_A+300	G1 * A3	Above 90	>30 mg/mmol
G+60_A-30	G2 * A1	Above 60, under 90	Lower than 3
G+60_A-300	G2 * A2	Above 60, under 90	3-30 mg/mmol
G+60_A+300	G2 * A3	Above 60, under 90	>30 mg/mmol
G+45_A-30	G3a * A1	Above 45, under 60	Lower than 3
G+45_A-300	G3a * A2	Above 45, under 60	3-30 mg/mmol
G+45_A+300	G3a * A3	Above 45, under 60	>30 mg/mmol
G+30_A-30	G3b * A1	Above 30, under 45	Lower than 3
G+30_A-300	G3b * A2	Above 30, under 45	3-30 mg/mmol
G+30_A+300	G3b * A3	Above 30, under 45	3-30 mg/mmol
G+15_A-30	G4 * A1	Above 15, under 30	Lower than 3
G+15_A-300	G4 * A2	Above 15, under 30	3-30 mg/mmol
G+15_A+300	G4 * A3	Above 15, under 30	>30 mg/mmol
G-15_A-30	G5 * A1	Under 15	Lower than 3
G-15_A-300	G5 * A2	Under 15	3-30 mg/mmol
G-15_A+300	G5 * A3	Under 15	>30 mg/mmol

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; mg/mmol, milligrams per millimole; mL/min, millilitre per minute; uACR, urine albumin-creatinine ratio.

Patients move between health states within discrete annual cycles. Bootstrapping/sampling method is used to randomly distribute patients based on an initial set of characteristics including demography, risk factors, baseline comorbidities and background medications. The eGFR and uACR of each patient are then individually tracked in the model (along with further risk factors discussed in section B.3.3.2.3 Progression of other risk factors, defining which CKD KDIGO health state patients occupy at any given point in time. While on treatment, progression of eGFR and uACR is informed by observations in the EMPA-KIDNEY trial. Following the treatment discontinuation clinical data from large observational studies/patient registries published in peer-reviewed journals replicated using bootstrapping inform the progression of eGFR and uACR. Annual cycles are used with a maximum time horizon of 50 years to capture lifetime outcomes. All

mortality events are captured in the death health state, defined as CVD death plus renal death plus non-specific death.

Patients are at risk of experiencing most adverse events and CKD complications at all times (i.e., CVD, BMD, anaemia, T2DM, hypertension, AKI, infections, incident cancer, metabolic complications, hospitalisations, and ESKD), however, only patients reaching ESKD are at risk of experiencing peritonitis, AV access thrombosis, and BSI. The risk of experiencing these at any point in time varies according to past medical history, eGFR, uACR and further risk factors as discussed in section B.3.3.2. The choice of the events and complications included in the model was based on published literature, or by their presence in the previously published commonly recognised predictive risk equations (see Appendix P) and verified by clinical expert opinion (Appendix O). The acute events and long-term complications (hereafter referred to as complications) incorporated in the model are described in Table 25.

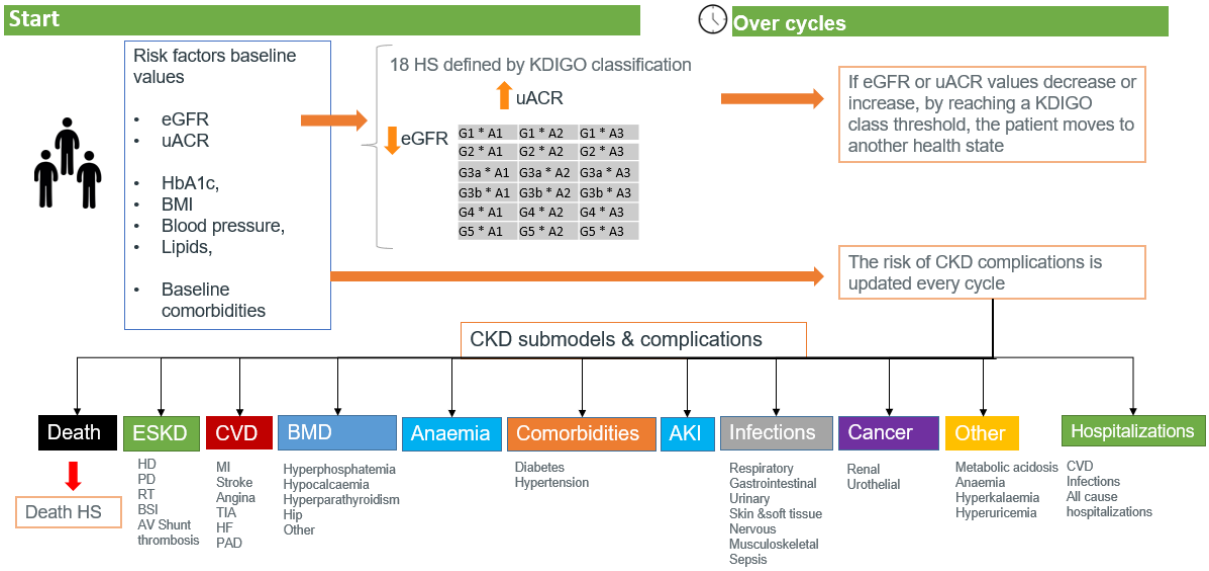
Table 25. Complications incorporated in the model

Event/complication	Sub-modules included
CVD	MI, stroke, angina, HF, TIA, PAD, CV death
BMD	Fracture, secondary hyperparathyroidism, hypocalcaemia, hyperphosphataemia
Anaemia	-
Comorbidities	DM, hypertension
AKI	-
Infections	Respiratory, urogenital, gastrointestinal, bloodstream, skin-and-soft tissue, nervous, musculoskeletal, sepsis
Incident cancer	Renal, urothelial
Other complications	Hyperuricaemia/gout, hyperkalaemia, metabolic acidosis
ESKD	HD, PD, KT, BSI, peritonitis, AV shunt thrombosis
ACH	includes hospitalisations caused due to any reason other than acute events already considered above that may require hospitalisation such as AKI, acute MI, or infections
Death	-

Abbreviations: ACH, all-cause hospitalisations; AKI, acute kidney injury; BMD, bone and mineral disorder; BSI, bloodstream infections; AV, Arteriovenous; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; HD, haemodialysis; HF, heart failure; KT, kidney transplant; MI, myocardial infarction; PAD, peripheral arterial disease; PD, peritoneal dialysis; TIA, transient ischaemic attack

Further details on the complications sub-modules incorporated in the model are provided in Appendix P. The interaction between baseline characteristics, eGFR, uACR, health states and associated complications are demonstrated in Figure 22.

Figure 22. CKD Markov microsimulation model schematic



Abbreviations: AKI, acute kidney injury; AV, arteriovenous; BMD, bone and mineral disorder; BMI, body mass index; BSI, bloodstream infections; CKD, chronic kidney disease; CVD, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HD, haemodialysis; HF, heart failure; HS, health state; KDIGO, Kidney Disease Improving Global Outcomes; MI, myocardial infarction; PAD, peripheral arterial disease; PD, peritoneal dialysis; RT, renal transplant; TIA, transient ischaemic attack; uACR, urine albumin-to-creatinine ratio.

The key features of the cost-effectiveness analysis used in the model are summarised in Table 26.

Table 26. Features of the economic analysis

Factor	Current appraisal	
	Chosen values	**Justification**
Model structure	Markov state microsimulation model, with health states defined by KDIGO classification	Microsimulation models allow to simulate individual patients by randomly distributing the baseline characteristics within specific limits and to track individual disease histories over time, as well as to study the impact of the different factors. This flexibility was deemed necessary to study a heterogeneous CKD population (103-105)
Health states	18	As per KDIGO classification (Table 24)
Time horizon	Lifetime (50 years)	To reflect lifetime cost and benefits of empagliflozin
Cycle length	Annual	To capture long-term events and disease progression
Disease progression	Based on eGFR and uACR	The most critical risk factors that determine CKD progression, as per clinical data
Complications	As per Table 25	Complications included in the model were selected based on their presence in the previously published commonly recognised risk equations and within published literature
Treatment waning effect	Disease state specific treatment effect was assumed	No waning effect was observed in the trial, nor in previous trials of empagliflozin for the treatment of T2DM and HF
Source of utilities	EMPA-KIDNEY trial and TLR	As per NICE Methods Guide
Source of costs	NHS and PSS price sources, and informed by TLR for other cost inputs	As per NICE Methods Guide
Discounting	3.5% per annum for costs, QALYs and life years	As per NICE Methods Guide
Perspective on outcomes	All direct health effects	As per NICE Methods Guide
Perspective on costs	NHS and PSS	As per NICE Methods Guide

Abbreviations: CKD, chronic kidney disease; EMPA, empagliflozin; KDIGO, Kidney Disease Improving Global Outcomes; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life years; TLR, targeted literature review

B.3.2.3 Intervention technology and comparators

The intervention in the cost-utility analysis is oral empagliflozin 10mg OD in addition to individually optimised SoC in adult patients with CKD, and the comparator is matching placebo with individually optimised SoC, in line with the NICE final scope and the EMPA-KIDNEY trial design.

A full incremental cost-effectiveness analysis versus dapagliflozin as a comparator has not been performed due to inherent differences in the EMPA-KIDNEY and DAPA-CKD populations, outcome definitions, and trial duration that could not be fully adjusted for as per section B.2.9 Indirect and mixed treatment comparisons. Expanded NMA and ITC results did not show any clinically meaningful differences, supporting a conclusion of similar health benefits (and therefore costs). Clinical expert opinion supports this conclusion (see Appendix O). Therefore, a cost-comparison has been presented for empagliflozin and dapagliflozin.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

This section describes the baseline characteristics of the three different populations for which cost-utility analysis is performed i.e., the full ITT population (hereafter referred to as full cohort), patients with DM, and patients without DM. Baseline characteristics for all populations were obtained from the EMPA-KIDNEY trial.

Table 27 outlines the baseline characteristics of the studied populations. Baseline characteristics determine the KDIGO health state at which the patient enters the model. Disease progression (based on eGFR and uACR) and the risk of occurrence of complications is also dependent on baseline characteristics as well as the evolution of further risk factors over time (see section B.3.3.2).

The EMPA-KIDNEY trial did not report data on some parameters that are required for the model, thus alternative sources were identified. The proportion of patients on anti-hypertension therapy was assumed to be the same as the percentage of patients with hypertension. Baseline values for HDL, TC, and proportions of patients with hypertension, metabolic acidosis, family history of DM, and receiving anti-hypertensive, atypical antipsychotic and corticoid steroid medication were obtained from published articles based on CRIC Study data (137, 138), and data used in development and validation of QDiabetes-2018 risk prediction algorithm (139).

Table 27. Baseline characteristics for full cohort, diabetics, and non-diabetics

Parameter	Unit	Full cohort	Diabetics	Non-Diabetics
Baseline characteristic				
Number[1]	N	6609	3040	3569
Age[1] (mean)	Years	63.30	68.00	59.30
Male[1]	%	66.80	67.20	66.50
Race[1]				
Caucasians	%	58.40	59.50	57.40
Black	%	4.00	5.70	2.50
Asians and Indians	%	36.20	33.20	38.80
Hispanic Caribbeans	%	1.40	1.60	1.30
Native Americans	%	0.00	0.00	0.00
Native Australians	%	0.00	0.00	0.00
Clinical risk factors				
Smoking[1]	%	44.60	47.60	42.10
eGFR[1]	m/min/1.73m^2	37.32	35.79	38.62
uACR[1]	mg/mmol	93.69	104.07	84.85
HbA1c[1]	%- point	6.27	7.17	5.50
BMI[1]	Kg/m^2	29.70	31.80	28.00
TC[2]	mg/dL	183.00	177.00	188.20
HDL[2]	mg/dL	48.10	45.70	50.20
SBP[1]	mmHg	136.50	139.20	134.30
Height[1]	cm	167.80	167.10	168.30
Controlled hypertension threshold	mmHg	140	140	140
Hb1Ac threshold for DM	%- point	6.5	6.5	6.5
eGFR class distribution				
eGFR G1[1]	%	0.00	0.00	0.00
eGFR G2[1]	%	7.71	5.60	9.50
eGFR G3a[1]	%	13.41	11.40	15.20
eGFR G3b[1]	%	44.34	45.10	43.60
eGFR G4[1]	%	34.53	37.90	31.70
eGFR G5[1]	%	0.00	0.00	0.00
uACR class distribution				
uACR A1[1]	%	20.10	21.30	19.10
uACR A2[1]	%	28.20	31.00	25.80
uACR A3[1]	%	51.70	47.70	55.10
History of comorbidities				
DM[1]	%	46.00	100	0
CVD[1]	%	26.70	36.30	18.50
Hypertension[3]	%	86.10	0.86	0.86
CHF[1]	%	9.90	14.20	6.30
AKI[1]	%	0.00	0.00	0.00
Metabolic acidosis[1]	%	0.00	0.00	0.00
Gestational DM[4]	%	0.42	0.42	0.42
Schizophrenia or BAD[4]	%	0.76	0.76	0.76
PCOS[4]	%	1.97	1.97	1.97
Learning disability[4]	%	0.99	0.99	0.99
Family history of disease				
Family history of DM[4]	%	15.00	15.00	15.00
Clinical management (medication)				
Anti-hypertensives[3]	**%**	86.1%	86.1%	86.1%
Statins[4]	**%**	6.4%	6.4%	6.4%
Atypical antipsychotics[4]	**%**	0.7%	0.7%	0.7%
Corticosteroids[4]	%	2.9%	2.9%	2.9%
Other classifications				
NGT[1]	%	59.4%	59.4%	59.4%
Pre-DM[1]	%	40.6%	40.6%	40.6%

Abbreviations: AKI, acute kidney injury; BAD, bipolar affective disorder; BMI, Body mass index; cm, centimetres; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; PCOS, polycystic ovary syndrome; TC, Total Cholesterol; LDL, Low-density lipoprotein; NGT, normal glucose tolerance; SBP, Systolic blood pressure; uACR, urine albumin-to-creatinine ratio.
Sources: 1 EMPA-KIDNEY Trial data on file - Clinical trial documentation; 2 Lash et. al 2009 (137); 3 Grams et. al 2020 (138); 4 Hippisley-Cox 2018 (139)

B.3.3.2 Risk of disease progression

As discussed in section B.3.2.2 Model structure, disease progression for individual patients through KDIGO health states is determined by progression of eGFR and uACR. Data informing the rate of disease progression in treatment and comparator arms was taken from two sources:

1. EMPA-KIDNEY trial: Patients' disease progression through KDIGO health states in the treatment and comparator arms was modelled through annual treatment specific transition probabilities derived from observed eGFR slopes (Table 29) and uACR observed changes over time in EMPA-KIDNEY while patients remain alive and on treatment as per Table 31.
2. Literature: A TLR of observational studies was performed for evidence on eGFR and uACR progression in CKD to inform model parameterisation for risk of disease progression following treatment discontinuation. The TLR retrieved 21 relevant studies – 15 studies for eGFR progression and six studies for uACR progression (

3. Table 28). Data from Naimark et al. 2016 (140) (from the CKD-PC registry) was ultimately used in the base-case of the model for eGFR progression, as it reported the absolute changes in eGFR required for modelling inputs. For uACR progression, data from Coresh et al. 2019 (141) was used in the base-case of the model, as it provided three-year uACR fold change which fitted to a lognormal distribution.

Table 28. Key articles identified in targeted literature search for eGFR and uACR

Article ID	Research group	Country	Populations
eGFR progression			
Grams et al. 2020 (138)	CRIC subjects	US	CKD with or without DM
Nichols et al. 2020 (142)	KAISER data	US	CKD with or without DM
KDIGO guidelines - Hemmelgarn et al. (143)	Older adults	US	CKD with DM, >65 years
Warren et al. 2018 (144)	ARIC study	US	CKD without DM; CKD with undiagnosed DM
KDIGO guidelines - Imai E et al. (145)	Annual health exam participants	Japan	Hypertensive, With proteinuria
Tsai et al. 2017 (146)	Tertiary medical centre EMR	Taiwan	CKD
Coresh 2014 (147)	CKD-PC	Global	ESKD
Naimark 2016 (140)	CKD-PC	Global	CKD
Moriya et al. 2013 (148)	JDCS	Japan	Japanese T2D patients
Jiang et al. 2018 (149)	HK registry	China	Chinese T2D patients
Boucquemont 2017 (150)	NephroTest cohort	France	CKD
Park et al. 2019 (151)	Hospital medical records	Korea	T2D
Yoshida et al. 2020 (152)	Hospital study	Japan	DKD
Go et al. 2018 (153)	KPNC CKD Outcomes Study	US	With and without DM
Anderson et al. 2012 (154)	CRIC study	US	CKD
uACR progression			
Min Jun 2017 (155)	ADVANCE-ON study	-	T2D
Coresh et al. 2019 (141)	CKD-PC	Global	ESKD
Sumida et al. 2017 (156)	Nationwide cohort	US	Incident kidney disease
Moriya et al. 2013 (148)	JDCS	Japan	Japanese T2D patients
Park et al. 2019 (151)	Hospital medical records	Korea	T2D
Nelson et al. 2019 (157)	CKD-PC dataset	Global	Patients with and without DM

Abbreviations: CKD, chronic kidney disease; CKD-PC, Chronic Kidney Disease Prognosis Consortium; CRIC, Chronic Renal Insufficiency Cohort Study; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; ESKD, end-stage kidney disease; HK, Hong Kong; JDCS, Japan diabetes complication study; KDIGO, Kidney Disease Improving Global Outcomes; KPNC, Kaiser Permanente Northern California; T2D, type 2 diabetes mellitus; US, United States

B.3.3.2.1 eGFR progression

In the EMPA-KIDNEY trial, the annual progression of eGFR in patients receiving empagliflozin (on top of SoC) were reported per KDIGO categories and overall (across all health states, irrespective of KDIGO class) (Table 29). In general, eGFR progression was calculated in the model taking eGFR slope change values per KDIGO class. Further, patients with health states G1 and G5 at baseline were not included in the EMPA-KIDNEY trial.

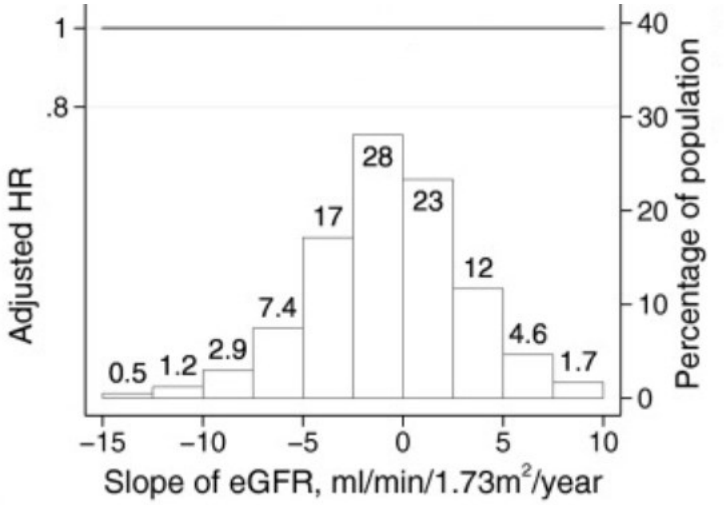
Table 29. Annual eGFR change in patients receiving empagliflozin and SoC

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Matched placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	-2.20 (-3.26, -1.14)	-3.39 (-3.96, -2.81)	NA	-2.76 (-3.92, -1.59)	-5.14 (-5.7, -4.58)
G3a	NA	-1.60 (-2.32, -0.89)	-3.45 (-3.91, -2.98)	NA	-2.29 (-3.04, -1.55)	-4.66 (-5.14, -4.19)
G3b	-0.58 (-0.96, -0.19)	-1.04 (-1.4, -0.67)	-2.90 (-3.2, -2.6)	-0.83 (-1.2, -0.46)	-1.56 (-1.92, -1.2)	-4.11 (-4.42, -3.8)
G4	-0.32 (-0.87, 0.22)	-0.62 (-1.04, -0.19)	-2.76 (-3.08, -2.45)	-0.15 (-0.71, 0.4)	-0.85 (-1.27, -0.43)	-3.76 (-4.09, -3.44)
All	-1.96 (-2.11, -1.82)			-2.68 (-2.82, -2.53)		

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA: not available; SoC, standard of care
Significant differences are in bold.
Source: EMPA-KIDNEY Trial data on file – Clinical trial documentation

Following treatment discontinuation: Figure 23 and Table 30 both show the distribution of eGFR decline (mL/min/1.73m^2) over 3 years compared to baseline observed in the CKD-PC cohort in Naimark et al. 2016 (140). Annual eGFR decline was estimated and fitted to a normal distribution to apply to annual cycles in the microsimulation model. The normal distribution is used to randomly sample and determine the annual eGFR for each patient per cycle in the model, thus simulating the heterogeneity in eGFR decline seen in a typical CKD cohort, with eGFR estimated in a prior cycle informing eGFR decline in the proceeding cycle.

Figure 23. Histogram showing distribution of eGFR slope in the CKD-PC population (Naimark et al)



Abbreviations: CKD-PC, Chronic Kidney Disease Prognosis Consortium; eGFR: estimated glomerular filtration rate; HR, hazard ratio
Source: Naimark et al. 2016 (140)

Table 30. Percentage of patients reporting specific eGFR slopes

eGFR slopes (mL/min/1.73 m²)	Percentage* of patients in the CKD-PC population
-15	0.5
-12.5	1.2
-10	2.9
-7.5	7.4
-5	17
-2.5	28
2.5	23
5	12
7.5	4.6
10	1.7

*Proportion of patients obtained from Naimark et al. 2016 (140) have been changed to percentages
Abbreviations: CKD-PC, Chronic Kidney Disease Prognosis Consortium; eGFR: estimated glomerular filtration rate
Source: Naimark et al. 2016 (140)

The normal distribution applied in the engine has a mean and a standard deviation of -0.6 and 1.43, respectively. To determine the new eGFR value of the following cycle, the eGFR value of the previous cycle and the random eGFR decline are summed. When a patient initiates RRT, with either HD or PD, the progression of eGFR is assumed to remain constant. In cases where patients

have a successful kidney transplant, patients move to the KDIGO stage G3A1 and reinitiate eGFR and uACR decline and disease progression from that health state.

B.3.3.2.2 uACR progression

The change in the uACR values compared to baseline over time were derived from the EMPA-KIDNEY trial and reported as ratios. uACR values were measured at 2, 18, 24, 30, and 36 months during the trial, values at 18 months were utilised to describe annual uACR progression in the model as 12 months uACR values were not available from the trial. uACR values were not one of the top 20 variables impacting the ICER in the one-way sensitivity analysis (OWSA), thus this assumption has limited impact on the results. The change in the uACR values in one year used in the model, are presented in Table 31.

Table 31. Change in the uACR values of empagliflozin and SoC over one year

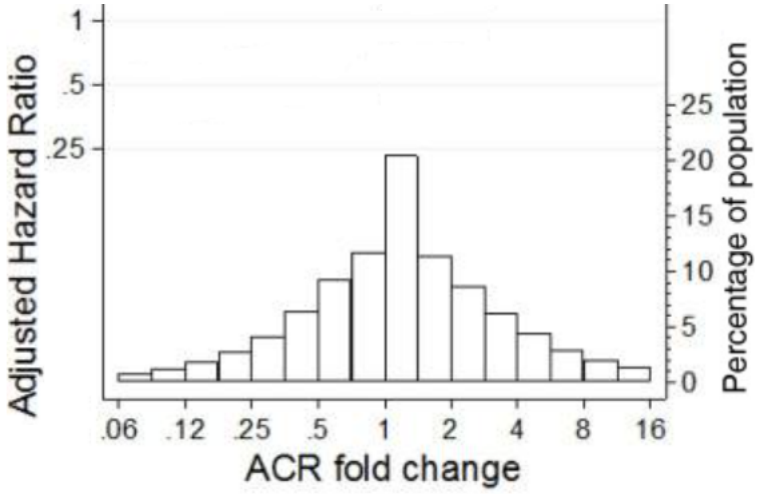
Health states	uACR change – Mean ratio (95% CI)					
	Empagliflozin 10mg			SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	1.26 (0.93, 1.69)	0.67 (0.55, 0.77)	NA	0.93 (0.67, 1.28)	0.75 (0.63, 0.88)
G3a	NA	0.87 (0.7, 1.05)	0.53 (0.46, 0.61)	NA	0.99 (0.81, 1.24)	0.71 (0.62, 0.81)
G3b	1.62 (1.46, 1.84)	0.84 (0.76, 0.94)	0.62 (0.56, 0.67)	1.65 (1.49, 1.86)	1.09 (0.99, 1.22)	0.81 (0.74, 0.88)
G4	2.08 (1.77, 2.44)	1.03 (0.91, 1.19)	0.68 (0.62, 0.74)	2.44 (2.13, 2.93)	1.51 (1.35, 1.73)	0.95 (0.86, 1.03)
All	0.86 (0.83, 0.89)			1.08 (1.04, 1.12)		

Abbreviations: CI, confidence interval; NA: not available; SoC, standard of care; uACR, urine albumin-to-creatinine ratio.
Significant differences are in bold.
Source: EMPA-KIDNEY Trial data on file - Clinical trial documentation

Following treatment discontinuation: Coresh et al. 2019 (141) used patient-level data from eligible patients in the CKD-PC registry to assess the change in uACR values, with follow-up periods of one, two and three years. The study measured uACR changes by comparing the three-year values versus baseline.

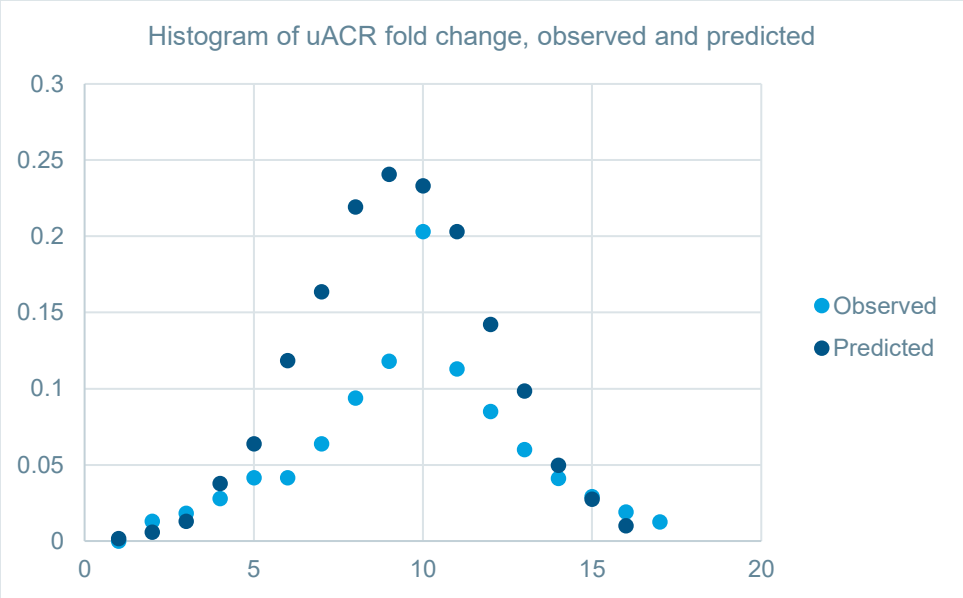
The histogram presented in Figure 24 shows the uACR progression over time. The distribution of uACR fold change (shown in Figure 25) was fitted to a lognormal distribution in the model. This distribution enables random sampling and quantification of the uACR fold change for an individual patient, thus simulating the heterogeneity in uACR decline seen in a typical CKD cohort. To employ these random changes to annual cycles of the model, the cubic root of the value was determined. Each annual uACR fold change is then multiplied by the uACR value of the previous cycle to obtain the uACR value of the following cycle.

Figure 24. Histogram showing uACR fold change in the CKD-PC population



Abbreviations: CKD-PC, Chronic Kidney Disease Prognosis Consortium; uACR: urine albumin-to-creatinine ratio
Source: Coresh et al. 2019 (141)

Figure 25. Distribution of patients per uACR fold change



Abbreviations: uACR: urine albumin-to-creatinine ratio
Source: Coresh et al. 2019 (141)

B.3.3.2.3 Progression of other risk factors

Progression of total cholesterol (TC), high-density lipoproteins (HDL), systolic blood pressure (SBP), glycated haemoglobin (HbA1c) and BMI is also incorporated in the model. These risk factors (along with eGFR and uACR) impact patient transition from one health state to another, as well as the probability of occurrence of complications in the model. Risk factor progression equations from the Framingham Heart Study [Wilson 1993 (158)] and United Kingdom Prospective Diabetes Study (UKPDS) 90 were used (159) to map the progression of these risk factors in the model.

For TC, HDL and SBP (irrespective of DM status), the Framingham progression equations were used which are based on two populations: the original 1948 Framingham cohort and offspring cohort. The individuals in original and offspring cohort returned for regular clinic visits after every two years and four years, respectively. Both these equations are applied up to 70 years in the model and no further progression is assumed after that. Table 32 demonstrates the coefficients of risk progression equations for TC, HDL and SBP by gender.

Table 32. Coefficients of the Framingham risk progression equations for TC, HDL, SBP (Framingham progression)

	TC		HDL		SBP	
	(mg/dL)		(mg/dL)		(mm Hg)	
Mean coefficients	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Age^1	-1.48310	-0.55890	-0.03900	0.00790	0.08740	0.43750
Age^2	0.08450	0.02640	0.00110	0.00040	-0.00660	-0.02680

	TC		HDL		SBP	
	(mg/dL)		(mg/dL)		(mm Hg)	
Mean coefficients	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Age^3	-0.00080	-	-	-	0.00020	0.00040

Note: The main driver of these equations is age. Abbreviations: HDL: high-density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol. Source: Framingham Heart Study (158)

5,102 patients with newly diagnosed DM were followed up for a total of 30 years in UKPDS 90. UKPDS 90 progression equations were used to model HbA1c and BMI in patients with T2DM (159). The coefficients of these risk factor progression equations are described in Table 33.

Table 33. Coefficients of the risk progression equations for HbA1c and BMI in patients with DM (UKPDS 90)

Risk factor (Y)	Estimate of coefficient		
Parameters		**HbA1c (%)**	**BMI (kg/m^2)**
Constant	Mean (SE)	1.419 (0.041)	0.830 (0.039)
Female	Mean (SE)	0.054 (0.012)	0.045 (0.011)
African Caribbean	Mean (SE)	0.066 (0.026)	-0.094 (0.016)
Asian-Indian	Mean (SE)	0.046 (0.020)	-0.087 (0.014)
Value of Y in previous year*	Mean (SE)	0.724 (0.005)	0.952 (0.003)
ln (year since DM diagnosis)	Mean (SE)	0.141 (0.007)	-0.165 (0.006)
First recorded value of Y	Mean (SE)	0.081 (0.007)	0.034 (0.003)

Abbreviations: BMI: body mass index; DM, diabetes mellitus; Hb1Ac: glycated haemoglobin; SE: standard error
* Three-year lag of Y for risk factors collected every three years. Source: UKPDS (159)

HbA1c is a variable included in QDiabetes-2018 prediction algorithm applied in the microsimulation to predict the risk of developing T2DM in patients with normal glucose tolerance (see Appendix P). As HbA1c change over time was not reported in EMPA-KIDNEY, the Framingham Offspring cohort [Pani et al. (160)] was used to model HbA1c over time in patients without DM. Based on this study, an increase of 0.014% in HbA1c per year is applied in the model. Table 34 shows the coefficients of risk progression equation for HbA1c. For patients without DM, it is considered that BMI progression follows a constant natural increase over time. In the model, a constant increase of 0.296 kg per year in the body weight until age 66 years is applied (161). After 66 years, a gradual decrease of 0.296 kg per year in the body weight is applied (162).

Table 34. Coefficients of the risk progression equation for HbA1c in patients without DM (Framingham Offspring cohort)

Age at examination 5 (years)	Estimate of coefficient		
	Non-Diabetic		
	N	**Mean (%)**	**SE**
<40	104	0.027	0.006
40–44	182	0.032	0.005
45–49	337	0.037	0.004
50–54	343	0.043	0.005
55–59	258	0.024	0.005
60–64	239	0.024	0.006
65–69	184	0.03	0.005
≥70	100	0.026	0.007

Abbreviations: DM, diabetes mellitus; SE: standard error
Source: Pani et al. (160)

B.3.3.2.4 Assumptions used in the model for disease progression

The following assumptions were made for disease progression, which were adopted in consultation with clinical experts who were directly involved in the process of developing the empagliflozin microsimulation model:

- It was assumed that the eGFR change over time can be characterised by annual eGFR decline sampled within an observed distribution range would be applicable as an adequate representation of the disease progression to be applied in every cycle
- Following initiation of RRT, no further eGFR change was assumed in the model.
- It is assumed that patients having a successful kidney transplantation would move to the KIDIGO health state G3a A1
- For simplicity, it is assumed that the annual uACR fold change data collected by Coresh et al. 2019 (141) could also be applied at other time points, i.e., it is assumed that the effect of the time-variant exposure equals the effect of the time-invariant exposure.
- The progression of BMI is calculated in the model with the assumption that the height of the patients remains constant over time.
- The Framingham progression equations for TC, HDL and SBP are applied up to 70 years and no further progression is assumed after that.
- For individuals without DM, it is considered that BMI progresses following a constant natural increase in body weight of 0.296 kg per year. This increase is applied until the age of 66 years after which a gradual decrease in the body weight is noted. The decrease in weight applied after 66 years is again 0.296 kg per year. The progression of BMI is calculated using these parameters with the assumption that the height of the patients remains constant over time.

A list of other assumptions used in the model is provided in section B.3.9.2**Error! Reference source not found.**.

B.3.3.3 Risk of complications

The risk of complications is based on the initial baseline characteristics and clinical risk factors of the patients. Patients are at risk of the same set of complications in any health state except death. The probability of patients experiencing any complication/ event per cycle is predicted by using either clinical data from literature (using transition probabilities or incidence rates) or commonly recognised predictive risk equations. A detailed account on the risk of complications considered in the model is provided in Appendix P. Risk of complications is modelled along with the risk of disease progression over a lifetime horizon until death.

B.3.3.4 Risk of all-cause mortality (death)

In the base-case of the model, the risk of all-cause mortality (ACM) was predicted using non-specific cause of death plus CV death plus renal death:

1. Non-specific cause death

   The non-specific cause death was estimated by subtracting CVD and renal failure deaths from the UK general population all-cause mortality. The general population mortality by age and gender was taken as per UK Office for National Statistics (ONS) life tables (163) and ONS lifetables selected are presented in Appendix Q.

2. CVD mortality

   Predictive risk equations developed by the Matsushita et al 2020 study (164) were used to estimate risk of CVD mortality. Further details are discussed in Appendix P.

3. Renal death (mortality in patients on RRT)

   The “renal death” tracker traces all the fatal events associated to PD, HD, and kidney transplant and moves patients to the death health state every time such an event occurs. The data for the renal death events has been sourced from the UKRR annual report (33). It is assumed that all renal deaths occurring are due to PD, HD, or kidney transplant as the UKRR annual report data does not indicate the cause of renal death. Appendix P details the risk of death as calculated from the UKRR report (33).

B.3.3.5 Adverse events

Lower limb amputations (leg, toe, and foot) sourced from the EMPA-KIDNEY trial are included in the base-case of the model. Lower limb amputations occurred more frequently in empagliflozin group (0.43 versus 0.29 events per 100 patient-years with placebo) (2). However, there were no statistically significant difference between the incidence rates in the empagliflozin group versus placebo. Table 35 shows the lower limb amputation events used in the model.

Table 35. Lower limb amputation rates per 100 patient-years

Adverse Event Modelled	EMPA 10 mg	Placebo
	Rate / 100 patient-years	Rate / 100 patient-years
Lower limb amputations	0.43	0.29
Leg amputation	0.12	0.02
Toe amputation	0.25	0.15
Foot amputation	0.08	0.02

Source: EMPA-KIDNEY Trial data on file - Clinical trial documentation

B.3.3.6 Discontinuation rates

The discontinuation rate used for empagliflozin and placebo in the model was sourced from the EMPA-KIDNEY trial. The annual discontinuation rate of 12.56 and 14.16 per 100 patient-years was applied while on treatment with empagliflozin and placebo respectively (79). As described in section B.3.3.2**Error! Reference source not found.**, after discontinuation of treatment in EMPA-KIDNEY trial, the progression of patients was modelled using observational data reported in the CKD-PC or CRIC registries.

B.3.4 Measurement and valuation of health effects

B.3.4.1 HRQoL data from clinical trials

EMPA-KIDNEY trial utilities are utilised in scenario analysis and discussed in Appendix N. The base-case cost-effectiveness analysis utilises HRQoL data obtained from the HRQoL SLR, discussed in section **Error! Reference source not found.** and as described in detail in Appendix H.

A qualitative comparison of the HRQoL outcomes between trials of empagliflozin and dapagliflozin was conducted to further substantiate the cost comparison approach (only a comparison to dapagliflozin is relevant to the decision problem). As HRQoL data from DAPA-CKD was not reported publicly, this was performed using HRQoL data available from the pivotal trials supporting the HF with LVEF≥40% indications for both medications.

Both empagliflozin and dapagliflozin resulted in improvements in HRQoL in the HF with LVEF≥40%. The mean difference in change from baseline to 12 months in KCCQ-CSS was 1.32 (95%CI: 0.45-2.19) for empagliflozin (102), and the mean difference in change from baseline to 8 months in KCCQ-CSS was 2.3 (95%CI: 1.5-3.2) for dapagliflozin (12-month KCCQ data was not available) (165).

The comparison shows consistency between HRQoL results between empagliflozin and dapagliflozin and is also reflected by the similar efficacy and safety of the interventions, as described above in section B.2.9 Indirect and mixed treatment comparisons and independent sources (91).

B.3.4.2 Health state utilities derived from published evidence

Structured literature searches were conducted in October 2020 to identify and collate the utility and disutility inputs for the health states and events/complications associated with CKD to be used in the model. Full details of the search strategy, study selection process and results are presented

in Appendix H. MEDLINE®, Embase®, EconLit™ (via Ovid platform), NICE website, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) website and Google Scholar were searched. The study selection process used pre-specified eligibility criteria to identify the relevant NICE TAs and studies using the PICOS framework, presented in Appendix H. A total of six TAs and 12 journal articles met the eligibility criteria. A full list of the included health state utility studies can be found in Table 14 and Table 15 in Appendix H.

In the base-case cost-effective analysis, utility weight inputs per health state (as per KDIGO classification) were required. Jesky 2016 (166) was selected for usage in the model as it met the criteria among all published evidence identified in the HRQoL SLR. As such, utilities are identical for the health states with same eGFR class in the base-case scenario (Table 36).

B.3.4.3 Mapping

No utility mapping was performed in the base-case scenario as the utilities are sourced from literature, specifically a study by Jesky et al (166) in which data were collected from participants using the EQ-5D-3L, and health states were converted into an EQ-5D^{index} score using a set of weighted preferences produced from the UK population. In a scenario analysis [Section **Error! Reference source not found.**], the literature derived health state utilities were replaced by baseline EMPA-KIDNEY trial utilities. The EQ-5D-5L descriptive system data collected from EMPA-Kidney trial were mapped onto the EQ-5D-3L value set using the mapping algorithm developed by the DSU based on the EEPRU dataset (167, 168). The UK-specific value sets proposed by Hernández-Alava et al. (2020) (168) were used to convert the five-digit EQ-5D health states into utility scores taking into account societal preferences for health (see Appendix N).

B.3.4.4 Complication related disutilities

The structured literature review, described in Appendix H, provided the disutility values for CVD, BMD, anaemia, AKI, and incident cancer shown in Table 36Table 36. Summary of utility values for cost-effectiveness analysis. These values were applied in the model only for the year in which the event occurs. The same disutility is applied in the event of recurrence. Disutilities for peritonitis, blood stream infections, and AV access thrombosis were not retrieved from literature. No disutility is applied for these complications, and they are assumed to be captured within utility for peritoneal or haemodialysis. Further disutilities for infections, metabolic events, DM, and hypertension have not been applied as they have been assumed to be included in the respective health state utility. Moreover, for events with a long-term impact, like stroke or myocardial infarction, a conservative approach is taken to only apply the disutility in year the event occurs, and not in the following years.

B.3.4.5 ACH related disutilities

Upon selection of the ACH module, the disutilities associated with acute events are superseded by a unique disutility applied every time an ACH event occurs in the model. In absence of data, the value used for ACH disutility was assumed equal to the utility loss with an MI (-0.06), applied during a 1-year cycle (169).

B.3.4.6 ESKD related utilities and disutilities

These utility inputs have mainly been sourced from Liem 2008 (170), Peasgood 2016 (171), and the technology assessment of dapagliflozin for treating CKD (6), as identified in the SLR described in Appendix H. The utility values used for ESKD in the model are provided in Table 36 and are applied as follows:

- For conservative therapy it is assumed to be same as G5 from the KDIGO classification
- For PD, HD and the first year of kidney transplant a state-specific annual utility is applied
- As patients move to G3A1 post kidney transplant, the utility of that group is used after year 1, however a disutility is applied to account for the immunosuppressive therapy in the follow-up years

B.3.4.7 AE related disutilities

These utility inputs have been sourced from Peasgood 2016 (171), as identified in the SLR described in Appendix H. Disutilities are applied for the acute event in the cycle it occurs in.

B.3.4.8 HRQoL data used in the cost-effectiveness analysis

Table 36Table 36 presents all HRQoL data used in the base-case of the cost-effectiveness analysis.

Table 36. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	95% CI		Source	Reference
		Min	Max		
KDIGO Health state name					
G+90_A-30	0.85	0.70	1.00	Jesky 2016 (166)	B.3.4.2
G+90_A-300	0.85	0.70	1.00		
G+90_A+300	0.85	0.70	1.00		
G+60_A-30	0.85	0.70	1.00		
G+60_A-300	0.85	0.70	1.00		
G+60_A+300	0.85	0.70	1.00		
G+45_A-30	0.80	0.69	1.00		
G+45_A-300	0.80	0.69	1.00		
G+45_A+300	0.80	0.69	1.00		
G+30_A-30	0.80	0.68	1.00		

State	Utility value: mean	95% CI		Source	Reference
		Min	Max		
G+30_A-300	0.80	0.68	1.00		
G+30_A+300	0.80	0.68	1.00		
G+15_A-30	0.74	0.62	0.85		
G+15_A-300	0.74	0.62	0.85		
G+15_A+300	0.74	0.62	0.85		
G-15_A-30	0.73	0.62	1.00		
G-15_A-300	0.73	0.62	1.00		
G-15_A+300	0.73	0.62	1.00		
Submodule Utilities/Disutilities					
CVD					
Myocardial infarction	-0.0550	-0.07	-0.04	Clarke et al. 2002 (169), Beaudet et. al 2014 (172)	B.3.4.4
Unstable angina	-0.0900	-0.13	-0.05		
Stroke (including TIA)	-0.1640	-0.22	-0.11		
CHF (hospitalisations)	-0.1080	-0.17	-0.05		
TIA	-0.0700	-0.13	-0.01	Sullivan 2016 (173)	
PAD and PVD	-0.0610	-0.09	-0.03	Bagust and Beale 2005 (174), Beaudet et. al 2014 (172)	
BMD					
Hip fractures	-0.0680	-0.08	-0.05	Sullivan 2016 (173)	B.3.4.4
Other fractures	-0.0680	-0.08	-0.05		
Anaemia	-0.0800	-0.07	-0.09	TA780 (175)	B.3.4.4
AKI	-0.0380	-0.06	-0.02	Sullivan 2016 (173)	B.3.4.4
Incident cancer					
Renal cancer	-0.0030	0.00	0.00	2000-2003 Medical Expenditure Panel Survey – Web Tables (176)	B.3.4.4
Urothelial cancer	-0.0030	0.00	0.00		
ACH	-0.0550	-0.07	-0.04	Clarke et al. 2002 (169)	
ESKD					
Peritoneal dialysis	0.5800	0.52	0.64	Liem 2008 (170)	B.3.4.4
Haemodialysis	0.5600	-0.01	1.13	Liem 2008 (170)	
Kidney transplant	0.7100	0.57	0.85	TA775 (6)	
Immunosuppressive therapy	-0.0100	-0.01	-0.01	Peasgood 2016 (171)	
AE disutilities					
Leg amputation	-0.1172	0.00	0.00	Peasgood 2016 (171)	B.3.4.4
Toe amputation	-0.1172	0.00	0.00	Peasgood 2016 (171)	
Foot amputation	-0.1172	0.00	0.00	Peasgood 2016 (171)	

Abbreviations: ACH, all-cause hospitalisations; AE, adverse event; AKI, acute kidney injury; BMD, bone-and-mineral disease; CHF, congestive heart failure; CI; confidence interval; CVD, cardiovascular disease; ESKD, end-stage kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; PAD, peripheral arterial disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack

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

A structured literature search was conducted to identify cost and resource use for the CKD health states and the relevant complications included in the cost-effectiveness model (CEM). Full details of the search strategy, study selection process and results are presented in Appendix I.

Data for cost inputs was searched in a five-step process (see Figure 3 in Appendix I): NICE TAs, NHS Reference Costs 2020/21, and databases MEDLINE®, Embase®, and EconLit™ (via Ovid platform) were searched, in addition to hand searching of ISPOR website and Google Scholar. The study selection process used pre-specified eligibility criteria to identify the NICE TAs and studies relevant to the decision problem and NICE reference case, using the PICOS framework presented in Table 18 in Appendix I.

A total of nine TAs and 16 journal studies were included. A full list of included TAs and studies are presented in Table 19 and Table 20 of Appendix I respectively. Costs for ACH, hyperphosphatemia, secondary hyperparathyroidism, and hypocalcaemia were not obtained from the structured literature search and expert clinical opinion informed costings (Appendix O).

All costs applied in the model were inflated to a 2020/21 cost-year, based on the Hospital and Community Health Services (HCHS) Pay and Prices inflation index (up to and including 2007/08), the HCHS index (between 2008/09 and 2014/15), and the NHS Cost Inflation Index (NHSCII) (from 2015/2016 onwards), as reported in the relevant Personal Social Services Research Unit (PSSRU) publications. No inflation was applied to NHS Reference Costs 2020/21. Please see Appendix Q for details on the inflation indices used.

B.3.5.1 Intervention and comparators' costs and resource use

The cost-effectiveness analysis compares empagliflozin 10mg OD on top of SoC against matching placebo on top of SoC, in line with the EMPA-KIDNEY trial. As per sections B.1.3.3 Current clinical pathway of CKD in the UK and B.1.3.4 Limitations of current pathway and unmet need, SoC is individually optimised and can include ACE inhibitors, ARBs, and CVD medications dependant on patients individual characteristics.

The average annual SoC cost was based on TA775 for dapagliflozin (6), which calculated a weighted average of the most frequently prescribed ACE inhibitor (ramipril), ARBs (losartan and irbesartan), statin (atorvastatin), and antiplatelet medication (aspirin) in CKD. Prices were updated using the British National Formulary (BNF) 2022 (177-181) to determine annual cost of SoC (Table 37).

Table 37. Calculation of SoC weighted average cost

Drug	Daily dose (mg)	Pack size	Tablets per day	Cost per pack	Annual cost	% patients with CKD treated with this therapy	Annual cost
Ramipril	10	28	1	£1.16	£15.12	33.20%	£34.68
Losartan	100	28	1	£1.56	£20.34	20.30%	
Irbesartan	300	28	1	£1.80	£23.46	20.30%	

Atorvastatin	80	28	2	£1.00	£26.07	55.70%	
Aspirin	150	28	2	£0.74	£19.29	32.40%	

Source: TA775 (6); Ramipril BNF (177); Losartan BNF (178); Irbesartan BNF (179); Atorvastatin BNF (180); Aspirin BNF (181)

The treatment cost values used in the base-case analysis are summarised below in Table 38. Treatment costs are applied in the first and subsequent years until discontinuation due to 1) treatment discontinuation, 2) initiation of RRT, or 3) death.

Table 38: Cost of treatment with empagliflozin and SoC

Treatment	Annual cost	Source
Empagliflozin (intervention)	£476.98	BNF (16)
Placebo (comparator)	£0	Assumption
SoC (Background therapy)	£34.68	TA775 (6); BNF (177-181)

Abbreviations: BNF, British National Formulary; CKD, chronic kidney disease; SoC, standard of care

B.3.5.2 Health state unit costs and resource use

The model incorporates annual CKD health state costs, as well as event-driven costs for CKD complications. The cost components are broadly categorised as:

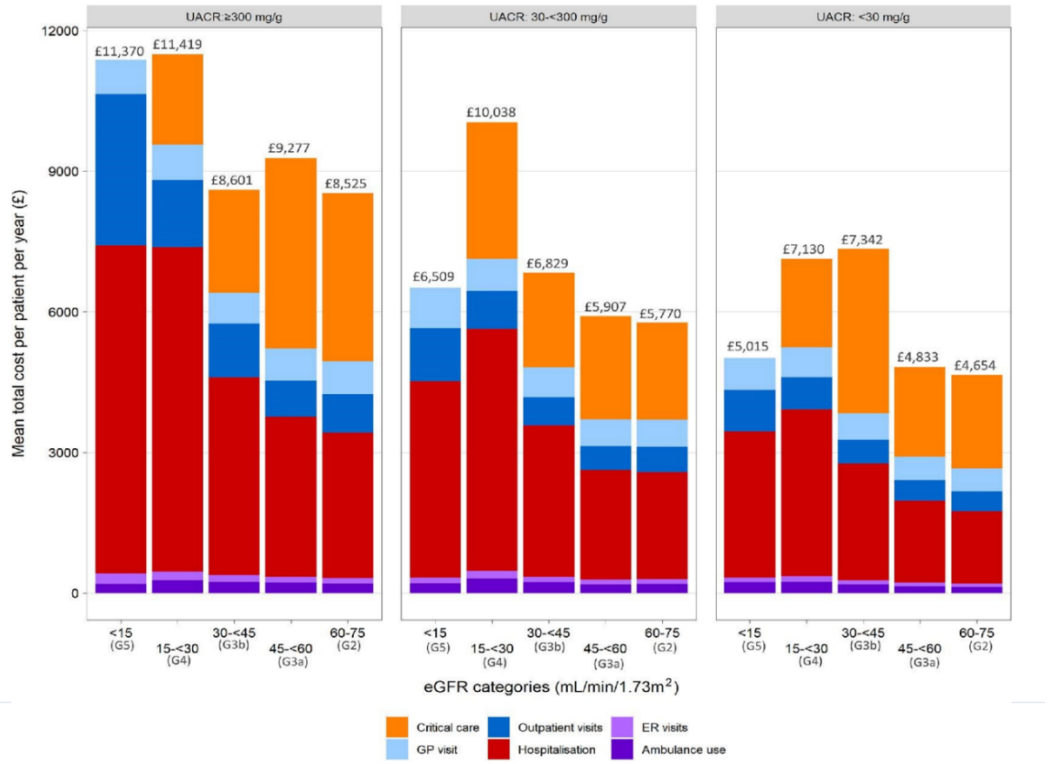
1. Health state costs – annual maintenance/monitoring costs per KDIGO category
2. Complications – include first year and follow-up costs for the long-term complications
    - First year costs apply to the initial resources used in the year the acute complication event occurs
    - Follow-up costs apply to ongoing resource usage in successive annual cycles whilst the complication persists (e.g., the CV events)
3. Event costs – for one-time acute events considered in the model (e.g., fractures, infections)
4. Chronic costs – apply to chronic CKD complications like anaemia with a constant cost applied

In the base-case analysis, health state costs, first year, and follow-up complication costs are added together to get the total costs per submodule. Costing methodology is summarised below.

Annual health state costs

Annual health state costs were sourced from Pollock et. al 2022 (20), which reported annual healthcare cost per patient by KDIGO stage (G2 to G5) and cost category (i.e., critical care, outpatient visits, general physician visits, emergency room visits, hospitalisation, and ambulance use) (Figure 26). Hospitalisation and critical care costs were excluded from annual health state costs in the cost-effectiveness model, as these are already accounted for in complications submodules. G1 costs were assumed be equal to G2 costs across albuminuria levels, as G1 costs were not directly reported in this paper (20). See Table 39 for the values used in the base-case analysis, which were applied as maintenance costs per health state.

Figure 26. Mean annual per patient healthcare costs for the overall CKD cohort, stratified by KDIGO classification group



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, emergency room; GP, general physician; KDIGO, Kidney Disease Improving Global Outcomes; uACR, urine albumin-to-creatinine ratio.
Source: Pollock 2022 (20)

Table 39. Maintenance costs per health state as per KDIGO classification (hospitalisation and critical care costs excluded)

Health State as per KDIGO classification	Annual cost (maintenance)
G+90_A-30	£1,187
G+90_A-300	£1,488
G+90_A+300	£1,941
G+60_A-30	£1,187
G+60_A-300	£1,488
G+60_A+300	£1,941
G+45_A-30	£1,221
G+45_A-300	£1,443
G+45_A+300	£1,901
G+30_A-30	£1,411
G+30_A-300	£1,666
G+30_A+300	£2,309
G+15_A-30	£1,770
G+15_A-300	£2,075
G+15_A+300	£2,790
G-15_A-30	£2,000
G-15_A-300	£2,445
G-15_A+300	£4,604

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; SE, standard error
Source: Pollock 2022 (20)

Cost of CVD

For all CVD complications, a first year (acute) cost is applied in the cycle when the complication occurs, and follow-up costs applied in successive annual cycles whilst the complication persists. Unit costs for acute and follow-up CVD complications are outlined in Table 40. Acute costs for CVD complications were sourced from NHS 2020/21 reference costs (latest available version in Q4 2022), where weighted averages of non-elective long stay inpatient costs were calculated using the relevant Healthcare Resource Group (HRG) codes (182).

Follow-up costs for CVD complications were sourced as follows: Danese 2016 which considered the cost of drugs, hospitalisations, and visits for stroke, TIA and unstable angina (183); TA773 which considered the cost of GP visits, cardiologist visits, and A&E referral for HF (4); Sundström 2022 which considered the cost of annual hospital healthcare for PAD and PVD (184); and TA10820 for MI (185).

Table 40. Acute event and follow-up costs for management of CVD complications

CVD complication	Acute costs	Source of acute costs	Follow-up costs	Source of Follow-up costs
MI	£3,136	NHS 2020/21 (182). Weighted average of EB10A-E non-elective long stay costs	£705	TA10820-Finerenone for treating CKD in people with type 2 diabetes (185)
Unstable angina	£2,273	NHS 2020/21 (182). Weighted average of EB13A-D non-elective long stay costs	£421	Danese 2015 (183)
Stroke (including TIA)	£6,278	NHS 2020/21 (182). Weighted average of AA35A-F non-elective long stay costs	£1,097	Danese 2015 (183)
CHF (hospitalisations)	£4,093	NHS 2020/21 (182). Weighted average of EB03A-E non-elective long stay costs	£941	TA773-Empagliflozin for treating chronic heart failure with reduced ejection fraction (186)
TIA	£2,854	NHS 2020/21 (182). Weighted average of AA29C-F non-elective long stay costs	£795	Danese 2015 (183, 187)
PAD and PVD (driven by smoking, stenting)	£4,650	NHS 2020/21 (182). Weighted average of YQ50A-F non-elective long stay costs	£130	Sundström 2022 (184)

Abbreviations: CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack

Cost of BMD

An event cost is applied in each cycle a patient has a BMD event. BMD costs are summarised in Table 41. The event costs of hyperphosphatemia, secondary hyperparathyroidism, and hypocalcaemia were calculated from the BNF 2022 (188-195) using the average prices of the drugs administered for treatment (phosphate binders for hyperphosphatemia/hypocalcaemia,

vitamin D analogues and calcimimetics for secondary hyperparathyroidism) and average prescribing distributions based on UK clinical guidelines and verified by clinical expert opinion (Appendix O). Costs of managing fractures were sourced from NHS 2020/21 reference cost data using a weighted average of the total cost for the relevant HRG codes (182).

Table 41. Cost of BMD

BMD	Cost type	Cost	Source
Hyperphosphatemia	Per-event	£251	BNF (189-193)
Secondary hyperparathyroidism	Per-event	£909	BNF (188, 194, 195)
Hypocalcaemia	Per-event	£251	BNF (189-193)
Hip fractures	Per-event	£4,814	NHS 2020/21 (182). Weighted average of HE11A-H total costs
Other fractures	Per-event	£2,607	NHS 2020/21 (182). Weighted average of HE21A-G, HE31A-G, HE41A-D, HE51A-H, HE71A-D total costs

Abbreviations: BMD, bone and mineral disorders; BNF, British National Formulary; NHS, National Health Service

Cost of AKI

An event cost is applied in each cycle a patient has an AKI event and includes first and recurrent hospitalisations. A weighted average of relevant HRG codes from the NHS 2020/21 reference cost data was calculated for this input (182) (Table 42). Based on interviews with UK nephrologists, it was assumed reasonable to only include an AKI hospitalisation cost since AKI not requiring hospitalisation (i.e., outpatient AKI) is unlikely to require additional appointments and tests outside of what is normal for patients with CKD (Appendix O).

Table 42. Cost of AKI

AKI	Cost type	Cost	Source
AKI – hospitalisation	Per-event	£2,693	NHS 2020/21 (182). Weighted average of LA07H, LA07J-N, LA07P total costs

Abbreviations: AKI, acute kidney injury; NHS, National Health Service.

Cost of infections

An event cost is applied in each cycle an infection event occurs. Cost of infections are listed in Table 43. Gastrointestinal, muscular, nervous system, and sepsis infection costs were sourced from the NHS 2020/21 reference cost data (182). Gastrointestinal infections costs considered non-admitted face-to-face attendance and follow-up visits for gastroenterology. Muscular infection, nervous system infection and sepsis considered the weighted non-elective long stay costs. Respiratory infection costs were sourced from Kohli 2021 which considered outpatient care of respiratory infection in at risk patients aged 65-74 (196). Skin and soft tissue infection costs were sourced from Humphreys 2023 which considered the mean total HCRU cost of cellulitis for patients aged 61-74 (197). The event cost of urinary tract infection was sourced from TA775 which considered the cost of one GP consultation lasting 9.22 minutes (6).

Table 43. Cost of infections

Infection type	Cost type	Cost	Source
Respiratory	Per-event	£129	Kohli 2021 (196)
Urinary tract	Per-event	£40	TA775-Dapagliflozin for treating CKD (6)
Skin and soft tissue	Per-event	£1,486	Humphreys 2023 (197)
Gastrointestinal	Per-event	£158	NHS 2020/21 (182). WF01A total cost
Muscular	Per-event	£4,490	NHS 2020/21 (182). Weighted average of HD25D-H non-elective long stay costs
Nervous system	Per-event	£3,672	NHS 2020/21 (182). Weighted average of AA22C-G non-elective long stay costs
Sepsis	Per-event	£3,287	NHS 2020/21 (182). Weighted average of WJ06A-H, WJ06J non-elective long stay costs

Abbreviations: CKD, chronic kidney disease; NHS, National Health Service

Cost of incident cancer

A one-time event cost is applied in the first annual cycle an incident cancer complication occurs. Costs of renal or urothelial cancer (which patients with CKD are at an increased risk of) are shown in Table 44. The cost for renal cancer was sourced from Amdahl 2017 which considered the annual cost for metastatic renal cell carcinoma (198). The cost for urothelial cancer was sourced from Sangar 2004 which considered the annual cost for prostate and bladder cancer (199).

Table 44. Cost of incident cancer

Incident cancer	Cost-type	Cost	Source
Renal cancer	One-time	£12,289	Amdahl 2017 (198)
Urothelial cancer	One-time	£13,241	Sangar 2004 (199)

Cost of other complications

For metabolic acidosis, hyperkalaemia, and hyperuricaemia (gout), an event cost is applied in each cycle a patient has the event. For anaemia, annual cycle costs are applied from its occurrence until renal transplant or death as this is a chronic condition. Costs of other CKD related complications are shown in Table 45. The annual cost of metabolic acidosis was sourced from Witham 2020 who considered the annual cost of sodium bicarbonate therapy (130). The annual cost of hyperuricemia/gout was sourced from Morlock 2016 who considered the total healthcare costs in gout patients (130). The event cost of hyperkalaemia was calculated as a weighted average of non-elective long/short stay costs using the relevant HRG codes from NHS 2020/21 reference cost data (182). The annual cost of hyperuricemia/gout was sourced from Morlock 2016 who considered the total healthcare costs in gout patients (130). The chronic cost of anaemia was sourced from TA481 (200).

Table 45. Cost of other complications

Complication	Cost type	Cost	Source
Metabolic Acidosis	Per-event	£1,272	Witham 2020 (130)

Hyperkalaemia	Per-event	£1,976	NHS 2020/21) (182). Weighted average of KC05G-H, KC05J-N non-elective long/short stay costs
Hyperuricaemia/gout	Per-event	£2,170	Morlock 2016 (201)
Anaemia	Annual	£1,326	TA481-Immunosuppressive therapy for kidney transplantation in adults (200)

Abbreviations: NHS, National Health Service

Cost of ESKD

ESKD costs include costs of RRT (PD, haemodialysis, or kidney transplant) and dialysis complications, or conservative therapy. PD includes CAPD or APD. For PD and haemodialysis, annual cycle costs are applied whilst patients remain on therapy. An event cost is applied in each cycle patients experience a dialysis complication (peritonitis, AV access thrombosis, bloodstream infections). For kidney transplant, costs are applied in the annual cycle of the transplant and follow-up immunosuppression costs are applied in subsequent annual cycles until graft rejection or death due to any cause. For PD and haemodialysis, the cost per cycle is applied every year that the patient is on therapy. For kidney transplant, the intervention cost is applied in the year of the event and follow-up costs are applied in subsequent years until graft rejection or death due to any cause. The cost of conservative therapy is applied annually whist patients remain on therapy. To avoid double counting, costs of RRT or conservative therapy are not applied to patients in the G5 health state.

Unit costs for ESKD are listed in Table 46. Annual cost of CAPD and APD were sourced from NHS 2020/21 reference cost data using relevant HRG codes and frequencies of sessions (182, 202). Cost of haemodialysis was sourced from TA10820 which considered the cost and frequency of haemodialysis sessions (185). Costs of AV access thrombosis and peritonitis were sourced from the NHS 2020/21 reference cost data using the relevant HRG codes (182). For AV thrombosis a weighted average of the total costs was calculated and for peritonitis the weighted average of non-elective long stay costs was calculated. Cost of bloodstream infections was sourced from Manoukian 2021 (203).

Kidney transplant costings followed assumptions from TA775 i.e., HRG codes from 2020/21 NHS reference cost data for pre-transplant, transplant, and post-transplant care, however costs for living and deceased donor transplants were considered separately. The weighted averages of the relevant HRG codes for the three components of kidney transplant costs were summed to determine a total cost (6, 182). Cost of immunosuppressive therapy to avoid transplant rejection is also applied for annual cycles post successful kidney transplant (6). The annual cost of conservative therapy for ESKD was sourced from Agus et. al 2017, which considered management costs for ESKD in patients refusing dialysis (204).

Table 46. Cost of ESKD

ESKD	Cost type	Cost	Source
CAPD	Annual	£29,871	NHS 2020/21 (182) LD11A total unit cost, converted to annual
APD	Annual	£33,388	NHS 2020/21 (182). Weighted average of LD12A-13A total unit costs, converted to annual
Haemodialysis	Annual	£27,606	TA10820-Finerenone for treating CKD in people with type 2 diabetes (185)
AV access Thrombosis	Per-event	£2,991	NHS 2020/21 (182). Weighted average of YQ42Z and YR48Z total costs
Peritonitis	Per-event	£5,969	NHS 2020/21) (182). Weighted average of FD01A-E non-elective long stay costs
Bloodstream infections	Per-event	£6,234	Manoukian 2021 (203)
Kidney transplant (living donor)	One-time	£37,284	TA775-Dapagliflozin for treating CKD (6) NHS 2020/21 (182). Total HRG LA03A, LA12A, LA13A, LA11Z, LA14Z
Kidney transplant (deceased donor)	One-time	£34,700	TA775-Dapagliflozin for treating CKD (6) NHS 2020/21 (182). Total HRG LA01A, LA02A, LA12A, LA13A
Immuno-suppression	Annual	£6,132	TA775-Dapagliflozin for treating CKD (6)
Conservative Therapy	Annual	£6,335	Agus et. al 2017 (204)

Abbreviations: AKI, acute kidney injury; APD, automated peritoneal dialysis; AV, arteriovenous; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; NHS, National Health Service; PD, peritoneal dialysis.

B.3.5.3 Adverse events unit costs and resource use

As described in section B.3.3.5 three adverse events (leg, foot, and toe amputation) were included in the model. An event is applied in each cycle patients experience adverse events. Amputation costs were sourced from relevant HRG codes from NHS 2020/21 reference costs (182) (Table 47).

Table 47. Cost of managing lower limb amputations

Amputation	Cost type	Cost	Source
Leg	Per-event	£17,625	NHS 2020/21 (182). Unit cost of YQ222B
Toe	Per-event	£9,195	NHS 2020/21 (182). Unit cost of YQ26A
Foot	Per-event	£9,195	NHS 2020/21 (182). Unit cost of YQ26A

Abbreviations: NHS, National Health Service

B.3.5.4 Summary of cost application in the model

The cost application method for each health state and complication submodule in the base-case cost-effectiveness analysis are presented in Table 48.

Table 48 Submodule-wise application of costs in the model

Submodule	Description	How costs are applied in model
Treatment	Empagliflozin 10mg + SoC, SoC only	Treatment costs are applied in the first and subsequent years until discontinuation due to 1)

Submodule	Description	How costs are applied in model
		treatment discontinuation, 2) initiation of RRT, or 3) death
Health states	KDIGO categories	Maintenance cost applied per state
CVD	MI UA Stroke CHF TIA PAD and PVD	For all CVD complications, a first year (acute) cost is applied in the cycle when the complication occurs, and follow-up costs applied in successive annual cycles whilst the complication persists
BMD	Hyperphosphataemia Secondary hyperparathyroidism Hypocalcaemia Hip fractures Other fractures	An event cost is applied in each cycle a patient has the event
Anaemia	Anaemia	Annual cycle costs are applied from its occurrence until renal transplant or death
DM	DM	No cost has been applied for DM as it is assumed that patients with DM will have a higher risk of events, therefore differences in costs are already considered. In case HS costs are available with and without DM, this can be considered
Hypertension	Hypertension Not controlled hypertension Resistant hypertension	No cost has been applied as for DM. It should be noted that the majority of patients with CKD receive ACE inhibitors or ARB or other anti-hypertensives (see baseline characteristics EMPA-KIDNEY (80))
AKI	AKI hospitalisation	An event cost is applied in each cycle a patient has the event
Infections	Respiratory tract Urinary tract Skin and soft tissue Gastrointestinal Muscular Nervous system Sepsis	An event cost is applied in each cycle a patient has the event
Incident cancer	Renal cancer Urothelial cancer	A one-time event cost is applied in the first annual cycle an incident cancer complication occurs
Other complications	Metabolic acidosis Hyperkalaemia Hyperuricaemia/gout	An event cost is applied in each cycle a patient has the event
ESKD	PD HD KT with immuno-suppressive therapy protocol Conservative therapy	Management cost applied per cycle in the specific arm of therapy of patient (conservative therapy, PD, HD, KT) • For PD, HD, and conservative therapy, annual cycle costs are applied whilst patients remain on therapy • For KT, costs are applied in the annual cycle of the transplant and follow-up immunosuppression costs are applied in subsequent annual cycles until graft rejection or death due to any cause

Submodule	Description	How costs are applied in model
	AV access thrombosis Peritonitis Bloodstream infections	An event cost is applied in each cycle patients experience a dialysis complication
Adverse Events	Leg Amputation Toe Amputation Foot Amputation	An event is applied in each cycle patients experience adverse events

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blockers; AV, arteriovenous; CKD, chronic kidney disease; DM, diabetes mellitus; EMPA, empagliflozin; ESKD, end-stage kidney disease; HD, haemodialysis; HS, health state; KDIGO, Kidney Disease: Improving Global Outcomes; KT, kidney transplant; MI, myocardial infarction; PAD, peripheral arterial disease; PD, peritoneal dialysis; PVD, peripheral vascular disease; RRT, renal replacement therapy; TIA, transient ischaemic attack; UA, unstable angina

B.3.5.5 Miscellaneous unit costs and resource use

The empagliflozin cost-effectiveness model includes an alternative ACH scenario in which cost of acute events including hospitalisations are turned off and replaced by costs for ACH (Appendix P). An ACH cost of £4,554 was calculated as a weighted average of all HRG non-elective long stay costs, excluding codes for patients under 18 and for obstetric procedures, using NHS 2020/21 reference cost data (182). This method was deemed appropriate through clinical expert opinion (Appendix O). The ACH option is not included in the base case scenario.

B.3.6 Severity

It is not anticipated that empagliflozin would qualify for a severity modifier in this indication.

B.3.7 Uncertainty

BI believes there is no aspect of the condition or technology presented in this submission that would impact the ability to generate high-quality evidence.

B.3.8 Managed access proposal

Not applicable. No patient access scheme is expected as the cost per QALY is low (dominant).

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

An overview of the base-case cost-effectiveness analysis settings and variables is provided in Table 49 and Table 50 respectively.

Table 49. Base-case model settings

Model parameter	Option Selected
Key model parameters	
Analysis type	BC
Seed	User-Defined
Seed value	0.2
Time horizon (years)	50 (lifetime), 4 years, 10 years
Number of patients	1000
Number of iterations	500 (only for PSA)
Discounting rate – effects	3.5%
Discounting rate – costs	3.5%
Half Cycle Correction	Yes
Cost approach	Option 1: Includes 1st and follow-up years (not conservative)
Utility approach	Option 1: Health state utilities plus disutilities per event/complication (not conservative)
Cohort baseline risk factors	
Patient cohort	Option 1 – EMPA-KIDNEY full cohort
eGFR	Distribution over eGFR classes according to EMPA-KIDNEY
eGFR midpoints	As per EMPA-KIDNEY
uACR	Distribution over uACR classes according to EMPA-KIDNEY
uACR midpoints	As per EMPA-KIDNEY
Treatment effect options	
Comparators	Empagliflozin versus SoC
eGFR	Annual eGFR change per KDIGO
uACR	Annual uACR change per KDIGO
Duration of Treatment	50 Years
Risk factor Progression/disease progression after treatment discontinuation	
eGFR progression	Fixed changes per eGFR and uACR classes (Grams 2020) (138)
uACR progression	Lognormal distribution uACR fold (Coresh 2019) (141)
Engine options	
Risk of Death	CVD death plus non-specific cause death plus Renal death
Risk prediction of CVD mortality	Matsushita et al 2020, low risk countries (164)
Risk of RRT	Tangri risk equations, 5 years, pooled with six variables (selected because DM is a parameter in the equation)
Age threshold after which RT is not performed	80 years
When in conservative therapy which cost to apply? (ESKD health state costs and/or conservative therapy costs)	Conservative therapy cost only
Risk prediction of CVD	Matsushita et al 2020 (164)

Abbreviations: BC, base-case; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR: Estimated glomerular filtration rate; ESKD, end-stage kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; PSA, probabilistic sensitivity analysis; RRT, renal replacement therapy; RT, renal transplant; SoC, standard of care; uACR, urine albumin-to-creatinine ratio

Table 50. Base-case variables applied in cost-effective analysis

Variable	Value	SE	Distribution	Reference
Baseline characteristics				
Age (mean in years)	63.30	14.00	Truncated normal	B.3.3.1 Βασελινε χηαραχτεριστιχσ
Male (%)	66.80	-	Binomial	
Caucasians (%)	58.40	-	Dirichlet	
Black (%)	4.00	-	Dirichlet	
Asians and Indians (%)	36.20	-	Dirichlet	
Hispanic Caribbeans (%)	1.40	-	Dirichlet	
Native Americans (%)	0.00	-	Dirichlet	
Native Australians (%)	0.00	-	Dirichlet	
Smoking (%)	44.60	-	Binomial	
eGFR (mL/min/1.73m^2)	37.32	14.45	Truncated normal	
uACR (mg/mmol)	93.69	144.29	Lognormal	
HbA1c (%- point)	6.27	1.25	Truncated normal	
BMI (Kg/m^2)	29.70	6.80	Truncated normal	
TC (mg/dL)	183.00	44.50	Truncated normal	
HDL (mg/dL)	48.10	15.60	Truncated normal	
SBP (mmHg)	136.50	18.30	Truncated normal	
Height (cm)	167.80	0.10	Truncated normal	
Controlled hypertension (mmHg)	140	-	-	
Hb1Ac threshold for DM (%- point)	6.5	-	-	
eGFR G1 (%)	0.00	-	Dirichlet	
eGFR G2 (%)	7.71	-	Dirichlet	
eGFR G3a (%)	13.41	-	Dirichlet	
eGFR G3b (%)	44.34	-	Dirichlet	
eGFR G4 (%)	34.53	-	Dirichlet	
eGFR G5 (%)	0.00	-	Dirichlet	
uACR A1 (%)	20.10	-	Dirichlet	
uACR A2 (%)	28.20	-	Dirichlet	
uACR A3 (%)	51.70	-	Dirichlet	
DM (%)	46.00	-	Binomial	
CVD (%)	26.70	-	Binomial	
Hypertension (%)	86.10	-	Binomial	
CHF (%)	9.90	-	Binomial	
AKI (%)	0.00	-	Binomial	
Metabolic acidosis (%)	0.00	-	Binomial	
Gestational DM (%)	0.42	-	Binomial	
Schizophrenia or BAD (%)	0.76	-	Binomial	
PCOS (%)	1.97	-	Binomial	
Learning disability (%)	0.99	-	Binomial	
Family history of DM (%)	15.00	-	Binomial	
Anti-hypertensives (%)	86.1	-	Binomial	
Statins (%)	6.4	-	Binomial	
Atypical antipsychotics (%)	0.7	-	Binomial	
Corticosteroids (%)	2.9	-	Binomial	
NGT (%)	59.4	-	Binomial	
Pre-DM (%)	40.6	-	Complement	
Risk of Heart failure (HF) - 5 year- cumulative incidence rate of HF by KDIGO classification in CRIC participants				
With DM				Appendix P; section P.1.3; Table 7
A1 - G12	1.2%	0.50%	Beta	
A1 - G3a	1.5%	0.39%	Beta	
A1 - G3b	1.5%	0.39%	Beta	
A1 - G45	5.5%	1.43%	Beta	

Variable	Value	SE	Distribution	Reference
A2 - G12	2.1%	1.11%	Beta	
A2 - G3a	2.8%	0.59%	Beta	
A2 - G3b	2.8%	0.53%	Beta	
A2 - G45	4.2%	1.02%	Beta	
A3 - G12	3.7%	1.38%	Beta	
A3 - G3a	3.0%	0.72%	Beta	
A3 - G3b	4.2%	0.50%	Beta	
A3 - G45	5.5%	0.73%	Beta	
Without DM				
A1 - G12	0.2%	0.15%	Beta	
A1 - G3a	0.4%	0.15%	Beta	
A1 - G3b	0.6%	0.20%	Beta	
A1 - G45	2.3%	0.81%	Beta	
A2 - G12	1.2%	0.67%	Beta	
A2 - G3a	0.6%	0.32%	Beta	
A2 - G3b	2.8%	0.59%	Beta	
A2 - G45	1.9%	0.62%	Beta	
A3 - G12	3.0%	1.47%	Beta	
A3 - G3a	2.3%	0.81%	Beta	
A3 - G3b	1.9%	0.51%	Beta	
A3 - G45	3.3%	0.79%	Beta	
Risk of Peripheral Artery Disease by hospitalisation (PAD) - Per eGFR class				
Per albuminuria class - <10				Appendix P; section P.1.2; Table 6
>90	1.00	0.00	Lognormal	
75-89	1.01	0.06	Lognormal	
60-74	1.16	0.07	Lognormal	
45-59	1.57	0.12	Lognormal	
30-44	2.15	0.22	Lognormal	
> 30	2.53	0.45	Lognormal	
Per albuminuria class - 10-29				
>90	1.38	0.10	Lognormal	
75-89	1.45	0.11	Lognormal	
60-74	1.48	0.12	Lognormal	
45-59	2.05	0.21	Lognormal	
30-44	2.46	0.33	Lognormal	
> 30	3.83	0.69	Lognormal	
Per albuminuria class - 30-299				
>90	2.06	0.17	Lognormal	
75-89	2.42	0.18	Lognormal	
60-74	2.41	0.18	Lognormal	
45-59	2.82	0.26	Lognormal	
30-44	3.02	0.35	Lognormal	
> 30	4.82	0.59	Lognormal	
Per albuminuria class - >300				
>90	4.35	0.72	Lognormal	
75-89	3.42	0.63	Lognormal	
60-74	4.01	0.55	Lognormal	
45-59	4.49	0.69	Lognormal	
30-44	6.09	0.96	Lognormal	
> 30	7.21	1.01	Gamma (used for large SE)	
Rate of PAD in the UK population - All	0.00173	0.0001	Lognormal	
Risk of Hypertension - % of patients with hypertension per eGFR level and related classification per HTN type				
eGFR classification- HTN				

Variable	Value	SE	Distribution	Reference
All	88.0%	4.5%	Beta	Appendix P; Section P.5; Table 14
60 +	75.0%	3.8%	Beta	
45-59	85.0%	4.3%	Beta	
30-44	92.0%	4.4%	Beta	
15-30	95.0%	3.7%	Beta	
<15	96.0%	3.5%	Beta	
eGFR classification- Uncontrolled HTN				
All	44.0%	2.2%	Beta	
60 +	34.0%	1.7%	Beta	
45-59	44.0%	2.2%	Beta	
30-44	44.0%	2.2%	Beta	
15-30	48.0%	2.4%	Beta	
<15	52.0%	2.7%	Beta	
eGFR classification- Treat resistant				
All	32.0%	1.6%	Beta	
60 +	23.0%	1.2%	Beta	
45-59	27.0%	1.4%	Beta	
30-44	31.0%	1.6%	Beta	
15-30	39.0%	2.0%	Beta	
<15	49.0%	2.5%	Beta	
Risk of bone and mineral disorders/Metabolic disorders				
Hyperparathyroidism- - eGFR classification				
89-60	20.3%	1.0%	Beta	Appendix P; section P.2.1; Table 8
59-50	26.0%	1.3%	Beta	
49-40	35.8%	1.8%	Beta	
39-30	61.8%	3.2%	Beta	
29-20	79.7%	4.1%	Beta	
<20	85.4%	4.4%	Beta	
Anaemia - eGFR classification				
89-60	8.1%	0.4%	Beta	Appendix P; section P.3; Table 11
59-50	7.3%	0.4%	Beta	
49-40	13.0%	0.7%	Beta	
39-30	17.1%	0.9%	Beta	
29-20	24.4%	1.2%	Beta	
<20	88.3%	4.5%	Beta	
Metabolic acidosis - eGFR classification				
89-60	4.1%	0.2%	Beta	Appendix P; section P.9.2; Table 22
59-50	4.1%	0.2%	Beta	
49-40	5.7%	0.3%	Beta	
39-30	10.6%	0.5%	Beta	
29-20	22.0%	1.1%	Beta	
<20	39.0%	2.0%	Beta	
Hyperkalaemia - eGFR classification				
89-60	0.8%	0.0%	Beta	Appendix P; section P.9.2; Table 22
59-50	5.7%	0.3%	Beta	
49-40	4.1%	0.2%	Beta	
39-30	14.6%	0.7%	Beta	
29-20	26.0%	1.3%	Beta	
<20	40.7%	2.1%	Beta	
Hyperphosphataemia - eGFR classification				
89-60	3.3%	0.2%	Beta	Appendix P; section P.2.1; Table 8
59-50	0.8%	0.0%	Beta	
49-40	2.4%	0.1%	Beta	
39-30	4.1%	0.2%	Beta	

Variable	Value	SE	Distribution	Reference
29-20	4.1%	0.2%	Beta	
<20	33.3%	1.7%	Beta	
Hypocalcaemia - eGFR classification				
>80	1.9%	0.1%	Beta	Appendix P; section P.2.1; Table 9
79-70	0.0%	0.0%	Beta	
69-60	1.5%	0.1%	Beta	
59-50	1.1%	0.1%	Beta	
49-40	1.9%	0.1%	Beta	
39-30	3.4%	0.2%	Beta	
29-20	7.6%	0.4%	Beta	
<20	16.7%	0.9%	Beta	
Incidence rate of fractures per CKD severity stage - Incidence rate for 1st fracture in CKD severity stage per 1000 patient-year				
All fractures				Appendix P; section P.2.2; Table 10
CKD 2 - eGFR (>60)	0.001	0.00	Lognormal	
CKD 3a - eGFR (45-60)	45.4	0.64	Lognormal	
CKD3b - eGFR (30-45)	54.4	1.05	Lognormal	
CKD 4 - eGFR (15-30)	64.3	2.14	Lognormal	
CKD 5 - eGFR (<15)	59.2	4.21	Lognormal	
Risk of infections - Adjusted incidence rate ratio per eGFR categories (1000 person-years at risk)				
All infections				Appendix P; section P.7.1; Table 18
eGFR >=105	79	0.5	Lognormal	
eGFR 90-104	74	0.3	Lognormal	
eGFR - 60-89	103	0.8	Lognormal	
eGFR - 30-59	227	1.8	Lognormal	
eGFR <30	419	8.9	Lognormal	
Peritonitis with PD	0.38	0.03	Lognormal	Appendix P; section P.7.1; Table 20
% of blood stream infections with HD	13.70	0.64	Lognormal	
Relative risk of infection with a successful transplant	1.00	0.05	Lognormal	
Rate of cancer - Age-sex adjusted crude rate per 1000 person-year				
Renal cancer				Appendix P; section P.8; Table 21
eGFR >=90	0.25	0.01	Lognormal	
eGFR - 60-89	0.22	0.01	Lognormal	
eGFR - 45-59	0.35	0.02	Lognormal	
eGFR - 30-44	0.59	0.03	Lognormal	
eGFR < 30	1.08	0.06	Lognormal	
Urothelial cancer				
eGFR >=90	0.19	0.01	Lognormal	
eGFR - 60-89	0.17	0.01	Lognormal	
eGFR - 45-59	0.20	0.01	Lognormal	
eGFR - 30-44	0.32	0.02	Lognormal	
eGFR < 30	0.58	0.03	Lognormal	
Patients in ESKD - what is the risk of the several events				
Patients with ESKD on conservative therapy				
Under elderly age threshold	5.0%	0.3%	Beta	Appendix P; section P.10.3
Under above age threshold	16.7%	0.9%	Beta	
Age threshold associated to conservative therapy in elderly	75	8.3	Normal	
Under the age threshold = 80 years old				
Patients initiating KRT with peritoneal dialysis (PD) - under 80 years old	19.2%	1.0%	Beta	Appendix P; section P.10; Table 25
Patients staying on PD	58.0%	3.0%	Beta	

Variable	Value	SE	Distribution	Reference
Patients on PD moving to HD - under 80 years old	18.7%	1.0%	Beta	
Patients on PD moving to RT - under 80 years old	14.7%	0.8%	Beta	
PD patients dying - under 80 years old	8.6%	0.4%	Beta	
Patients initiating KRT with haemodialysis (HD) - under 80 years old	72.9%	3.7%	Beta	
HD patients with successful HD	74.2%	3.8%	Beta	
Patients on HD moving to RT - under 80 years old	5.6%	0.3%	Beta	
Patients on HD moving to PD - under 80 years old	3.1%	0.2%	Beta	
Patients on HD dying - under 80 years old	17.1%	0.9%	Beta	
Patient on HD suffering from AV access thrombosis	34.2%	1.7%	Beta	
Patients initiating KRT with renal transplant (RT) - under 80 years old	7.9%	0.4%	Beta	
Patients with failed RT	2.9%	0.1%	Beta	
Patients with failed RT that moved to PD	0.0%	0.0%	Beta	
Patients with failed RT that moved to HD	44.8%	2.3%	Beta	
Patients with failed RT and died	55.2%	2.8%	Beta	
Patients with failed RT that gets a new transplant	0.0%	0.0%	Beta	
Above the age threshold = 80 years old				
Age limit to get a kidney transplant= 80 years old	80	4.08	Beta	
Patients initiating KRT with peritoneal dialysis (PD) - above 80 years old	20.8%	1.1%	Beta	
PD patients moving to HD - above 80 years old	68.5%	3.5%	Beta	
PD patients moving to RT - above 80 years old	0.0%	0.0%	Beta	
PD patients on PD dying - above 80 years old	31.5%	1.6%	Beta	
Patients initiating KRT with haemodialysis (HD) - above 80 years old	79.2%	4.0%	Beta	
Patients moving to RT - above 80 years old	0.0%	0.0%	Beta	
Patients moving to PD - above 80 years old	15.3%	0.8%	Beta	
Patients on HD dying - above 80 years old	84.7%	4.3%	Beta	
Patients initiating KRT with renal transplant (RT) - above 80 years old	0.0%	0.0%	Beta	
Patients receiving PD instead of RT	1.6%	0.1%	Beta	
Patients receiving PD instead of RT - above 80 years old	20.8%	1.1%	Beta	
Patients receiving HD instead of RT	6.3%	0.3%	Beta	
Patients receiving HD instead of RT - above 80 years old	79.2%	4.0%	Beta	
Risk of AKI				
Annual incidence of AKI in the UK population	1.5%	0.1%	Beta	Appendix P; section P.6
HR of AKI per eGFR and uACR levels in patients without DM				
ACR classes (mg/g) (0-29) - eGFR classes (mL/min/1.73m^2)				
>=75	0.85	0.64	Lognormal	Appendix P; section P.6; Table 15
60-74	0.71	0.82	Lognormal	
45-59	1.00	0.00	Lognormal	
30-44	1.74	0.35	Lognormal	
15-29, >15	4.90	1.36	Lognormal	
ACR classes (mg/g) (30-299) - eGFR classes (mL/min/1.73m^2)				

Variable	Value	SE	Distribution	Reference
>=75	0.42	0.16	Lognormal	
60-74	0.62	0.32	Lognormal	
45-59	1.71	0.32	Lognormal	
30-44	2.06	0.52	Lognormal	
15-29, >15	6.30	1.78	Lognormal	
ACR classes (mg/g) (300-999) - eGFR classes (mL/min/1.73m^2)				
>=75	1.04	1.05	Lognormal	
60-74	1.47	2.71	Lognormal	
45-59	2.49	0.73	Lognormal	
30-44	2.69	1.12	Lognormal	
15-29, >15	7.70	3.17	Lognormal	
ACR classes (mg/g) (+ 1000) - eGFR classes (mL/min/1.73m^2)				
>=75	1.04	1.05	Lognormal	
60-74	1.47	2.71	Lognormal	
45-59	2.49	0.73	Lognormal	
30-44	2.69	1.12	Lognormal	
15-29, >15	7.70	3.17	Lognormal	
HR of AKI per eGFR and uACR levels in patients with DM				
ACR classes (mg/g) (0-29) - eGFR classes (mL/min/1.73m^2) (0-29)				
>=75	0.76	0.14	Lognormal	Appendix P; section P.6; Table 16
60-74	0.89	0.12	Lognormal	
45-59	1.00	0.00	Lognormal	
30-44	1.48	0.32	Lognormal	
15-29, >15	3.24	0.53	Lognormal	
ACR classes (mg/g) (30-299) - eGFR classes (mL/min/1.73m^2) (30-299)				
>=75	0.42	0.05	Lognormal	
60-74	2.02	3.78	Lognormal	
45-59	1.60	0.12	Lognormal	
30-44	2.27	0.23	Lognormal	
15-29, >15	3.89	1.20	Lognormal	
ACR classes (mg/g) (300-999) - eGFR classes (mL/min/1.73m^2) (300-999)				
>=75	0.62	0.17	Lognormal	
60-74	1.22	0.63	Lognormal	
45-59	2.26	0.27	Lognormal	
30-44	5.87	6.68	Lognormal	
15-29, >15	1.84	0.21	Lognormal	
ACR classes (mg/g) (+ 1000) - eGFR classes (mL/min/1.73m^2) (1000)				
>=75	0.62	0.17	Lognormal	
60-74	1.22	0.63	Lognormal	
45-59	2.26	0.27	Lognormal	
30-44	5.87	6.68	Lognormal	
15-29, >15	1.84	0.21	Lognormal	
The proportions of patients with AKI having hospitalisations, according to eGFR categories - % inpatients				
>90	79.9%	4.1%	Beta	Appendix P; section P.6; Table 17
60–89	82.3%	4.2%	Beta	
45–59	83.9%	4.3%	Beta	
30–44	89.9%	4.6%	Beta	
15–29	96.7%	3.3%	Beta	
>15	93.5%	4.0%	Beta	
Risk of all cause hospitalizations-- All cause hospitalisations per 100 person- year				
uACR less than 30mg/g				Appendix P; section P.12; Table 28
eGFR less than 30	43.08	2.20	Lognormal	
eGFR between 30 and less than 45	31.03	1.58	Lognormal	

Variable	Value	SE	Distribution	Reference
eGFR between 45 and less than 60	24.87	1.27	Lognormal	
eGFR more or equal to 60	20.26	1.03	Lognormal	
uACR between 30 and less than 300 mg/g				
eGFR less than 30	38.72	1.98	Lognormal	
eGFR between 30 and less than 45	43.33	2.21	Lognormal	
eGFR between 45 and less than 60	29.49	1.50	Lognormal	
eGFR more or equal to 60	31.54	1.61	Lognormal	
uACR more or equal than 300 mg/g				
eGFR less than 30	45.00	2.30	Lognormal	
eGFR between 30 and less than 45	41.67	2.13	Lognormal	
eGFR between 45 and less than 60	39.36	2.01	Lognormal	
eGFR more or equal to 60	38.59	1.97	Lognormal	
Management Costs (£)				
G+90_A-30	1,187	121.2	Gamma	Section B.3.5.2; Table 39
G+90_A-300	1,488	151.8	Gamma	
G+90_A+300	1,941	198.0	Gamma	
G+60_A-30	1,187	121.2	Gamma	
G+60_A-300	1,488	151.8	Gamma	
G+60_A+300	1,941	198.0	Gamma	
G+45_A-30	1,221	124.6	Gamma	
G+45_A-300	1,443	147.3	Gamma	
G+45_A+300	1,901	193.9	Gamma	
G+30_A-30	1,411	144.0	Gamma	
G+30_A-300	1,666	170.0	Gamma	
G+30_A+300	2,309	235.7	Gamma	
G+15_A-30	1,770	180.6	Gamma	
G+15_A-300	2,075	211.7	Gamma	
G+15_A+300	2,790	284.7	Gamma	
G-15_A-30	2,000	204.1	Gamma	
G-15_A-300	2,445	249.5	Gamma	
G-15_A+300	4,604	469.8	Gamma	
First Year Hospitalisation Costs				
CVD co-morbidities and complications				
Myocardial infarction	3,136	320.0	Gamma	Section B.3.5.2; Table 40
Unstable angina	2,273	232.0	Gamma	
Stroke (including TIA)	6,278	640.6	Gamma	
Congestive heart failure (CHF) (hospitalisations)	4,093	417.7	Gamma	
Transient Ischemic Attack (TIA)	2,855	291.3	Gamma	
PAD and PVD (driven by smoking, stenting)	4,650	474.5	Gamma	
End Stage Renal disease and events				
Conservative Therapy	6,335	646.5	Gamma	Section B.3.5.2; Table 46
Continuous ambulatory peritoneal dialysis (CAPD)	29,871	3048.0	Gamma	
Automated peritoneal dialysis (APD)	33,388	3407.0	Gamma	
Haemodialysis	27,606	2817.0	Gamma	
Kidney transplant (living donor)	37,284	3804.6	Gamma	
Kidney transplant (deceased donor)	34,700	3540.9	Gamma	
Acute kidney injury (AKI) - outpatient	0	0.0	Gamma	
Acute kidney injury (AKI) - hospitalisation	2,693	274.8	Gamma	
Peritonitis	5,969	0.0	Gamma	
AV access thrombosis	2,991	305.2	Gamma	
Bloodstream infections	6,234	636.1	Gamma	
Metabolic and mineral disorder				
Metabolic acidosis	1,272	129.8	Gamma	

Variable	Value	SE	Distribution	Reference
Hyperkalaemia	1,976	201.6	Gamma	Section B.3.5.2; Table 41 and Table 45
Hyperphosphataemia	251	25.6	Gamma	
Secondary Hyperparathyroidism	909	92.8	Gamma	
Hyperuricaemia/Gout	2,170	221.4	Gamma	
Hypocalcaemia	251	25.6	Gamma	
Bone and skeleton disorders				
Hip fractures	4,814	491.2	Gamma	Section B.3.5.2; Table 41
Other fractures	2,607	266.0	Gamma	
Infections				Section B.3.5.2; Table 43
Respiratory infections	129	13.2	Gamma	
Urinary tract infection	40	4.1	Gamma	
Skin and soft tissue infections	1,486	151.7	Gamma	
Gastrointestinal infection	158	16.1	Gamma	
Muscular infections	4,490	458.2	Gamma	
Nervous system	3,672	374.7	Gamma	
Sepsis	3,287	335.4	Gamma	
Anaemia	1,326	135.3	Gamma	Section B.3.5.2; Table 45
Incident Cancer				Section B.3.5.2; Table 44
Renal cancer	12,289	1254.0	Gamma	
Urothelial cancer	13,241	1351.2	Gamma	
All-cause hospitalisations	4,554	464.7	Gamma	Appendix P
Follow-up (after first year) Hospitalisation Costs				
CVD co-morbidities and complications				
Myocardial infarction	705	71.9	Gamma	Section B.3.5.2; Table 40
Unstable angina	421	42.9	Gamma	
Stroke (including TIA)	1,097	112.0	Gamma	
Congestive heart failure (CHF) (hospitalisations)	941	96.1	Gamma	
Transient Ischemic Attack (TIA)	795	81.1	Gamma	
PAD and PVD (driven by smoking, stenting)	130	13.2	Gamma	
End Stage Renal disease and events				Section B.3.5.2; Table 46
Immunosuppressive Therapy for KT	6,132	625.7	Gamma	
Incident Cancer				Section B.3.5.2; Table 44
Renal cancer	0		Gamma	
Urothelial cancer	0		Gamma	
Adverse event costs				
Leg Amputation	17,625	1798.5	Gamma	Section B.3.5.3; Table 47
Toe Amputation	9,195	938.3	Gamma	
Foot Amputation	9,195	938.3	Gamma	
Health State Utilities				Section 3.4.8; Table 36
G+90_A-30	0.85	0.08	Beta	
G+90_A-300	0.85	0.08	Beta	
G+90_A+300	0.85	0.08	Beta	
G+60_A-30	0.85	0.08	Beta	
G+60_A-300	0.85	0.08	Beta	
G+60_A+300	0.85	0.08	Beta	
G+45_A-30	0.80	0.08	Beta	
G+45_A-300	0.80	0.08	Beta	
G+45_A+300	0.80	0.08	Beta	
G+30_A-30	0.80	0.08	Beta	
G+30_A-300	0.80	0.08	Beta	
G+30_A+300	0.80	0.08	Beta	

Variable	Value	SE	Distribution	Reference
G+15_A-30	0.74	0.06	Beta	
G+15_A-300	0.74	0.06	Beta	
G+15_A+300	0.74	0.06	Beta	
G-15_A-30	0.73	0.10	Beta	
G-15_A-300	0.73	0.10	Beta	
G-15_A+300	0.73	0.10	Beta	
Submodule Utilities/Disutilities				
CVD co-morbidities and complications				
Myocardial infarction	-0.06	0.01	Beta	Section 3.4.8; Table 36
Unstable angina	-0.09	0.02	Beta	
Stroke (including TIA)	-0.16	0.03	Beta	
Congestive heart failure (CHF) (hospitalisations)	-0.11	0.03	Beta	
Transient Ischemic Attack (TIA)	-0.07	0.03	Beta	
PAD and PVD (driven by smoking, stenting)	-0.06	0.01	Beta	
End Stage Renal disease and events				
Conservative Therapy	0.00	0.00	Beta	
Peritoneal dialysis	0.58	0.03	Beta	
Haemodialysis	0.56	0.29	Beta	
Kidney transplant	0.71	0.07	Beta	
Immunosuppressive therapy	-0.01	0.00	Beta	
Acute kidney injury	-0.04	0.01	Beta	
Acute kidney injury - outpatient	-0.04	0.01	Beta	
Acute kidney injury - hospitalisation	-0.04	0.01	Beta	
Duration of 0 utility for events (days)	0.00	0.00	Gamma	
Peritonitis	0.00	0.00	Beta	
AV access Thrombosis	0.00	0.00	Beta	
Bloodstream infections	0.00	0.00	Beta	
Bone and skeleton disorders				
Hip fractures	-0.07	0.01	Beta	
Other fractures	-0.07	0.01	Beta	
Anaemia	-0.08	0.004	Beta	
Incident Cancer				
Renal cancer	-0.0030	0.0002	Beta	
Urothelial cancer	-0.0030	0.0002	Beta	
All cause hospitalisations	-0.06	0.003	Beta	
Adverse event disutilities - Leg Amputation	-0.12	0.01	Beta	
Adverse Event disutilities - Toe Amputation	-0.12	0.01	Beta	
Adverse Event disutilities - Foot Amputation	-0.12	0.01	Beta	
Risk factor progression - Empagliflozin + SoC (All CKD patients)				
Duration of treatment effect	50	2.55	Lognormal	Section B.3.9.1; Table 49
Incremental treatment effects per health state				
eGFR: G2A2	-2.20	0.54	Normal	Section B.3.3.2.1; Table 29
eGFR: G2A3	-3.39	0.29	Normal	
eGFR: G3aA1	0.00	0.00	Normal	
eGFR: G3aA2	-1.60	0.36	Normal	
eGFR: G3aA3	-3.45	0.24	Normal	
eGFR: G3bA1	-0.58	0.20	Normal	
eGFR: G3bA2	-1.04	0.19	Normal	
eGFR: G3bA3	-2.90	0.15	Normal	
eGFR: G4A1	-0.32	0.28	Normal	
eGFR: G4A2	-0.62	0.22	Normal	
eGFR: G4A3	-2.76	0.16	Normal	
uACR ratio: G2A2	1.26	0.20	Lognormal	

Variable	Value	SE	Distribution	Reference
uACR ratio: G2A3	0.67	0.06	Lognormal	Section B.3.3.2.2; Table 31
uACR: G3aA1	0.00	0.00	Lognormal	
uACR ratio: G3aA2	0.87	0.09	Lognormal	
uACR ratio: G3aA3	0.53	0.04	Lognormal	
uACR ratio: G3bA1	1.62	0.10	Lognormal	
uACR ratio: G3bA2	0.84	0.05	Lognormal	
uACR ratio: G3bA3	0.62	0.03	Lognormal	
uACR ratio: G4A1	2.08	0.17	Lognormal	
uACR ratio: G4A2	1.03	0.07	Lognormal	
uACR ratio: G4A3	0.68	0.03	Lognormal	
Adverse effects - Mean rate per 100-patient-year				
Leg Amputation (<= 2 legs per patient)	0.12	0.01	Lognormal	Section B.3.3.5; Table 35
Toe Amputation (<= 10 toes per patient)	0.25	0.01	Lognormal	
Foot Amputation (<= 2 foot per patient)	0.08	0.004	Lognormal	
Risk factor progression – SoC (All CKD patients)				
Duration of treatment effect	50	2.55	Lognormal	Section B.3.9.1; Table 49
Incremental treatment effects per health state				
eGFR: G2A2	-2.76	0.59	Normal	Section B.3.3.2.1; Table 29
eGFR: G2A3	-5.14	0.29	Normal	
eGFR: G3aA1	0.00	0.00	Normal	
eGFR: G3aA2	-2.29	0.38	Normal	
eGFR: G3aA3	-4.66	0.24	Normal	
eGFR: G3bA1	-0.83	0.19	Normal	
eGFR: G3bA2	-1.56	0.18	Normal	
eGFR: G3bA3	-4.11	0.16	Normal	
eGFR: G4A1	-0.15	0.28	Normal	
eGFR: G4A2	-0.85	0.21	Normal	
eGFR: G4A3	-3.76	0.17	Normal	
uACR ratio: G2A2	0.93	0.16	Lognormal	Section B.3.3.2.2; Table 31
uACR ratio: G2A3	0.75	0.06	Lognormal	
uACR ratio: G3aA1	0.00	0.00	Lognormal	
uACR ratio: G3aA2	0.99	0.11	Lognormal	
uACR ratio: G3aA3	0.71	0.05	Lognormal	
uACR ratio: G3bA1	1.65	0.10	Lognormal	
uACR ratio: G3bA2	1.09	0.06	Lognormal	
uACR ratio: G3bA3	0.81	0.04	Lognormal	
uACR ratio: G4A1	2.44	0.20	Lognormal	
uACR ratio: G4A2	1.51	0.10	Lognormal	
uACR ratio: G4A3	0.95	0.05	Lognormal	
Adverse effects - Mean rate per 100-patient-year				
Leg Amputation (<= 2 legs per patient)	0.02	0.001	Lognormal	Section B.3.3.5; Table 35
Toe Amputation (<= 10 toes per patient)	0.15	0.008	Lognormal	
Foot Amputation (<= 2 foot per patient)	0.02	0.001	Lognormal	
Treatment effect on event rate (All comparator vs SoC)				
Hospitalized Heart Failure (HHF)	0.80	0.1173	Lognormal	Appendix P
Acute Kidney Injury (AKI)	0.78	0.1020	Lognormal	

Abbreviations: AKI, acute kidney injury; BAD, bipolar affective disorder; BMI, Body mass index; CI, confidence interval; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; PCOS, polycystic ovary syndrome; TC, Total Cholesterol; LDL, Low-density lipoprotein; NGT, normal glucose tolerance; SBP, Systolic blood pressure; SE, standard error; uACR, urine albumin-to-creatinine ratio.

B.3.9.2 Assumptions

The following assumptions were made in the empagliflozin cost-effectiveness analysis, which were adopted in close consultation with clinical experts who were directly involved in the process of developing the empagliflozin microsimulation model:

- In G5 health state, costs of RRT or conservative therapy are not applied to avoid double counting
- No cost or disutility has been applied for DM as it is assumed that patients with DM will have a higher risk of events, therefore differences in costs are already considered
- For conventional therapy used for the treatment of ESKD, the utility weight is assumed to be same as G5 from the KDIGO classification
- For ESKD, BMD, infections and other events like hypertension, no disutility is applied as it is assumed to be included in their respective health state utility
- No disutilities were retrieved in the literature for complication events peritonitis, blood stream infections, and AV access thrombosis. Therefore, a conservative approach was taken to assume these are captured in the utility of peritoneal or haemodialysis
- The all-cause mortality in patients receiving RRT tracker traces all the fatal events associated to PD, haemodialysis, and kidney transplant
- The model assumes that recurrent strokes include TIA events
- Kidney transplant as a form of RRT was not assumed as an option for patients older than 80 years.
- As no evidence on risk of fractures was available for eGFR levels above 60 mL/min/1.73m^2 in literature, the model assumed them to be zero
- It was assumed that all cases of BSI would lead to hospitalisation
- For AKI, no data is available for eGFR values under 15 mL/min/1.73m^2 in literature, thus it was assumed to have the equal HR as those in class 15-29 mL/min/1.73m^2
- The proportion of patients on anti-hypertension therapy was assumed to be the same as the percentage of patients with hypertension
- To exclude the risk of overlap/mismatch in CV death count, fatal cases of UA were assumed to be included in CVM via fatal MI or sudden cardiac death, while TIA is by definition a non-fatal event. Similarly, to avoid double counting, HF is captured in the model through (non-fatal) hospitalisations only
- In all scenarios, it is assumed that the starting mean uACR is 93.69 mg/mmol (the estimated mean uACR value in the EMPA-Kidney trial)
- The model was run with half cycle correction, assuming the event happens at the beginning of the cycle

- For parameters which are binary, the model is run assuming that either the parameter is present, or it is not present, and then a weighted average is calculated
- Data reported from the EMPA-KIDNEY trial reported at 18-months was assumed to be applicable to annual cycles in the model in the absence of data reported at 12-months
- For PSA, knowing that confidence limits for relative risks are calculated on the log scale implies that the appropriate distributional assumption is lognormal. Unlike relative risk parameters, transition probabilities are bound on an interval from 0 to 1. Therefore, these parameters are commonly varied using a beta distribution. The same rationale applies to utility and disutility values although, in some diseases it can be argued that the QoL could drop below zero (i.e., worse than death). Hence a beta or gamma distribution is generally used to describe (dis)utilities. Cost data is made up of counts of resources weighted by their unit costs and can only be zero or positive and are mainly skewed. Therefore, a gamma distribution is employed to represent the uncertainty of cost parameters
- If 95% CI was not available for any parameter, a percent change of 20% from the point estimate was assumed for the cost parameters whereas a 10% change was used for clinical parameters
- The validation performed on the model assume no treatment effect

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 51 shows the discounted base-case deterministic cost-effectiveness results of empagliflozin 10mg OD on top of SoC (intervention) compared to SoC (comparator) over a lifetime (50 years) horizon. SoC resulted in per-patient costs, life years and QALYs of £93,406.65, 8.48 and 6.24, respectively. Empagliflozin on top of SoC resulted in an incremental gain in life years (+1.055) and QALYs (+0.849), while decreasing the cost by -£5,460.23 per person. Empagliflozin on top of SoC demonstrates a highly cost-effective deterministic results compared to SoC at usual threshold values with a dominant ICER of -£6,431.37/QALY gained. NHB at £20,000 and £30,000 per QALY was 1.12 and 1.03 respectively. This is driven by negative incremental costs and positive incremental QALY gains for patients in the empagliflozin on top of SoC treatment group.

The clinical outcomes of the model and disaggregated results of the base-case analysis are presented in Appendix J, and a summary of the net health benefit is presented in Table 52.

Table 51. Base-case: deterministic cost-effectiveness analysis results for empagliflozin as add on to SoC compared to SoC only

Technology	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Empagliflozin + SoC	87,946.42	9.54	7.09	-5,460.23	0.849	Dominant -6,431.37
SoC	93,406.65	8.48	6.24	-	-	-

Abbreviations: ICER; incremental cost-effectiveness ratio; LY, Life Years; SoC, standard of care; QALY, Quality-Adjusted Life Years

Table 52. Net health benefit

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Empagliflozin + SoC	87,946.42	7.09	-5,460.23	0.849	1.12	1.03
SoC	93,406.65	6.24	-	-		

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit

A full incremental analysis versus SGLT2 inhibitors, i.e., dapagliflozin, on top of SoC would be justifiable in the case of clinically and statistically meaningful differences in management and outcomes versus empagliflozin on top of SoC. However, as outlined above in section B.2.9 and section B.3.4.1 HRQoL data from clinical trials, quantitative and qualitative comparison of outcomes for efficacy, safety and HRQoL did not reveal any clinically or statistically meaningful differences, supporting the conclusion of similar health benefits between dapagliflozin and empagliflozin, both in combination with SoC. This finding has been further validated through clinical

expert opinion (see Appendix O). Further, there are no meaningful differences in the clinical management of empagliflozin and dapagliflozin in patients with CKD as both are dosed and administered in the same form and frequency (i.e., 10mg oral OD). As the list price and expected clinical management of patients with CKD receiving empagliflozin on top of SoC is identical compared to that of dapagliflozin on top of SoC (20), a cost comparison in similar eligible populations reveals no differences between the two treatments (Table 53).

Table 53: Cost-comparison for empagliflozin (intervention) versus dapagliflozin (comparator)

Technologies	Acquisition costs (£)	Resource costs (£)	Adverse events (£)	Other costs (£)*	TOTAL COSTS (£)▪
Empagliflozin +SoC	2,572.19	20,355.03	291.17	64,728.04	87,946.42
Dapagliflozin + SoC	2,572.19	20,355.03	291.17	64,728.04	87,946.42
Net	0	0	0	0	0

Abbreviations: SoC, standard of care.
*Other costs include KRT, conservative therapy for ESKD, CVD complications, anaemia, other CKD complications, BMD, AKI, infections, incident cancers
▪Time horizon: 50-years (lifetime)

B.3.11 Sensitivity analyses

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to translate parameter uncertainty into decision-making uncertainty through simultaneous sampling of critical parameters from their respective distributions. Five hundred PSA iterations utilising one thousand patients from the full EMPA-KIDNEY cohort over a lifetime horizon were utilised to ensure that stable estimates of the mean model outputs were obtained.

The PSA incorporated parameters informing risk factor progression, risk of CKD complications, risk of adverse events, all-cause mortality, and CV mortality in the model, as well as cost and utilities. Observed standard error (SE) was used to determine the probabilistic distribution of all parameters, except for costs where the SE was assumed equal to 20% of the mean. Risk factor progression and risk of CKD complication parameters were typically assigned lognormal, normal or beta distributions. All cost parameters were assigned a gamma distribution, whilst health state utilities, and CKD complication and AE disutilities were assigned a beta distribution. Details on the parameters, SEs, and assumptions are provided in section B.3.6.1.

As per Table 54, probabilistic incremental life-years, costs and QALYs were +1.03, -£5,005.96 and +0.83 respectively. The probabilistic ICER was highly cost-effective at £-5,998.34/QALY gained. This is highly comparable with deterministic ICER of -£6,431.37/QALY gained, and incremental deterministic results of +1.055 life-years, -£5,460.23 costs and +0.849 QALYs per person (see

section B.3.10.1). The probability of cost-effectiveness at willingness-to-pay thresholds (WTP) of both £20,000/QALY and £30,000/QALY was 100%. The PSA scatterplot in Figure 27 demonstrates a consistent reduction in cost associated with an increase in QALYs as a majority of events are in the southeast quadrant. The cost-effectiveness acceptability curve in

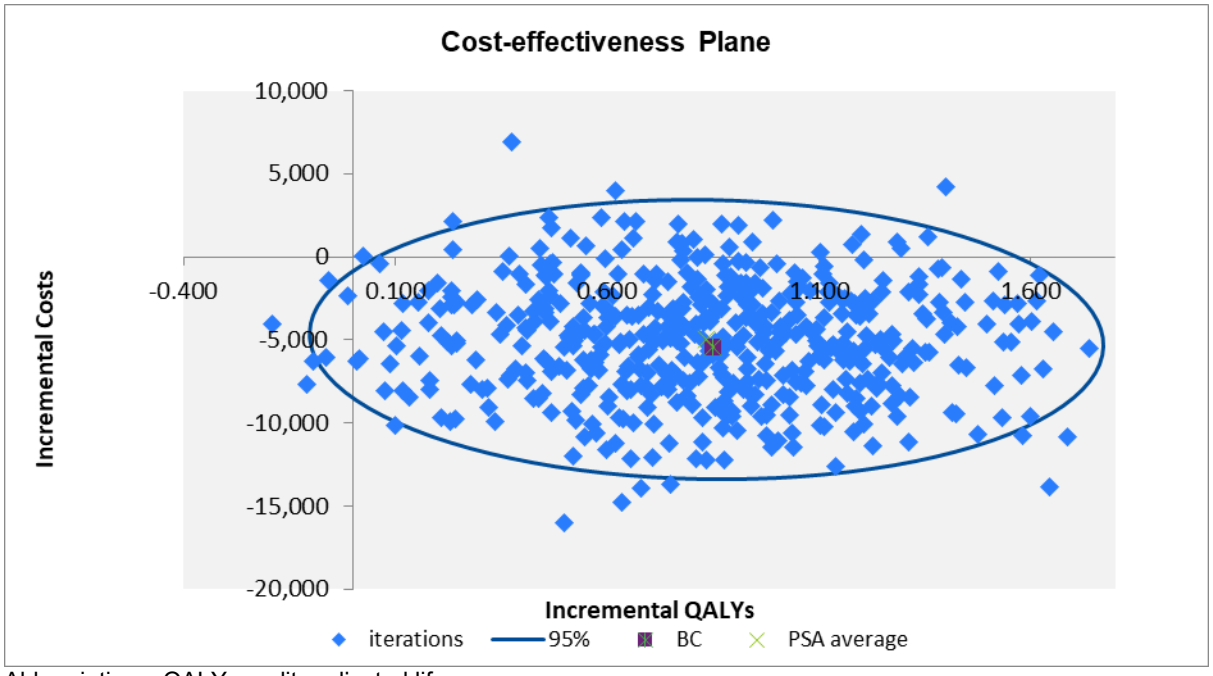
Figure 28 reflects this dominance with a 93% probability of cost-effectiveness with a WTP threshold of £0 and a 99% probability with a WTP threshold of £4,000.

Table 54. Base-case: probabilistic cost-effectiveness analysis results for empagliflozin as add on to SoC compared to SoC only

Technology	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Empagliflozin + SoC	88,690.35	9.55	7.06	-5,005.96	0.83	Dominant -5,998.34
SoC	93,696.31	8.52	6.23	-	-	-

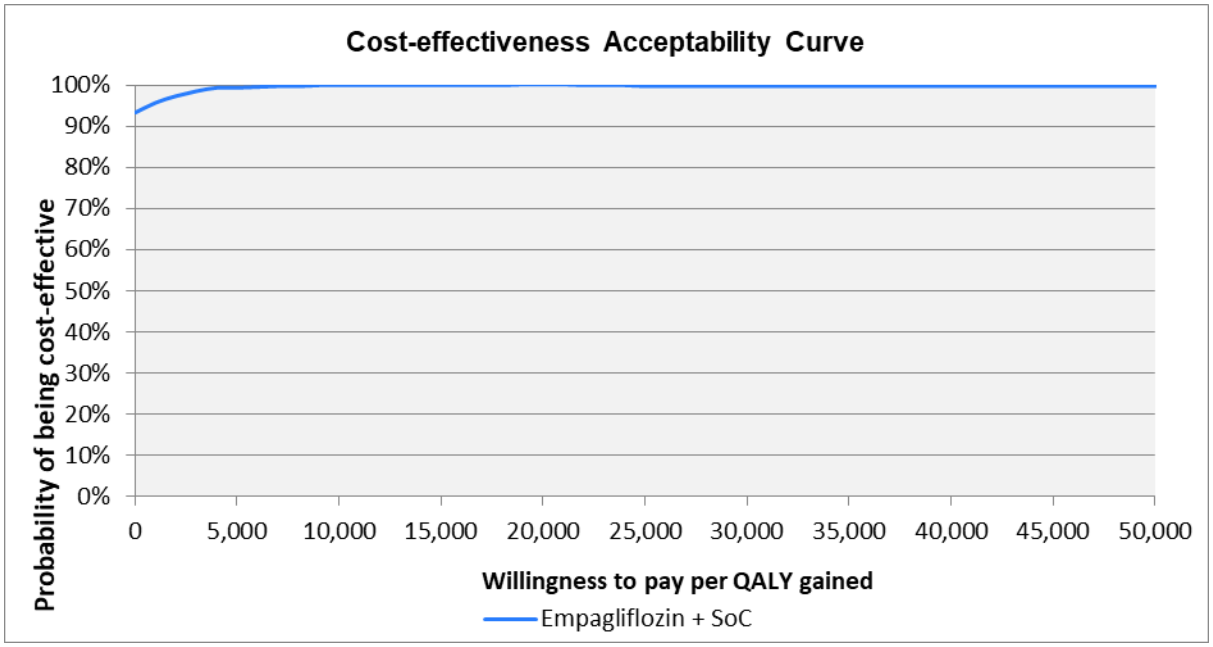
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life years

Figure 27. PSA cost-effectiveness plane for empagliflozin on top of SoC



Abbreviations: QALY, quality-adjusted life years

Figure 28. PSA cost-effectiveness acceptability curve for empagliflozin on top of SoC



Abbreviations: QALY, quality-adjusted life years

B.3.11.2 Deterministic sensitivity analysis

Deterministic OWSA was performed to assess how varying individual parameters sequentially whilst holding all other parameters constant impacted the model predicted cost, outcomes and ICER of empagliflozin on top of SoC compared to SoC alone. Analyses were performed on an exhaustive list of parameters (clinical data, costs, utilities and disutilities, response to treatment) with the majority of upper and lower values defined by the observed 95% confidence interval if available. If this was not available, a percent change of 20% from the point estimate was assumed for the cost parameters and 10% change was used for clinical parameters. Table 55 presents the OWSA results for the top 20 most influential parameters in the model. Figure 29 demonstrates the tornado diagram for these results. Empagliflozin on top of SoC remained highly dominant in all scenarios with a maximum ICER of -£2,278/QALY in the OWSA.

Table 55: Deterministic one-way sensitivity analysis inputs and results

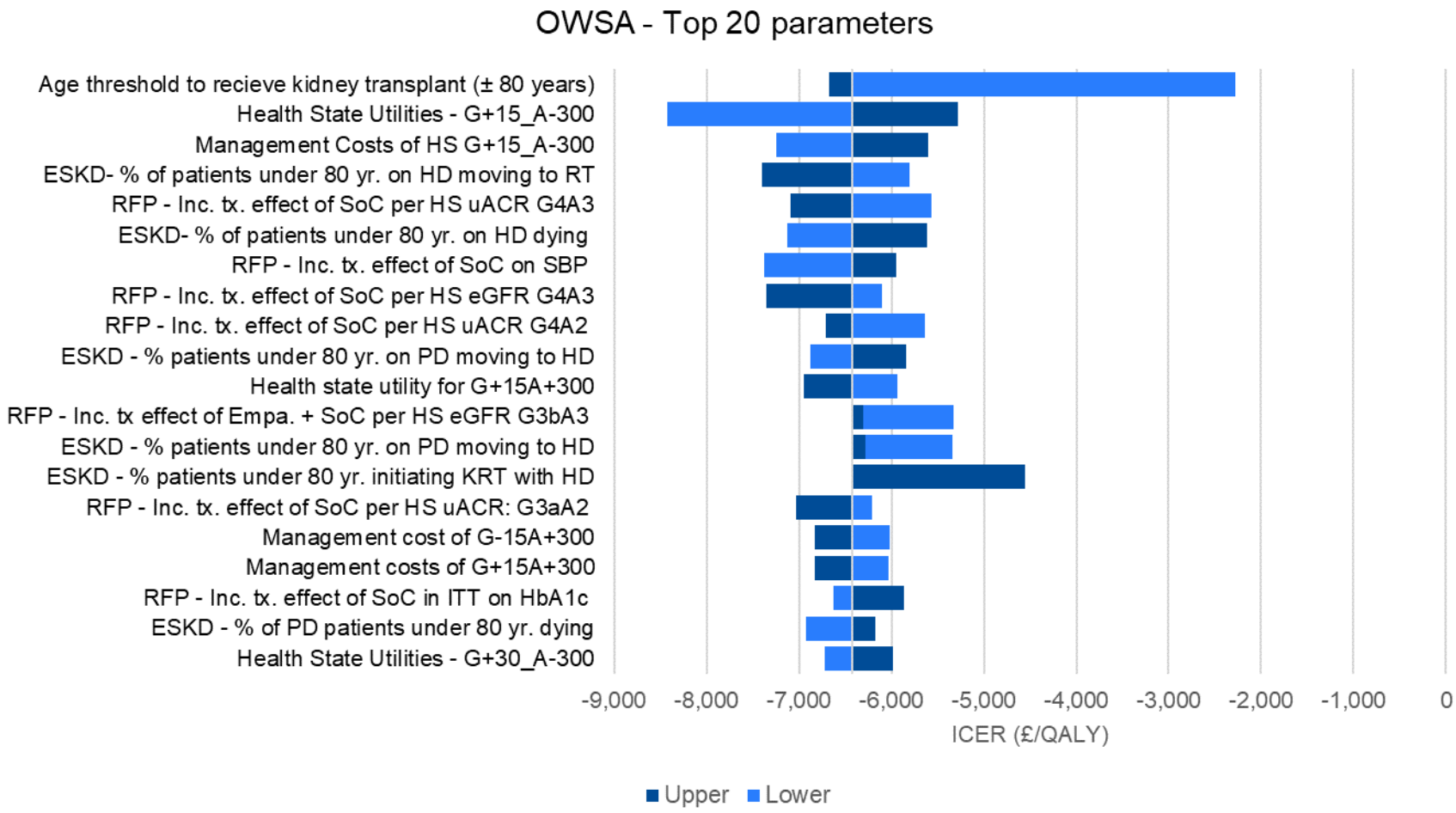
Parameter	Input-Low	ICER (£/QALY) Input-Low	Input -High	ICER (£/QALY) Input-High
Patients in ESKD, parameters and risk of events - Above the age threshold = 80 years old - Age limit to get a kidney transplant= 80 years old	72	-2,278	88	-6,677
Health State Utilities - G+15_A-300	0.6200	-8,431	0.8500	-5,278
Management Costs - G+15_A-300	£1659.60	-7,250	£2489.40	-5,605

Parameter	Input-Low	ICER (£/QALY) Input-Low	Input -High	ICER (£/QALY) Input-High
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of patients on HD moving to RT - under 80 years old	0.0504	-5,800	0.0616	-7,403
Risk factor progression - Incremental treatment effects per health state - uACR: G4A3 - SoC	0.8600	-5,570	1.0400	-7,091
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of patients on HD dying - under 80 years old	0.1539	-7,128	0.1881	-5,611
Risk factor progression - Incremental treatment effects for the full cohort - SBP - SoC	-1.7000	-7,373	-0.8800	-5,951
Risk factor progression - Incremental treatment effects per health state - eGFR: G4A3 - SoC	-4.0900	-6,100	-3.4400	-7,354
Risk factor progression - Incremental treatment effects per health state - uACR: G4A2 - SoC	1.3500	-5,643	1.7100	-6,705
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of patients on PD moving to HD - under 80 years old	0.1683	-6,872	0.2057	-5,840
Health State Utilities - G+15_A+300	0.6200	-5,942	0.8500	-6,947
Risk factor progression - Incremental treatment effects per health state - eGFR: G3bA3 - Empagliflozin + SoC	-3.2000	-5,323	-2.6000	-6,310
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of patients on HD moving to PD - under 80 years old	0.0279	-5,341	0.0341	-6,285
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of patients initiating KRT with hemodialysis (HD) - under 80 years old	0.6562	-5,437	0.8020	-4,550
Risk factor progression - Incremental treatment effects per health state - uACR: G3aA2 - SoC	0.8100	-6,209	1.2300	-7,038
Management Costs - G-15_A+300	£3683.32	-6,021	£5524.98	-6,834

Parameter	Input-Low	ICER (£/QALY) Input-Low	Input -High	ICER (£/QALY) Input-High
Management Costs - G+15_A+300	£2231.91	-6,028	£3347.86	-6,828
Risk factor progression - Incremental treatment effects for the full cohort - HbA1c - SoC	-0.4100	-6,624	0.1200	-5,866
Patients in ESKD, parameters and risk of events - Under the age threshold = 80 years old - % of PD patients dying - under 80 years old	0.0774	-6,921	0.0946	-6,178
Health State Utilities - G+30_A-300	0.6800	-6,723	1.0000	-5,990

Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HD, haemodialysis; ICER, incremental cost-effectiveness ratio KRT, kidney replacement therapy; PD, peritoneal dialysis; QALY, quality-adjusted life year; uACR, urine albumin-to-creatinine ratio; SBP, Systolic blood pressure; SoC, standard of care.

Figure 29: Deterministic OWSA tornado diagram for ICER results



Abbreviations: eGFR, Estimated glomerular filtration rate; ESKD, End stage kidney disease; HD, haemodialysis; HS, Health state; KRT, Kidney replacement therapy; ITT, Intention to treat; PD, Peritoneal dialysis; RFP, Risk factor progression, RRT, Renal replacement therapy; SBP, systolic blood pressure; SoC, Standard of care; uACR, Urine albumin creatinine ratio; yr., year

B.3.11.3 Scenario analysis

Scenario analyses were performed to test the robustness of conclusions on cost-effectiveness to the choice of risk equations, parameters and assumptions applied in the model as compared to the base-case. The results of these scenario analyses are presented in Table 56.

Table 56: Scenario analyses: ICERs for empagliflozin on top of SoC compared to SoC alone

Scenario	Description	ICER (£/QALY)	% Change Relative to Base-Case ICER
Base-case	Section B3.6	Dominant	-
eGFR threshold at 20mL/min/1.73m^2 to estimate the risk of RRT	Use of an eGFR threshold of 20mL/min/1.73m^2 to apply risk equations for RRT as opposed to 15mL/min/1.73m^2 in the base-case.	-2,337.86	-63.7%
Major et al. risk equation to predict risk of RRT	Use of the Major et. al (205) risk equation is utilised to predict the initiation of RRT instead of the Tangri et. al 2016 six variable risk equation as per the base-case. Major et. al is a UK primary care population validated version of the Tangri equation, however, diabetes is not included as a risk factor.	-5,126.43	-20.3%
EMPA-KIDNEY derived trial utilities to predict QALYs	Use of EMPA-KIDNEY trial utilities to predict QALYs as opposed to the literature derived health state utilities as per the base-case. Complications related disutilities are not applied, and as G5 utilities are not provided in the trial, the literature values are applied.	-5,814.94	-9,6%
ACH	The use of ACH replaces acute costs for CVD events first year (MI, stroke, TIA), cancer first year, infections, AKI, fractures and replaces them with an average ACH cost.	-6,508.25	1.2%

Abbreviations: ACH, all-cause hospitalisations; AKI, Acute kidney injury; CVD, cardiovascular disease; MI, myocardial infarction; QALYs, quality-adjusted life years; TIA, transient ischaemic attack.

B.3.11.4 Summary of sensitivity analyses results

Probabilistic and deterministic cost effectiveness results were similar for the base-case results (ICERs -£5,998.34/QALY gained and -£6,431.37/QALY gained). The PSA CEAC demonstrated the probability of cost-effectiveness for empagliflozin on top of SoC of 100% at WTP thresholds of both £20,000/QALY and £30,000/QALY. Deterministic OWSA demonstrated a maximum and minimum ICER of -£2,278/QALY gained, and -£8,431/QALY gained. Results from scenario analyses considering ACH and the EMPA-KIDNEY utilities result in ICERs with less than 10% change from the base-case.

Deterministic sensitivity analyses do not change the cost-effectiveness conclusions presented above as all ICERs remained dominant, and PSA results further demonstrate that parameter uncertainty does not negate the deterministic ICER as a robust estimate of the cost-effectiveness of empagliflozin 10mg OD on top of SoC for the treatment of adult patients with CKD with eGFR ≥20 and <45mL/min/1.73m^2; or eGFR ≥45 and <90mL/min/1.73m^2 with uACR ≥22.6 mg/mmol, in line with the EMPA-KIDNEY full cohort.

B.3.12 Subgroup analysis

Results of subgroup analyses for patients with and without T2DM are summarised in Appendix S.

B.3.13 Benefits not captured in the QALY calculation

The health economic impact reflected in this submission is limited to the NHS perspective as required by the reference case. For CKD, however, a broader, societal, perspective that reflects the spill-over effects such a progressively debilitating disease can have on patients, their carers and society would be relevant. Most notably, the impact of CKD on the patient and carer productivity is not negligible and, if included, would further increase the potential for empagliflozin to offer cost-savings to not only the NHS but also to individuals and other sectors of society (66).

In addition, the HRQoL impact of caring for CKD patients in the progressive stages of their disease (particularly ESRD) is also meaningful and should be considered, if not quantitatively but qualitatively, within the appraisal committee discussions. It further should be noted that for those patients who receive a kidney transplant, there are even further spill-over effects to donors in terms of HRQoL impact. Therefore, BI believes that if all relevant health effects and costs were included in this analysis, the dominance of treatment with SGLT2 inhibitors could further increase.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The CKD model is covering a broad range of outcomes, including major time-dependent risk factors (eGFR, uACR, lipids, SBP, DM status), health outcomes based on transitions between health states (KDIGO category) and events (CVD incidence, death by cause, RRT, fractures, infections, etc). Four main outcomes were prioritised for internal and external validation, given the major role they play in the prediction of LYs, QALYs and costs:

1. ACM
2. Cardiovascular mortality (CVM)
3. ASCVD
4. ESKD

In addition, the progression of time-dependent risk factors eGFR and uACR was cross-checked compared to published values, as their progressions are determinant of the patient's transition between KDIGO health states in the model. Lifetime predictions of the remaining model outcomes were additionally reported. The validation described here is based on the version of the CKD model version reflective of the final model concept described above in section B.2.2.2 (v6.03.88, 15 November 2023), without assuming any treatment effect. More details on validation are provided in Appendix R.

B.3.15 Interpretation and conclusions of economic evidence

A de novo microsimulation cost-effectiveness model for empagliflozin 10mg OD on top of SoC compared to SoC alone was developed to address the current decision problem. Development of the model was informed by an SLR of UK full economic evaluations assessing the cost-effectiveness of CKD treatments (see section B.3.1) and considering limitations and critiques of previous models (see section B.3.1). Patient baseline characteristics inputs were obtained from the EMPA-KIDNEY trial (Table 27), with some inputs, not available from EMPA-KIDNEY trial obtained through SLR and TLR (see section B.3.5). Disease progression risk equations, health state utilities and cost parameters were obtained from the literature (see Appendix P, Appendix H, Appendix I).

The probabilistic base-case cost-effectiveness analysis for the full ITT population demonstrated that empagliflozin on top of SoC compared to SoC was highly dominant with an incremental cost of -£5,005.96 and incremental QALYs of +0.83 leading to an ICER of -£5,998.34/QALY gained. Further, probabilistic ICER results of -£5,998.34/QALY gained are closely aligned with the deterministic ICER results of -£6,431.37/QALY gained.

Negative incremental costs associated with empagliflozin 10mg OD on top of SoC are driven by a reduction in costs associated with ESKD compared to SoC alone. Patients treated with empagliflozin on top of SoC experience slower progression to ESKD compared with SoC alone (10.21 years and 7.57 years respectively in deterministic base-case), thus accumulating fewer RRT costs. The cost of treatment associated with the different stages of CKD and CKD complications increases for patients treated with empagliflozin on top of SoC, attributable to the improved survival and thus a longer period to incur the costs, however these increased costs are compensated for by the greater reduction in ESKD costs for patients treated with empagliflozin on top of SoC.

Positive incremental QALYs for empagliflozin on top of SOC are attributable to reduced all-cause mortality for patients (+1.03 LYs gained in probabilistic base-case) and slower disease progression leading to increased delay or avoidance of ESKD and RRT which is associated with particular low utility values. The increase in QALYs aligns with previous evaluations of SGLT2 inhibitors. In TA775 which compared dapagliflozin on top of SoC to SoC, dapagliflozin on top of SoC was associated with 9.260 LYs and 6.800 QALYs, SoC was associated with 8.254 Lys and 6.031 QALYs. The application of a microsimulation model, which incorporated a more heterogenous mix of patients and considered more complications, as well as increased costs driven by inflation (particularly RRT costs) resulted in higher costs of disease management with both empagliflozin on top of SoC and SoC than those presented in TA775.

The model demonstrates that empagliflozin 10mg OD on top of SoC is highly cost effective for the broad population of patients with CKD, including those with T2DM, across the range of eGFR and uACR levels studies in the EMPA-KIDNEY trial. An additional supplementary efficacy analysis (including patients from EMPA-REG OUTCOME, EMPEROR-Reduced and EMPEROR-Preserved with uACR and eGFR values outside of the EMPA-KIDNEY eligibility criteria) supports the generalisability of the EMPA-KIDNEY results to a broad population of patients at various stages of CKD. Empagliflozin has previously been shown to be cost-effective in patients with T2DM (3). The EMPA-REG OUTCOME results show a consistent effect in renal outcomes among T2DM patients, across a range of eGFR and uACR, including patients with an eGFR up to 90. Empagliflozin expands the evidence base for the broader use of SGLT2 inhibitors in patients with CKD and T2DM, which is already supported by TA775, the NICE CKD guidelines and UKKA guidelines.

The generalisability of the model results to the NHS is supported by the applicability of the EMPA-KIDNEY trial to the broader CKD population in the UK (see section B.2.5.1 Applicability to clinical practice), and whilst there are likely inherent differences between the population in EMPA-KIDNEY and the real-world NHS CKD population, the patient population in EMPA-KIDNEY is similar to those seen in clinical practice as confirmed through clinical expert opinion (Appendix O).

Of note, the target population in this submission is patients who meet the EMPA-KIDNEY renal inclusion criteria.

The results of the cost effectiveness analysis demonstrate that empagliflozin on top of SoC is dominant over SoC alone for the treatment of CKD in patients with a broad range of eGFR and uACR levels, regardless of T2DM status. Specifically, this includes patients with eGFR ≥45–90 mL/min/1.73m^2 and albuminuria (uACR ≥22.6 mg/mmol), and patients with eGFR 20–45 mL/min/1.73m^2, across broad range of albuminuria values.

Prior CKD/DKD trials i.e., DAPA-CKD and CREDENCE only included CKD/DKD patients with albuminuria (uACR ≥22.6 mg/mmol and ≥33.9mg/mmol, respectively). However, the benefits of SGLT2 inhibition in patients without albuminuria are already recognised among patients with CKD and comorbid T2DM. This is reflected in NICE TA775, in which dapagliflozin is recommended in CKD patients as an add-on to optimised standard care in patients with eGFR 25–75 mL/min/1.73m^2 and either a uACR of ≥22.6 mg/mmol or T2DM. The ITC subgroup analysis, as detailed in Appendix N, revealed no statistical differences between empagliflozin and dapagliflozin across any outcome among patients with T2DM. Thus, empagliflozin and dapagliflozin are expected to provide similar effects among patients with CKD and T2DM. Complementary evidence from the cardiovascular outcome trial (CVOT) EMPA-REG OUTCOME in patients with T2DM confirm that the renal benefits of empagliflozin extend to patients with eGFR >45–90mL/min/1.73m^2, across broad range of albuminuria values. Post-hoc analysis illustrating evidence of these benefits in the T2DM CKD population is provided in Appendix M (84).

Results from our ITC and the NMA by Herrington et al. (2022) reveal that there are no statistically meaningful differences in the efficacy and safety of SGLT2 inhibitors in CKD patients (91). Moreover, qualitative comparisons of HRQoL outcomes between empagliflozin and dapagliflozin did not reveal any clinically meaningful differences. Since the list prices and expected clinical management in CKD patients for empagliflozin and dapagliflozin, both in combination with SoC, were also shown to be the same (Table 53), a cost comparison revealed no differences between the two treatments.

Inclusion of the broad population represented in the EMPA-KIDNEY trial in the microsimulation model lends this submission as relevant to the heterogenous CKD population in the UK. Consideration of different kinds of patients and the numerous CKD related complications experienced allows the model to reflect the burden both to patients and the NHS more accurately. Our economic assessment demonstrates that the cost impact of CKD to the NHS is substantial and that access to SGLT2 inhibitor treatment options for this population would have considerable impact on the reduction and avoidance of downstream healthcare consumption for many CKD

patients. However, it should be noted that the economic impact reflected in this economic analysis are limited to the NHS perspective as required by the reference case, and a broader perspective of health effects and costs reflecting societal spill-over effects, for example the impact of CKD on patient and carer productivity and HRQoL, would further increase the potential for health benefits and cost-savings to individuals and other sectors of society (66). If all relevant costs were included in this analysis, the dominance of treatment with empagliflozin could further increase.

A positive recommendation for empagliflozin for the population addressed in this submission would extend the benefits of empagliflozin to a broad range of CKD patients, including those who do not currently have access to SGLT2 inhibitors. Furthermore, the availability of an additional SGLT2 inhibitor facilitates patient and healthcare practitioner choice and provides a valuable alternative option at a time when supply chains are under pressure.

In conclusion, the cost-effectiveness analysis presented demonstrates that empagliflozin represents a cost-effective use of NHS resources as an add-on to SoC for the treatment of adult patients with CKD.

B.4 References

1. EMPA-KIDNEY Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transplant. 2022;37(7):1317-29.
2. EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117-27.
3. NICE. Empagliflozin in combination therapy for treating type 2 diabetes [TA336]. [Available from: https://www.nice.org.uk/guidance/ta336] (Accessed 16 June 2023).
4. NICE. Empagliflozin for treating chronic heart failure with reduced ejection fraction [TA773]. [Available from: https://www.nice.org.uk/guidance/ta773] (Accessed 16 June 2023).
5. NICE. Type 2 diabetes in adults: management [NG28]. [Available from: https://www.nice.org.uk/guidance/ng28] (Accessed 16 June 2023).
6. NICE. Dapagliflozin for treating chronic kidney disease [TA775]. 2022 [Available from: https://www.nice.org.uk/guidance/ta775/resources] (Accessed 16 June 2023).
7. NICE. Chronic kidney disease: assessment and management [NG203]. National Institute for Health and Care Excellence 2021. [Available from: https://www.nice.org.uk/guidance/ng203] (Accessed 16 June 2023). 2021.
8. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2020;383(15):1436-46.
9. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine. 2019;380(24):2295-306.
10. Kidney Disease: Improving Global Outcomes, CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):1-150.
11. NICE. Our principles: The principles that guide the development of NICE guidance and standards. 2023. [Available from: https://www.nice.org.uk/about/who-we-are/our-principles] (Accessed 16 June 2023).
12. Cookson R, Propper C, Asaria M, Raine R. Socio-economic inequalities in health care in England. Fiscal studies. 2016;37(3-4):371-403.
13. Bailey CJ, Day C, Bellary S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Curr Diab Rep. 2022;22(1):39-52.
14. EMC. Jardiance 10 mg film-coated tablets. 2023 [Available from: https://www.medicines.org.uk/emc/product/5441/smpc] (Accessed 27 March 2023).
15. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney Int. 2018;94(1):26-39.
16. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press. https://bnf.nice.org.uk/drugs/empagliflozin/medicinal-forms/ [Accessed on May 19th 2023].
17. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786-802.
18. Levey S, Coresh J. Chronic kindey disease. The Lancet. 2011;379(9811):165-80.
19. G. B. D. Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33.
20. Pollock C, James G, Garcia Sanchez JJ, Carrero JJ, Arnold M, Lam CSP, et al. Healthcare resource utilisation and related costs of patients with CKD from the UK: a report from the DISCOVER CKD retrospective cohort. Clin Kidney J. 2022;15(11):2124-34.
21. National Health Service. Quality and Outcomes Framework, 2021-22 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2021-22] (Accessed 16 June 2023).

22. Cozzolino M, Bolasco P, Ronco C, Conte G, Mene P, Mereu MC, et al. Clinical Management of Chronic Kidney Disease Patients in Italy: Results from the IRIDE Study. Nephron. 2018;140(1):39-47.
23. Dashtban A, Mizani MA, Denaxas S, Nitsch D, Quint J, Corbett R, et al. A retrospective cohort study predicting and validating impact of the COVID-19 pandemic in individuals with chronic kidney disease. Kidney Int. 2022;102(3):652-60.
24. Iwagami M, Caplin B, Smeeth L, Tomlinson LA, Nitsch D. Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using primary and secondary care patient data. Br J Gen Pract. 2018;68(673):e512-e23.
25. Roberts G, Holmes J, Williams G, Chess J, Hartfiel N, Charles JM, et al. Current costs of dialysis modalities: A comprehensive analysis within the United Kingdom. Peritoneal Dialysis International. 2022:08968608211061126.
26. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27 Suppl 3(Suppl 3):iii73-80.
27. National Health Service. Chronic Kidney Disease - The human and financial cost. Insight Health Economics Ltd. 2012 [Available from: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf] (Accessed 16 June 2023).
28. James G, Garcia Sanchez JJ, Carrero JJ, Kumar S, Pecoits-Filho R, Heerspink HJL, et al. Low Adherence to Kidney Disease: Improving Global Outcomes 2012 CKD Clinical Practice Guidelines Despite Clear Evidence of Utility. Kidney Int Rep. 2022;7(9):2059-70.
29. UK Renal Registry. UK Renal Registry 23rd Annual Report – data to 31/12/2019. [Available from: https://ukkidney.org/sites/renal.org/files/publication/file-attachments/23rd_UKRR_ANNUAL_REPORT_0.pdf (Accessed 16 June 2023).
30. Herrington WG, Frankel AH. UK Kidney Association Clinical Practice Guideline: SGLT-2 inhibition in adults with kidney disease 2023 update. 2023.
31. Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. Lancet. 2017;389(10075):1238-52.
32. BMJ best practice. Chronic Kidney Disease - Straight to the point of care. 2023. Available from: [https://bestpractice.bmj.com/topics/en-gb/84/aetiology] (Accessed 16 June 2023).
33. UK Renal Registry. UK Renal Registry 24th Annual Report – data to 31/12/2020. 2022 [Available from: https://ukkidney.org/sites/renal.org/files/24th_UKKR_ANNUAL_REPORT_Citation.pdf] (Accessed 16 June 2023).
34. Lopez-Novoa JM, Rodriguez-Pena AB, Ortiz A, Martinez-Salgado C, Lopez Hernandez FJ. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. J Transl Med. 2011;9:13.
35. Johnson RJ, Sanchez-Lozada LG, Newman LS, Lanaspa MA, Diaz HF, Lemery J, et al. Climate Change and the Kidney. Ann Nutr Metab. 2019;74 Suppl 3:38-44.
36. Glaser J, Lemery J, Rajagopalan B, Diaz HF, Garcia-Trabanino R, Taduri G, et al. Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy. Clin J Am Soc Nephrol. 2016;11(8):1472-83.
37. Kidney care UK. Facts about kidneys. [Available from: https://www.kidneycareuk.org/news-and-campaigns/facts-and-stats/] (Accessed 16 June 2023).
38. KRUK. Kidney disease: A UK public health emergency - The health economics of kidney disease to 2033. Kidney Research UK 2023. [Available from: https://www.kidneyresearchuk.org/about-us/influencing-change/health-economics-report/] (Accessed 16 June 2023).
39. Garcia Sanchez JJ, Power A, Abdul Sultan A, Ärnlöv J, Cabrera C, De Nicola L, et al. Pos-323 inside Ckd: Projecting the Future Burden of Chronic Kidney Disease in Europe Using Microsimulation Modelling. Kidney International Reports. 2021;6(4):S139-S40.
40. National Health Service. Health Survey for England. Kidney and liver disease. 2016 [Available from: http://healthsurvey.hscic.gov.uk/media/63736/HSE2016-Adult-kid-liv.pdf] (Accessed 16 June 2023).

41. Hirst JA, Hill N, O'Callaghan CA, Lasserson D, McManus RJ, Ogburn E, et al. Prevalence of chronic kidney disease in the community using data from OxRen: a UK population-based cohort study. Br J Gen Pract. 2020;70(693):e285-e93.
42. Carpio EM, Ashworth M, Asgari E, Shaw C, Schartau P, Durbaba S, et al. Hypertension and cardiovascular risk factor management in a multi-ethnic cohort of adults with CKD: a cross sectional study in general practice. J Nephrol. 2022;35(3):901-10.
43. Nitsch D, Caplin B, Hull S, Wheeler D. National Chronic Kidney Disease Audit - National Report (Part 1) 2017.
44. ClinicalTrials.gov. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD). 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03036150] (Accessed 27 March 2023).
45. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004;65(3):1031-40.
46. Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HG. Economic modelling of chronic kidney disease: a systematic literature review to inform conceptual model design. Pharmacoeconomics. 2019;37:1451-68.
47. Hounkpatin HO, Harris S, Fraser SDS, Day J, Mindell JS, Taal MW, et al. Prevalence of chronic kidney disease in adults in England: comparison of nationally representative cross-sectional surveys from 2003 to 2016. BMJ Open. 2020;10(8):e038423.
48. Fraser SD, Blakeman T. Chronic kidney disease: identification and management in primary care. Pragmatic and observational research. 2016;7:21-32.
49. Caplan EO, Sheer R, Schmedt N, Evers T, Cockrell M, Tindal M, et al. Glomerular filtration rate change and outcomes in type 2 diabetes. Am J Manag Care. 2021;27(8 Suppl):S160-S7.
50. Cohen-Solal M, Funck-Brentano T, Urena Torres P. Bone fragility in patients with chronic kidney disease. Endocr Connect. 2020;9(4):R93-R101.
51. Cockwell P FL. The global burden of chronic kidney disease. The Lancet. 2020;395(10225):662-4.
52. Tangri N, Chadban S, Cabrera C, Retat L, Sánchez JJG. Projecting the Epidemiological and Economic Impact of Chronic Kidney Disease Using Patient-Level Microsimulation Modelling: Rationale and Methods of Inside CKD. Adv Ther. 2023;40(1):265-81.
53. Vanholder R, Annemans L, Brown E, Gansevoort R, Gout-Zwart JJ, Lameire N, et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nat Rev Nephrol. 2017;13(7):393-409.
54. Medicines and Healthcare Products Regulatory Agency. Dialysis Guidance. 2023 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1059540/Dialysis_Guidance_pdf_version.pdf] (Accessed 16 June 2023).
55. Fraser SD, Barker J, Roderick PJ, Yuen HM, Shardlow A, Morris JE, et al. Health-related quality of life, functional impairment and comorbidity in people with mild-to-moderate chronic kidney disease: a cross-sectional study. BMJ Open. 2020;10(8):e040286.
56. Nguyen NTQ, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. Chronic kidney disease, health-related quality of life and their associated economic burden among a nationally representative sample of community dwelling adults in England. PLoS One. 2018;13(11):e0207960.
57. United States Renal Data System. USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022.
58. Gandjour A, Armsen W, Wehmeyer W, Multmeier J, Tschulena U. Costs of patients with chronic kidney disease in Germany. PLoS One. 2020;15(4):e0231375.
59. Quinn KL, Stall NM, Yao Z, Stukel TA, Cram P, Detsky AS, et al. The risk of death within 5 years of first hospital admission in older adults. Cmaj. 2019;191(50):E1369-e77.
60. Nichols GA, Ustyugova A, Déruaz-Luyet A, O'Keeffe-Rosetti M, Brodovicz KG. Health Care Costs by Type of Expenditure across eGFR Stages among Patients with and without Diabetes, Cardiovascular Disease, and Heart Failure. J Am Soc Nephrol. 2020;31(7):1594-601.

61. Golestaneh L, Alvarez PJ, Reaven NL, Funk SE, McGaughey KJ, Romero A, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. Am J Manag Care. 2017;23(10 Suppl):S163-s72.
62. NIDDK USRDS. Patient Experience: Prognostic Expectations, Values Around Life Prolongation, and the Significance of Religious or Spiritual Beliefs. 2022 [Available from: https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/12-patient-experience-prognostic-expectations-values-around-life-prolongation-and-the-importance-of-religious-or-spiritual-beliefs] (Accessed 02 June 2023). Contract No.: 02 June
63. Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health and Quality of Life Outcomes. 2020;18(1):310.
64. Michalopoulos SN, Gauthier-Loiselle M, Aigbogun MS, Serra E, Bungay R, Clynes D, et al. Patient and Care Partner Burden in CKD Patients With and Without Anemia: A US-Based Survey. Kidney Med. 2022;4(4):100439.
65. Lowney AC, Myles HT, Bristowe K, Lowney EL, Shepherd K, Murphy M, et al. Understanding What Influences the Health-Related Quality of Life of Hemodialysis Patients: A Collaborative Study in England and Ireland. J Pain Symptom Manage. 2015;50(6):778-85.
66. European Kidney Patients Federation. The realities of living with CKD: People with T2D and CKD speak up. 2023 [Available from: https://ekpf.eu/report-realities-of-living-with-ckd/] (Accessed 16 June 2023).
67. Cantor MH. Strain among caregivers: a study of experience in the United States. Gerontologist. 1983;23(6):597-604.
68. Belasco A, Barbosa D, Bettencourt AR, Diccini S, Sesso R. Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis. Am J Kidney Dis. 2006;48(6):955-63.
69. Gayomali C, Sutherland S, Finkelstein FO. The challenge for the caregiver of the patient with chronic kidney disease. Nephrol Dial Transplant. 2008;23(12):3749-51.
70. National Health Service. Chronic kidney disease 2019 [Available from: https://www.nhs.uk/conditions/kidney-disease/] (Accessed 16 June 2023).
71. NICE. Renal replacement therapy and conservative management [NG107]. 2018 [Available from: https://www.nice.org.uk/guidance/ng107/resources/renal-replacement-therapy-and-conservative-management-pdf-66141542991301] (Accessed 16 June 2023).
72. DOF EMP 23-04.
73. Ontarget Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. New England Journal of Medicine. 2008;358(15):1547-59.
74. DOF EMP 23-05.
75. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]. 2023 [Available from: https://www.nice.org.uk/guidance/cg181] (Accessed 16 June 2023).
76. Stevens PE, de Lusignan S, Farmer CK, Tomson CR. Engaging primary care in CKD initiatives: the UK experience. Nephrology Dialysis Transplantation. 2012;27(suppl_3):iii5-iii11.
77. UK KR. Kidney health inequalities in the UK. An agenda for change. 2019.
78. Beba H, Ranns C, Hambling C, Diggle J, Brown P. PCDS consensus statement: A strategy for managing the
supply shortage of the GLP-1 RAs Ozempic and Trulicity. Diabetes and primary Care. 2022;24(5):1-3.
79. DOF EMP 23-06.
80. ClinicalTrials.gov. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin). 2023 [Available from: https://clinicaltrials.gov/ct2/show/NCT03594110] (Accessed 27 March 2023).
81. ClinicalTrials.gov. BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT01131676] (Accessed 27 March 2023).

82. ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03057977] (Accessed 27 March 2023).
83. ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT03057951] (Accessed 27 March 2023).
84. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34.
85. Al-Jobori H, Daniele G, Cersosimo E, Triplitt C, Mehta R, Norton L, et al. Empagliflozin and Kinetics of Renal Glucose Transport in Healthy Individuals and Individuals With Type 2 Diabetes. Diabetes. 2017;66(7):1999-2006.
86. Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity (Silver Spring). 2014;22(4):1042-9.
87. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, et al. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. Diabetes. 2016;65(5):1190-5.
88. DOF EMP 23-07.
89. Wheeler DC, Stefansson BV, Batiushin M, Bilchenko O, Cherney DZI, Chertow GM, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrol Dial Transplant. 2020;35(10):1700-11.
90. DOF EMP 23-08.
91. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-801.
92. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. New England journal of medicine. 2020;383(23):2219-29.
93. Ruilope LM AR, Anker SD, Bakris GL, Filippatos G, Nowack C, Kolkhof P, Joseph A, Mentenich N, Pitt B; FIGARO-DKD study investigators. Design and Baseline Characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. Am J Nephrol. 2019;50(5):345-56.
94. Neal B PV, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the CANagliflozin cardioVascular Assessment Study (CANVAS)—a randomized placebo-controlled trial. Am Heart J 2013;166:217–23.
95. Neal B, Perkovic V, Mahaffey KW, e Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-57.
96. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019;380(4):347-57.
97. Dekkers CCJ, Wheeler DC, Sjostrom CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-Transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. Nephrology dialysis transplantation. 2018;33(11):2005-11.
98. Bernard Zinman MD, Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D. for the EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine. 2015;373(22):2117-28.
99. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international. 2014;85(4):962-71.

100. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M, et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021;143(4):298-309.
101. Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, et al. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation. 2021;143(4):310-21.
102. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61.
103. Evans MP, E.;Furuland, H.;Bennett, H.;Linde, C.;Qin, L.;McEwan, P.;Bakhai, A. The value of maintaining normokalaemia and enabling RAASi therapy in chronic kidney disease. BMC Nephrology. 2019;20(1):31.
104. Palaka ED, O.;McEwan, P.;Qin, L.;Bennett, H.;Grandy, S. Estimating the clinical and economic burden of additional hospitalisation associated with hyperkalaemia and RAASI therapy management: a modelling study in patients with chronic kidney disease or heart failure. Value in Health. 2018;21(Supplement 3):S319.
105. Scottish Medicines Consortium. Tolvaptan 15mg, 30mg, 45mg, 60mg and 90mg tablets (Jinarc®) 2015.
106. Nuijten MA, D. L.;Marx, S. E.;Curry, A. S.;Sterz, R. Cost effectiveness of paricalcitol versus a non-selective vitamin D receptor activator for secondary hyperparathyroidism in the UK: A chronic kidney disease markov model. Clinical Drug Investigation. 2010;30(8):545-57.
107. Thompson MB-W, S.;Bernard, L.;Fenton, A.;Hutchison, C.;Di Iorio, B. Economic evaluation of sevelamer for the treatment of hyperphosphatemia in chronic kidney disease patients not on dialysis in the United Kingdom. Journal of Medical Economics. 2013;16(6):744-55.
108. Jacobsen EC, M.;Cooper, D.;Marks, A.;Brazzelli, M.;Scotland, G. Cost-effectiveness and value of information analysis of multiple frequency bioimpedance devices for fluid management in people with chronic kidney disease having dialysis. Cost Effectiveness and Resource Allocation. 2021;19(1):24.
109. Bernard LM, D.;Dunn, E.;Hutchison, C.;Grima, D. T. A modeled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom. Journal of Medical Economics. 2013;16(1):1-9.
110. Gutzwiller FSP, A. M.;Ademi, Z.;Blank, P. R.;Braunhofer, P. G.;Szucs, T. D.;Schwenkglenks, M. Cost Effectiveness of Sucroferric Oxyhydroxide Compared with Sevelamer Carbonate in the Treatment of Hyperphosphataemia in Patients Receiving Dialysis, from the Perspective of the National Health Service in Scotland. PharmacoEconomics. 2015;33(12):1311-24.
111. Garside RP, M.;Anderson, R.;Mealing, S.;D'Souza, R.;Stein, K. The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: A UK perspective. Nephrology Dialysis Transplantation. 2007;22(5):1428-36.
112. Taylor MJE, H. A.;Chaplin, S.;Goldsmith, D.;Molony, D. A. An economic evaluation of sevelamer in patients new to dialysis. Current Medical Research and Opinion. 2008;24(2):601-8.
113. Scottish Medicines Consortium. Patiromer (as patiromer sorbitex calcium) 8.4g and 16.8g powder for oral suspension (Veltassa®). https://www.scottishmedicines.org.uk/media/5566/patiromer-veltassa-resub-final-october-2020-for-website.pdf
114. Ward TB, G.;Ramirez de Arellano Serna, A. POSA53 The Cost-Effectiveness of Patiromer for the Treatment of Hyperkalaemia in Patients with Chronic Kidney Disease and Heart Failure in the UK. Value in Health. 2022;25(1 Supplement):S43.
115. Scottish Medicines Consortium. Paricalcitol, capsules 1,2 and 4 micrograms. https://www.scottishmedicines.org.uk/media/2118/paricalcitol_capsules__zemplar___final_june_2008doc_for_website.pdf
116. Scottish Medicines Consortium. Etelcalcetide 2.5mg, 5mg, and 10mg solution for injection (Parsabiv®). https://www.scottishmedicines.org.uk/media/1676/etelcalcetide_parsabiv_final_august_2017_amended_030917_for_website.pdf

117. Scottish Medicines Consortium. Lanthanum carbonate, 500mg, 750mg, 1,000mg, chewable tablets (Fosrenol®). 2010.
118. All Wales Medicine Strategy. Paricalcitol (Zemplar®▼) capsules for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency. https://awttc.nhs.wales/files/appraisals-asar-far/final-recommendation-paricalcitol-zemplar-238/
119. NICE. Patiromer for treating hyperkalaemia. 2020 [Available from: https://www.nice.org.uk/guidance/ta623/resources/patiromer-for-treating-hyperkalaemia-pdf-82609015577029] (Accessed 16 June 2023).
120. Palmer AJA, L.;Roze, S.;Lamotte, M.;Rodby, R. A.;Bilous, R. W. An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. Journal of Human Hypertension. 2004;18(10):733-8.
121. Palmer AJV, W. J.;Ray, J. A. Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: A UK health economics analysis. International Journal of Clinical Practice. 2007;61(10):1626-33.
122. McEwan P, Darlington O, Miller R, McMurray JJ, Wheeler DC, Heerspink HJ, et al. Cost-effectiveness of dapagliflozin as a treatment for chronic kidney disease: A health-economic analysis of DAPA-CKD. Clinical Journal of the American Society of Nephrology. 2022;17(12):1730-41.
123. Gutzwiller FSB, P. G.;Szucs, T. D.;Schwenkglenks, M. Health economic evaluation of non-calcium-based phosphate binders in Scotland. Nephrology Dialysis Transplantation. 2014;29(SUPPL. 3):iii271.
124. Treharne CL, F. X.;Arici, M.;Crowe, L.;Farooqui, U. Peritoneal dialysis and in-centre haemodialysis: A cost-utility analysis from a UK payer perspective. Applied Health Economics and Health Policy. 2014;12(4):409-20.
125. Vegter ST, K.;Keith, M. S.;Postma, M. J. Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in chronic kidney disease before and during dialysis. Value in Health. 2011;14(6):852-8.
126. Schlackow IK, Seamus;Herrington, William;Emberson, Jonathan;Haynes, Richard;Reith, Christina;Collins, Rory;Landray, Martin J.;Gray, Alastair;Baigent, Colin;Mihaylova, Borislava;Sharp Collaborative Group. Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease. Kidney international. 2019;96(1):170-9.
127. Scottish Medicines Consortium. Finerenone 10mg and 20mg film-coated tablets (Kerendia®) [Available from: https://www.scottishmedicines.org.uk/media/7206/finerenone-kerendia-final-oct-2022docxfor-website.pdf.
128. Brennan AA, R.;Davis, S.;Sakai, H.;Abbott, V. The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease. Value in Health. 2007;10(1):32-41.
129. Mihaylova BS, Iryna;Herrington, William;Lozano-Kuhne, Jingky;Kent, Seamus;Emberson, Jonathan;Reith, Christina;Haynes, Richard;Cass, Alan;Craig, Jonathan;Gray, Alastair;Collins, Rory;Landray, Martin J.;Baigent, Colin;Sharp Collaborative Group. Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;67(4):576-84.
130. BiCARB study group. Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC medicine. 2020;18(1):91.
131. Ball P, Willis M, Nilsson A, Traina S, Roe R, Kellerborg K. PDB33 Use of a New Discrete Event Simulation MODEL to Predict the Cost Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes in England. Value in Health. 2020;23:S511.
132. Scottish Medicines Consortium. Sodium zirconium cyclosilicate 5g and 10g powder for oral suspension (Lokelma®). https://www.scottishmedicines.org.uk/media/5065/sodium-zirconium-cyclosilicate-lokelma-final-jan-2020-amended-060220-for-website.pdf
133. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. 2007 [Available from:

https://www.nice.org.uk/guidance/ta117/resources/cinacalcet-for-the-treatment-of-secondary-hyperparathyroidism-in-patients-with-endstage-renal-disease-on-maintenance-dialysis-therapy-pdf-82598077917637] (Accessed 16 June 2023).
134. Rutter CM, Zaslavsky AM, Feuer EJ. Dynamic microsimulation models for health outcomes: a review. Medical Decision Making. 2011;31(1):10-8.
135. Willis M, Asseburg C, Slee A, Nilsson A, Neslusan C. Development and internal validation of a discrete event simulation model of diabetic kidney disease using CREDENCE trial data. Diabetes Therapy. 2020;11:2657-76.
136. DOF EMP 23-09.
137. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. Clinical Journal of the American Society of Nephrology. 2009;4(8):1302-11.
138. Grams ME, Surapaneni A, Appel LJ, Lash JP, Hsu J, Diamantidis CJ, et al. Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association. 2021;36(9):1685-93.
139. Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. Bmj. 2017;359:j5019.
140. Naimark DM, Grams ME, Matsushita K, Black C, Drion I, Fox CS, et al. Past Decline Versus Current eGFR and Subsequent Mortality Risk. J Am Soc Nephrol. 2016;27(8):2456-66.
141. Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. The Lancet Diabetes & Endocrinology. 2019;7(2):115-27.
142. Nichols GA, Déruaz-Luyet A, Brodovicz KG, Kimes TM, Rosales AG, Hauske SJ. Kidney disease progression and all-cause mortality across estimated glomerular filtration rate and albuminuria categories among patients with vs. without type 2 diabetes. BMC Nephrology. 2020;21(1):167.
143. Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, Larsen E, Ghali WA, et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006;69(12):2155-61.
144. Warren B, Rebholz CM, Sang Y, Lee AK, Coresh J, Selvin E, et al. Diabetes and Trajectories of Estimated Glomerular Filtration Rate: A Prospective Cohort Analysis of the Atherosclerosis Risk in Communities Study. Diabetes Care. 2018;41(8):1646-53.
145. Imai E, Yasuda Y, Matsuo S. A Decade After the KDOQI CKD Guidelines: A Perspective From Japan. American Journal of Kidney Diseases. 2012;60(5):729-30.
146. Tsai C-W, Ting I-W, Yeh H-C, Kuo C-C. Longitudinal change in estimated GFR among CKD patients: A 10-year follow-up study of an integrated kidney disease care program in Taiwan. PLOS ONE. 2017;12(4):e0173843.
147. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518-31.
148. Moriya T, Tanaka S, Kawasaki R, Ohashi Y, Akanuma Y, Yamada N, et al. Diabetic retinopathy and microalbuminuria can predict macroalbuminuria and renal function decline in Japanese type 2 diabetic patients: Japan Diabetes Complications Study. Diabetes Care. 2013;36(9):2803-9.
149. Jiang G, Luk AOY, Tam CHT, Xie F, Carstensen B, Lau ESH, et al. Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes. Kidney International. 2019;95(1):178-87.
150. Boucquemont J, Loubère L, Metzger M, Combe C, Stengel B, Leffondre K. Identifying subgroups of renal function trajectories. Nephrol Dial Transplant. 2017;32(suppl_2):ii185-ii93.
151. Park HC, Lee YK, Cho A, Han CH, Noh JW, Shin YJ, et al. Diabetic retinopathy is a prognostic factor for progression of chronic kidney disease in the patients with type 2 diabetes mellitus. PLoS One. 2019;14(7):e0220506.

152. Yoshida Y, Kashiwabara K, Hirakawa Y, Tanaka T, Noso S, Ikegami H, et al. Conditions, pathogenesis, and progression of diabetic kidney disease and early decliner in Japan. BMJ Open Diabetes Res Care. 2020;8(1).
153. Go AS, Yang J, Tan TC, Cabrera CS, Stefansson BV, Greasley PJ, et al. Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. BMC Nephrol. 2018;19(1):146.
154. Anderson AH, Yang W, Hsu CY, Joffe MM, Leonard MB, Xie D, et al. Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2012;60(2):250-61.
155. Jun M, Ohkuma T, Zoungas S, Colagiuri S, Mancia G, Marre M, et al. Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON. Diabetes Care. 2018;41(1):163-70.
156. Sumida K, Molnar MZ, Potukuchi PK, George K, Thomas F, Lu JL, et al. Changes in Albuminuria and Subsequent Risk of Incident Kidney Disease. Clinical Journal of the American Society of Nephrology. 2017;12(12):1941-9.
157. Nelson RG, Grams ME, Ballew SH, Sang Y, Azizi F, Chadban SJ, et al. Development of Risk Prediction Equations for Incident Chronic Kidney Disease. JAMA. 2019;322(21):2104-14.
158. Wilson PW, Evans JC. Coronary artery disease prediction. Am J Hypertens. 1993;6(11 Pt 2):309s-13s.
159. Leal J, Alva M, Gregory V, Hayes A, Mihaylova B, Gray AM, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med. 2021;38(10):e14656.
160. Pani LN, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001–2004. Diabetes care. 2008;31(10):1991-6.
161. Iyen B, Weng S, Vinogradova Y, Akyea RK, Qureshi N, Kai J. Long-term body mass index changes in overweight and obese adults and the risk of heart failure, cardiovascular disease and mortality: a cohort study of over 260,000 adults in the UK. BMC public health. 2021;21(1):1-13.
162. Zaninotto P, Lassale C. Socioeconomic trajectories of body mass index and waist circumference: results from the English Longitudinal Study of Ageing. BMJ open. 2019;9(4):e025309.
163. Office for National Statistics (ONS). National life tables – life expectancy in the UK National life tables – life expectancy in the UK: 2017 to 2019. 24 Feb, 2022. Accessed 24 Feb, 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2017to2019
164. Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EClinicalMedicine. 2020;27:100552.
165. Kosiborod MN, Angermann CE, Collins SP, Teerlink JR, Ponikowski P, Biegus J, et al. Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial. Circulation. 2022;146(4):279-88.
166. Jesky MD, Dutton M, Dasgupta I, Yadav P, Ng KP, Fenton A, et al. Health-related quality of life impacts mortality but not progression to end-stage renal disease in pre-dialysis chronic kidney disease: a prospective observational study. PloS one. 2016;11(11):e0165675.
167. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: the switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. Journal of Health Economics. 2017;55:139-52.
168. Alava MH, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. The University of Sheffield. 2020.
169. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Medical Decision Making. 2002;22(4):340-9.
170. Liem YS, Bosch JL, Hunink MM. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value in Health. 2008;11(4):733-41.

171. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The impact of diabetes-related complications on preference-based measures of health-related quality of life in adults with type I diabetes. Medical Decision Making. 2016;36(8):1020-33.
172. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value in Health. 2014;17(4):462-70.
173. Sullivan PW, Ghushchyan VH. EQ-5D scores for diabetes-related comorbidities. Value in health. 2016;19(8):1002-8.
174. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health economics. 2005;14(3):217-30.
175. NICE. TA780-Nivolumab with ipilimumab for untreated advanced renal cell carcinoma.
176. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical Decision Making. 2011;31(6):800-4.
177. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/ramipril/medicinal-forms/#tablet [Accessed on May 19th 2023].
178. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/losartan-potassium/medicinal-forms/ [Accessed on May 19th 2023].
179. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/irbesartan/medicinal-forms/ [Accessed on May 19th 2023].
180. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/atorvastatin/medicinal-forms/#tablet [Accessed on May 19th 2023].
181. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/aspirin/medicinal-forms/ [Accessed on May 19th 2023].
182. National Health Service. NHS Costs 2020/21. [Available from: https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/] (Accessed 16 June 2023).
183. Danese M, Gleeson M, Kutikova L, Griffiths R, Azough A, Khunti K, et al. Costs of cardiovascular (CV) events in the United Kingdom (UK) using real-world data. Value in Health. 2015;18(7):A387.
184. Sundström J, Bodegard J, Bollmann A, Vervloet MG, Mark PB, Karasik A, et al. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2· 4 million patients from 11 countries: The CaReMe CKD study. The Lancet Regional Health-Europe. 2022;20:100438.
185. NICE. Finerenone for treating chronic kidney disease in type 2 diabetes [TA877]. National Institute for Health and Care Excellence 2023. [Available from: https://www.nice.org.uk/guidance/ta877/resources] (Accessed 16 June 2023).
186. NICE. Empagliflozin for treating chronic heart failure with reduced ejection fraction [TA773]. National Institute for Health and Care Excellence 2022. [Available from: https://www.nice.org.uk/guidance/ta773/resources] (Accessed 16 June 2023).
187. Luengo-Fernandez R, Gray AM, Rothwell PM. A population-based study of hospital care costs during 5 years after transient ischemic attack and stroke. Stroke. 2012;43(12):3343-51.
188. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/etelcalcetide/medicinal-forms/ [Accessed on April 20th 2023].
189. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/calcium-acetate/medicinal-forms/ [Accessed on April 20th 2023].
190. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/sevelamer/medicinal-forms/[Accessed on April 20th 2023].

191. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/calcium-carbonate/medicinal-forms/ [Accessed on April 20th 2023].
192. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/sucroferric-oxyhyroxide/medicinal-forms/ [Accessed on April 20th 2023].
193. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/lanthanum/medicinal-forms/ [Accessed on April 20th 2023].
194. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/alfacalcidol/medicinal-forms/ [Accessed on April 20th 2023].
195. Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press https://bnf.nice.org.uk/drugs/cincalcet/medicinal-forms/ [Accessed on April 20th 2023].
196. Kohli MA, Maschio M, Mould-Quevedo JF, Ashraf M, Drummond MF, Weinstein MC. The cost-effectiveness of expanding vaccination with a cell-based influenza vaccine to low risk adults aged 50 to 64 years in the United Kingdom. Vaccines. 2021;9(6):598.
197. Humphreys I, Akbari A, Griffiths R, Graham-Woollard D, Morgan K, Noble-Jones R, et al. Evaluating the cost of managing patients with cellulitis in Wales, UK: A 20-year population-scale study. Int Wound J. 2023.
198. Amdahl J, Diaz J, Sharma A, Park J, Chandiwana D, Delea TE. Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in the United Kingdom. PLoS One. 2017;12(6):e0175920.
199. Sangar VK, Ragavan N, Matanhelia SS, Watson MW, Blades RA. The economic consequences of prostate and bladder cancer in the UK. BJU international. 2005;95(1):59-63.
200. NICE. Immunosuppressive therapy for kidney transplant in adults [TA481]. National Institute for Health and Care Excellence 2017. [Available from: https://www.nice.org.uk/guidance/ta481/evidence] (Accessed 16 June 2023).
201. Morlock R, Chevalier P, Horne L, Nuevo J, Storgard C, Aiyer L, et al. Disease control, health resource use, healthcare costs, and predictors in gout patients in the United States, the United Kingdom, Germany, and France: a retrospective analysis. Rheumatology and therapy. 2016;3(1):53-75.
202. National Health Service. Renal Dialysis. 2021 [Available from: https://www.england.nhs.uk/wp-content/uploads/2021/03/Renal-Dialysis-CA3-2021.pdf] (Accessed 16 June 2023).
203. Manoukian S, Stewart S, Graves N, Mason H, Robertson C, Kennedy S, et al. Bed-days and costs associated with the inpatient burden of healthcare-associated infection in the UK. Journal of Hospital Infection. 2021;114:43-50.
204. Agus A, Phair G, Brazil K, Burns A, Roderick P, Thompson C, et al., editors. Cost of conservative management in patients with end stage kidney disease who decline dialysis: lessons from a multi-centre observational study in the UK. Health Economics Association of Ireland Meeting; 2017.
205. Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. The kidney failure risk equation for prediction of end stage renal disease in UK primary care: an external validation and clinical impact projection cohort study. PLoS medicine. 2019;16(11):e1002955.

Appendices

Appendix C SmPC

Appendix D Identification, selection, and synthesis of clinical evidence

Appendix E Subgroup analysis

Appendix F Adverse reactions

Appendix G Published cost-effectiveness studies

Appendix H Health-related quality-of-life studies

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

Appendix J Clinical outcomes and disaggregated results from the model

Appendix K Price details of treatments included in the submission

Appendix L Checklist of confidential information

Appendix M Supplementary efficacy analysis of other empagliflozin outcome trials

Appendix N Additional health related quality of life (HRQoL) and indirect treatment comparison data

Appendix O Clinical expert opinion

Appendix P Complications submodules and risks

Appendix Q UK life tables and inflation indices

Appendix R Model validation

Appendix S Results of subgroup analysis from the model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

Summary of Information for Patients (SIP)

June 2023

File name	Version	Contains confidential information	Date
ID6131_EMPAGLIFLOZIN_SIP	2.0	Yes	4th July 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Empagliflozin (Jardiance®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

People with chronic kidney disease (CKD)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Committee for Medicinal Products for Human Use (CHMP) (part of the European Medicines Agency [EMA]) gave a positive opinion on empagliflozin in adults for the treatment of CKD on 22 June 2023. This means the EMA will now recommend that the EC grants approval. Marketing authorisation within the UK (to be granted by the Medicines and Healthcare products Regulatory Agency [MHRA]) is pending. Please refer to section B.1.2 of the submission for further information.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: BI is part of the 'Industry Partnership Programme 2023' with Kidney Research UK (KRUK) and have contributed £30,000 in sponsorship. Sponsorship of the programme is used to support the Fellows

and the PPI programme (Public and Patient Involvement) including patient voices and patient reader panel.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

CKD is a long-term medical condition in which the kidneys do not work as well as they should. Patients don't typically have symptoms in the early stages of CKD, but once the condition advances symptoms may include (1):

- tiredness
- swollen ankles, feet or hands
- shortness of breath
- feeling sick
- blood in urine

Kidney Care UK (KCUK) estimate around 3.5 million people in the UK have CKD (2), although a new report by Kidney Research UK (KRUK) suggests this could be much higher, up to 7.2 million (3).

There are various causes and risk factors for CKD, type 2 diabetes (T2D) and hypertension (high blood pressure) being common ones (1).

If the CKD is progressive (which means kidney function deteriorates over time) a person living with CKD is at an increased risk of kidney failure and may ultimately need to start a treatment to replace their kidney function in the form of either dialysis or kidney transplant. In addition to having an increased risk of kidney failure, people with CKD have a higher chance of suffering cardiovascular diseases (CVD) in the form of heart attacks, heart failure, strokes and damage to the blood supply to the legs and feet (4). This increased risk of heart disease is one of the major factors causing people with CKD being at an increased risk of dying earlier than similar people without CKD (3).

CKD is associated with a reduction in health-related quality of life. A number of studies have reported that people with kidney failure (also known as end stage kidney disease [ESKD]) experience significantly reduced quality of life relative to those with normal kidney function. Quality of life in CKD varies depending on disease stage, treatment and the presence of complications and other diseases such as diabetes and cardiovascular disease (5).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

CKD is diagnosed using two different kinds of tests. A blood test measures the level of kidney function, and a urine test can be used to measure how much protein is leaking out of the kidneys. Any result outside of the usual range for kidney filtering function (known as estimated glomerular

filtration rate [eGFR]) or protein in the urine (known as urinary albumin-creatinine ratio [uACR]; above a certain level referred to as albuminuria) could mean that CKD is present (1,6). Specifically, an eGFR of less than 60 ml/min/1.73m^2 or a uACR of more than 3 mg/mmol. If eGFR or uACR measurements remain outside of the normal ranges over the course of 3 months, or if other markers of kidney damage are present, then CKD will be diagnosed (6).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Patients with CKD are currently managed through a combination of lifestyle and risk factor management, alongside medicines to directly manage their kidney disease where appropriate.

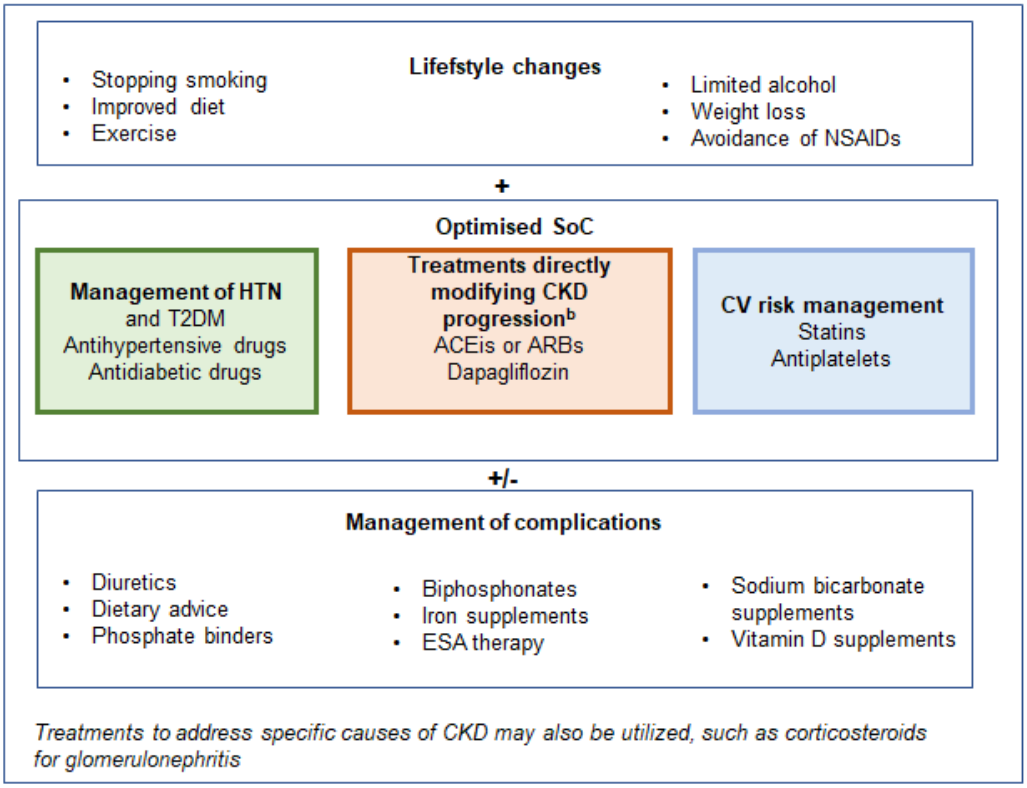
Current guidance suggests that people diagnosed with CKD should be provided with information and lifestyle advice, including stopping smoking, managing alcohol consumption and weight, eating a healthy, balanced diet and undertaking exercise. Beyond lifestyle advice, people living with CKD often have underlying conditions which may be causing the kidney problems, including high blood pressure, diabetes, and cholesterol (1). Appropriate medications can help to manage these co-existing conditions.

The treatment of CKD also includes the use of angiotensin-converting enzyme inhibitors (or ACE inhibitors – the names of which usually end with "-pril") or angiotensin-II receptor blockers (ARBs – the names of which usually end with "-sartan"). However, patients receiving an ACE inhibitor or an ARB are still at risk of harm from CKD (4).

A newer class of drugs named sodium-glucose cotransporter-2 (SGLT2) inhibitors were originally developed to treat T2D and have since demonstrated evidence of benefits in patients with CKD (4). Currently, NICE Clinical Guidelines recommended SGLT2 inhibitors in selected patients who have both CKD and T2D and are taking the highest dose of an ACE inhibitor or ARB they can tolerate. In such patients, an SGLT2 inhibitor may be offered if their albuminuria (uACR / protein in the urine) is above certain levels (6).

In addition, NICE recommend the SGLT2-inhibitor dapagliflozin in selected patients with CKD (those who are receiving the highest tolerated licensed dose of ACE inhibitor or ARB, unless contraindicated, and with an eGFR of 25 mL/min/1.73m2 to 75 mL/min/1.73m2 at the start of treatment and have albuminuria (uACR of 22.6 mg/mmol or more) or have T2D (6,7).

An overview of the management of CKD.



The UK Kidney Association (UKKA) has recently (May 2023) published new guidelines on the use of SGLT2 inhibitors in adults with kidney disease. A patient friendly summary of the guidelines is available at: https://guidelines.ukkidney.org/section-6-lay-summaries-and-patient-information-leaflets/. These guidelines recommend broader use of SGLT2 inhibitors than the current NICE guidelines, including in some patients without albuminuria (protein in the urine). (4)

For patients who have reached end-stage-kidney-disease (ESKD), also known as renal failure, the limited treatment options include dialysis or a kidney transplant (1).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The Chronic Kidney Disease-Personal Impact Index uncovered data on the direct and indirect effects of living with CKD. Data was collected through social media analysis, interviews, and surveys (8). The analysis included patients from Brazil, China, Sweden, UK, and the US.

Overall, 56% of patients reported a significant impact on their quality of life due to CKD, with 36% experiencing this impact immediately or within three months of diagnosis. Additionally, 50% of patients reported a significant impact on their daily activities, with 43% experiencing it shortly after diagnosis.

The top three burdens on patients' personal lives resulting from CKD and associated co-morbidities were mental well-being (39%), sleep schedule (35%), and diet or meal replacement (27%). These findings highlight the burden of living with CKD, particularly for patients with moderate to severe cases (8).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Empagliflozin is an oral medication (tablet) that works by inhibiting the kidney protein sodium-glucose cotransporter-2 (SGLT2) which helps sodium and glucose to be reabsorbed into the bloodstream (9). It is known as an SGLT2 inhibitor. In simple terms, it prevents sugar from being reabsorbed into the blood as it is filtered through the kidney, and so blood sugar (glucose) goes into urine instead. This reduces the levels of sugar in a person's blood. Inhibition of SGLT2 reduces blood glucose and sodium levels (which can damage blood vessels and cause high blood pressure in the long-term), and empagliflozin also has a protective effect on the heart and kidneys.

The exact mechanism of the kidney-protective effect is not yet well defined, however SGLT2 inhibition results in increased excretion of sodium in the urine. This is believed to activate a feedback mechanism that reduces the blood pressure within the filtering part of the kidney, which can cause damage if it is high for too long. This effect may offer clinical advantages over current standard of treatment in patients with CKD and may represent the mechanism contributing to the kidney protective outcomes with empagliflozin (10,11).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Empagliflozin is not intended to be used in combination with another medicine for the treatment of CKD.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of empagliflozin is 10 mg once daily administered orally. No special storage conditions are required, and oral administration avoids the need for patient or clinician training as with intravenous or subcutaneous treatments. As empagliflozin is administered orally once daily, no significant impacts on patients and carers are expected and it should be easy to incorporate into patients' daily routines (12).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Empagliflozin has been studied in a range of clinical trials in different patient groups. These trials included patients with type 2 diabetes (T2D), different forms of heart failure and, more recently, CKD.

Empagliflozin, which was originally developed to treat high blood sugar in people with diabetes, showed in an earlier study of patients with T2D that it offered beneficial effects on both the heart and kidney outcomes (13). Researchers thought it could work in a wider range of patients, such as those with CKD, with or without T2D, and so conducted the EMPA-KIDNEY study.

EMPA-KIDNEY is a clinical trial which tested whether taking 10mg of empagliflozin once daily prevents worsening of kidney disease or CV death in people with CKD. It also assessed whether empagliflozin helps to prevent a range of other outcomes such deaths from any cause, hospitalisations for any reason, and hospitalisations because of heart failure, or CV death (14,15).

The trial was conducted with 6609 patients, across 240 hospitals in 8 countries (from across North America, East Asia, and Europe). Patients with CKD, with or without T2D, were eligible for the trial if they had an eGFR between 20 and 45 ml/min/1.73m^2, or if they have eGFR between 45 and 90 ml/min/1.73m^2 with protein in their urine (specifically uACR $\geq$22.6 mg/mmol, also referred to as albuminuria). Patients were excluded from the trial if their eGFR was below 20 or had certain types of underlying disease, such as polycystic kidney disease (14,15).

Patients were randomised to either empagliflozin or placebo (on top of standard of care) and followed up for an average of just 2 years, as the trial was stopped early (in March 2022) due to positive results (14).

Further information on the EMPA KIDNEY trial can be found at: Welcome — EMPA-KIDNEY (empakidney.org).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the EMPA-KIDNEY trial, treatment with empagliflozin made patients 28% less likely to experience the primary outcome of kidney disease progression or CV death, over an average of around 2 years of receiving treatment, vs standard of care treatment alone. The number of patients needed to be treated with empagliflozin for 2 years to prevent one person experiencing either a kidney disease progression outcome or dying from CV cause was 28. Empagliflozin also reduced the risk of patients being hospitalised (for any reason) by 14% (14).

In the EMPA-KIDNEY trial, empagliflozin reduced the chances of patients with CKD reaching end stage kidney disease or dying form CV causes by 27% or reaching end-stage-kidney-disease (renal failure) alone by 33%. These outcomes are particularly important to patients as CKD is a long-term condition that often gets worse, and therefore it is important to slow the progression of disease (14).

EMPA-KIDNEY provides new information about the benefits of empagliflozin in a wide range of people with CKD who are at risk of worsening disease, including those with and without T2D, and those with and without albuminuria. It also provides additional information about the safety of the treatment, adding to the body of evidence available (14).

There are some limitations when considering the clinical trial results. Some patient groups were excluded from the trial (those with eGFR below 20 ml/min, and those with some forms of kidney disease [e.g polycystic kidney disease]). Additionally, patients were only in the trial for an average of 2 years (as the trial stopped early due to evidence of positive efficacy). This length of trial makes the long-term effects of treatment less clear (14).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the EMPA-KIDNEY trial, patients self-reported on their quality of life using a general questionnaire known as the EQ-5D. This is a generic (i.e., not CKD specific) questionnaire that captures important determinants of quality of life across five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. In EMPA-KIDNEY, there were no real differences in EQ-5D scores between patients who received empagliflozin or those who received a placebo pill (both on top of usual standard care). (16)

While no direct effects on quality of life were observed during the trial, which was only around 2 years in duration, empagliflozin may lead to an improvement in quality of life indirectly as it can prevent disease progression, which in turn reduces the chances of CKD-related events and comorbidities that negatively affect quality of life.

Slowing CKD progression and avoiding dialysis or kidney transplantation is highly desirable, given the effects of dialysis and kidney transplantation on quality of life and cardiovascular morbidity and mortality, as well as the substantial costs associated with kidney-replacement therapy (14).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In EMPA-KIDNEY, empagliflozin demonstrated a safety profile (including all serious adverse events and non-serious AEs) consistent with the safety profile observed across all empagliflozin trials. Individual patient safety outcomes were generally similar between empagliflozin and the placebo (standard of care only) group in EMPA-KIDNEY trial (14).

Like all medicines, this medicine can cause side effects, although not everybody gets them. Patients should refer to the patient information leaflet for information on key side effects and what to do if experiencing them. The patient information leaflet is available at: https://www.medicines.org.uk/emc/files/pil.5441.pdf. (17).

Diabetic Ketoacidosis (DKA)

DKA occurs when the body is unable to properly absorb sugar from the bloodstream and instead uses a different chemical called ketones to generate energy. If these build up, they can cause the blood to become acidic and can cause serious complications, coma or death if left untreated. There was no statistically significant increase in DKA in the EMPA-Kidney trial, but 6 patients experienced a DKA event whilst treated with empagliflozin, compared to 1 with placebo. 1 patient who experienced a DKA event on empagliflozin was not diabetic but had clinical circumstances which contributed to the event (14).
The overall rate of DKA is uncommon with empagliflozin, with between 1:100 and 1:1000 patients experiencing an event (12,17).

Patients should contact a doctor or the nearest hospital straight away if they have signs of DKA.

These are the signs of diabetic ketoacidosis:

- increased levels of “ketone bodies” in your urine or blood
- rapid weight loss
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing

Hypoglycaemia (low blood sugar)

Hypoglycaemia is seen very commonly (may affect more than 1 in 10 people) If patients take empagliflozin with another medicine that can cause low blood sugar, such as a sulphonylurea or insulin, the risk of getting low blood sugar is higher. In EMPA-KIDNEY, 77 patients on empagliflozin and 77 patients on placebo (2.3% in both arms), experienced severe hypoglycaemia (defined as low blood sugar causing sever cognitive impairment that requires assistance from another person for recovery). The signs of low blood sugar may include: shaking, sweating, feeling very anxious or confused, fast heartbeat; excessive hunger, headache. If patients have symptoms of low blood sugar, they should eat glucose tablets, a high sugar snack or drink fruit juice. They should also measure their blood sugar if possible and rest. Patients are also advised to speak to their health care provider if they experience these symptoms. Their health care provider will suggest how to best treat their low blood sugar levels (17).

Other adverse events associated with empagliflozin include urinary and genital tract infections (UTI's and GTIs) which can be common (may affect up to 1 in 10 people). These are thought to occur as treatment with empagliflozin causes sugar to be excreted in the urine, which increases infection risks (17). In EMPA KIDNEY, less than 0.1% of patients on empagliflozin or placebo experienced serious genital infection. Serious UTIs were experienced in 52 (1.6%) patients taking empagliflozin compared to 54 (1.6%) of patients in the placebo arm (14).

Patients should maintain good personal hygiene and genital areas should be washed carefully to avoid infections. The signs of a UTI are:

- burning sensation when passing urine
- urine that appears cloudy
- pain in the pelvis, or mid-back pain (when kidneys are infected).
- An urge to pass urine or more frequent urination may be due to the way Jardiance works, but they can also be signs of urinary tract infection.

If patients note an increase in such symptoms, they should contact their health care provider (17).

Dehydration is seen very commonly (may affect more than 1 in 10 people). In EMPA-KIDNEY, 83 (2.5%) of patients treated with empagliflozin, compared with 76 (2.3%) of patients on placebo, experienced symptomatic dehydration (defined as whether a participant has experienced symptoms that attribute to dehydration e.g., feeling faint). Serious dehydration was experienced in 30 (0.9%) patients on empagliflozin compared to 24 (0.7%) on placebo (14).

The signs of dehydration are not specific but may include:

- unusual thirst
- light-headedness or dizziness upon standing
- fainting or loss of consciousness

Patients should seek advice from their doctor who may suggest stopping taking empagliflozin temporarily until they recover to prevent loss of too much body fluid (17).

Patients should also talk to their doctor, pharmacist, or nurse before taking this medicine, and during treatment if they might be at risk of dehydration (e.g., if they are being sick, have diarrhoea or fever, or unable to eat or drink, taking medicines that increase urine production [diuretics] or lower blood pressure, if they are 75 years old or older). (17)

Cases of necrotising fasciitis of the perineum or Fournier's gangrene (which destroys tissues under the skin) have been reported in patients with diabetes mellitus taking SGLT2 inhibitors. This is a

rare but serious and potentially life-threatening event that requires urgent attention. Patients should speak to their doctor immediately if they develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of necrotising fasciitis of the perineum or Fournier's gangrene. (17)

A full list of adverse events and their frequency is listed in the empagliflozin patient information leaflet/ SmPC as follows (12,17):

Very Common (≥1 in 10 patients experience these)

- Hypoglycaemia (low blood sugar) – when used in combination with other diabetes medications called sulphonylureas or insulin
- Volume depletion (low blood pressure or dehydration)

Common (≥1/100 to <1/10 patients experience these)

- genital yeast infection (thrush)
- passing more urine than usual or needing to pass urine more often
- UTIs
- itching
- rash or red skin – this may be itchy and include raised bumps, oozing fluid or blisters
- thirst
- blood tests may show an increase in blood fat (cholesterol) levels in your blood
- constipation

Uncommon (≥1/1 000 to <1/100 patients experience these)

- hives
- straining or pain when emptying the bladder
- blood tests may show a decrease in kidney function (creatinine or urea)
- blood tests may show increases in the amount of red blood cells in your blood (haematocrit)
- diabetic ketoacidosis
- Swelling of the skin

Rare (≥1/10 000 to <1/1 000 patients experience these)

- necrotising fasciitis of the perineum or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus

Very rare (<1/10 000 patients experience these)

- inflammation of the kidneys (tubulointerstitial nephritis)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of treatment with empagliflozin to patients with CKD include a reduction in the rate of decline of renal function. This means patients may delay or avoid progressing to end-stage-kidney-disease (renal failure) and so the need for dialysis or a renal transplant, both of which have significant impact on quality of life. As demonstrated in the model (described later), by preventing renal decline, patients may also be less likely to experience other complications or comorbidities that occur in patients with CKD. Importantly, empagliflozin demonstrated a reduction in all-cause (i.e., for any reason) hospitalisations vs standard of care alone. So empagliflozin can help patients to avoid hospitalisations, which benefits both patients and the NHS.

Empagliflozin may also offer wider benefits such as improvements in quality of life for carers if a patient they care for can delay or prevent needing dialysis. For patients and carers, avoiding dialysis can also mean being more productive at work or being able to have a job and not spending time and money on transport to the hospital.

Empagliflozin for the treatment of CKD is one 10 mg tablet daily, taken at any time during the day with no need to increase or change doses.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The key disadvantages to patients would include the requirement to take an additional medication on top of their current pills, the potential for increasing the need to urinate which may impact on certain jobs and the risk of adverse events associated with treatment. The causes of these disadvantages range from the practicalities of taking additional treatments and the mode of action of the treatment itself. The mode of administration as a once daily tablet, taken at any time, does not present any additional disadvantages to patients.

The impact of these disadvantages compared to current treatments varies dependent on the current treatment being compared to, with different adverse events associated with different medicines. The mode and frequency of administration is less of a disadvantage compared to some other treatments, which require twice daily dosing.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The model predicts how a group of patients with CKD will progress over their lifetime, this includes how their CKD may advance, what complications and additional conditions they may experience or develop, and how and when they may die.

At the start of the model, the group of patients have eGFR levels (a measure of renal function) and uACR levels (a measure of renal damage) reflective of those seen in the EMPA-KIDNEY trial. These levels will change over the years. Individual patient characteristics – such as whether they have T2D, CVD, and how old they are – are used to predict how fast each patients' CKD progresses. The model also uses these characteristics to predict the occurrence of CKD-related complications (including anaemia, acute kidney injury, bone disorders, and many more) for each patient and also if/when they may develop comorbidities they don't already have (e.g., hypertension and T2D).

The model splits the group of patients into two – one group are modelled to receive empagliflozin (on top of 'standard of care' treatments) and the other group to receive standard of care only. Treatment effects of empagliflozin on the rate of eGFR and uACR change, as demonstrated in the EMPA-KIDNEY trial, are then applied to the relevant patients. These treatment effects were only applied for as long as patients were predicted to remain on treatment.

The model calculates the total costs as well as the years alive and the quality of life during those years alive, for the group who were modelled to receive empagliflozin vs those who received standard of care alone.

The model demonstrated that treatment with empagliflozin, vs standard of care alone, extends patients' lives by 1.055 years on average, through slowing the rate of decline in renal function and so delaying or preventing patients from reaching kidney failure and/or death due to renal causes. The model demonstrated that treatment with empagliflozin, vs standard of care alone, provides patients with an additional 0.849 quality-adjusted-life-years (QALYs) over the course of their life, on average. A QALY is a standard measure of health-related quality of life. One full QALY is the equivalent of living 1 year in perfect health, whereas 0.5 QALY is the equivalent of 1 year with 50% health, or 6 months with perfect health.

In EMPA-KIDNEY, the EQ-5D quality of life questionnaire was used – this is a generic (i.e., not CKD specific) questionnaire typically used in clinical trials. During the EMPA-KIDNEY trial (in which patients were followed for an average of ~2 years) there were no real differences in EQ-5D scores between patients who received empagliflozin or those who received standard of care. In the model, however, which considers the patients' lifetime, treatment with empagliflozin indirectly improved quality of life through preventing CKD progression. This meant patients stayed in earlier disease stages for longer (which are associated with better quality of life) and delayed or avoided entering late stages of CKD (which are associated with poorer quality of life, especially if dialysis is required).

The model cost calculations include direct costs of empagliflozin and standard of care drugs, and NHS costs in the care of the patients – this could be treatment costs for managing anaemia, or the cost of a hospital stay after a CV event such as a heart attack.
The results of the model demonstrate the empagliflozin was more effective and less costly (known as 'dominant') vs standard of care alone in the treatment of CKD. The incremental cost-effectiveness ratio (ICER; a standard measure of cost-effectiveness) was -£6,431.37/QALY gained. NICE generally accept that an ICER below £20,000–£30,000/QALY is cost-effective, and so empagliflozin is highly cost effective.

As with all models, assumptions are made. The impact of these was tested during further analyses, in which higher or lower, or more/less extreme assumptions are made. None of the sensitivity analyses conducted changed the overall result of the model. The one which had the biggest change on the results (but still showed that empagliflozin was a cost-effective treatment) was the assumption that patients aged 80 year or older would not be offered a renal transplant. If the age of 72 years was instead used, the ICER (£/QALY) was -£2,278. If the age was 88, it was -£6,677/QALY.

As per the methods set out by NICE, the model only includes benefits and costs from the perspective of the NHS and the NHS and personal social services (PSS). This means wider but important indirect costs to the economy – such as lost patient and carer productivity (e.g., time spent during or travelling to dialysis, and/or unable to work) and travel costs – are not accounted for in the model. If these were to be included in the model, the results would likely show that empagliflozin is even more cost-effective than the current results.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

EMPA-KIDNEY is the first trial in CKD in patients with and without albuminuria (protein in their urine, an important marker of kidney risk) and demonstrated treatment benefits across the range of patients included. This new evidence means SGLT2 inhibitors could be recommended across a broader range of patients, giving new options to patients who previously had limited options.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Inequalities are well established in CKD, both from the perspective of how likely people in lower socioeconomic groups are to get CKD, but also how likely they are to progress to end stage kidney disease. Further inequalities are seen from a racial and ethnic perspective, where individuals from Black, Asian and minor ethnic backgrounds are more likely to progress towards end stage kidney disease faster and are less likely to obtain kidney transplants.

Having empagliflozin available as an additional treatment option for CKD available to primary care (e.g., GP practices) as well as secondary care (e.g., kidney specialist centres / hospitals) may help to reduce some of these inequalities, as not all patients have equal access to some services.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf
- Empagliflozin (Jardiance) Patient Information Leaflet: Jardiance 10 mg film-coated tablets - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)
- Empagliflozin (Jardiance) Summary of product characteristics: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Type 2 diabetes: Type 2 Diabetes - Symptoms, Causes, Treatment
- Chronic Kidney Disease; Chronic kidney disease (CKD) | Kidney Care UK
- EMPA KIDNEY: EMPA-KIDNEY: the study of heart and kidney protection with empagliflozin — Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) (ox.ac.uk)

4b) Glossary of terms

Response:

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:
1. NHS. Overview - Chronic Kidney Disease [Internet]. 2023 [cited 2023 Jun 27]. Available from: https://www.nhs.uk/conditions/kidney-disease/ 2. Kidney Care UK. Facts about kidneys [Internet]. 2023. Available from: https://www.kidneycareuk.org/news-and-campaigns/facts-and-stats/ 3. Kidney Research UK. Kidney disease: A UK Public Health Emergency. The Health Economics of Kidney Disease to 2033 [Internet]. 2023 [cited 2023 Jun 27]. Available from: https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf 4. UKKA Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease. Lay summary for patients. [Internet]. 2023 [cited 2023 Jun 27]. Available from: https://guidelines.ukkidney.org/section-6-lay-summaries-and-patient-information-leaflets/ 5. Kerr M. Chronic Kidney Disease in England: The Human and Financial Cost [Internet]. 2012 [cited 2023 Jun 27]. Available from: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf 6. NICE. Chronic kidney disease: assessment and management - NICE Guideline [NG203] [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/ng203 7. NICE. Dapagliflozin for treating chronic kidney disease. Technology appraisal guidance [TA775] [Internet]. 2022. Available from: https://www.nice.org.uk/guidance/ta775/evidence 8. James M, et al. POS-229. The Chronic Kidney Disease-Personal Impact Index (CKD-PII): Analysis of The Global Day-To-Day Personal Impact Of Disease On Patients With CKD. Kidney International Reports. Volume 6, Issue 4, Supplement S96-S97, 2021. 9. Ndefo UA, Anidiobi NO,Basheer A, Eaton AT. Empagliflozin (Jardiance): A Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes. 2015;P T. 2015;40(6):364-8. 10. Lopaschuk GD, Verma S[b]. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci.* 2020;2020;5(6):632-44. 11. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature Reviews Cardiology. 2020;2020;17(12):761-72.

12. Boehringer Ingelheim Ltd. Summary of Product Characteristics: Jardiance (empagliflozin) 10 mg film-coated tablets (GB). 2023 [Internet]. 2023. Available from: https://www.medicines.org.uk/emc/product/5441/smpc

13. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New Engl J Medicine [Internet]. 2015;373(22):2117–28. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1504720

14. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2023; 388:117-127.

15. Herrington WG, Wanner C, Green JB, Hauske SJ, Judge P, Mayne KJ, et al. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transpl. 2022;37(7):gfac040.

16. Boehringer Ingelheim Ltd. EMPA-KIDNEY Clinical Trial Report. Data on File. 2023.

17. Boehringer Ingelheim Ltd. Package leaflet: Information for the patient: Jardiance® 10 mg film-coated tablets Jardiance® 25 mg film-coated tablets [Internet]. Available from: https://www.medicines.org.uk/emc/files/pil.5441.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

Company response to clarification questions

1st August 2023

File name	Version	Contains confidential information	Date
ID6131_Empagliflozin_clarification Qs_Company response_[redacted]	1	No, CIC redacted	1st August 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Clinical effectiveness

A1. Priority: Please provide baseline characteristics of the UK/Western European recruits to EMPA-KIDNEY including:

1. **Hba1c for the diabetic group;**
2. **Smoking %; hypertension (mean BPs and treatments such as ACEI and ARBs, diuretics);**
3. **Statins;**
4. **Mean duration of diabetes and treatments (% on insulin).**

Company response: Of the 1,133 United Kingdom (UK) patients randomised in EMPA-KIDNEY, 400 (35.3%) had a diabetes diagnosis at baseline with 380 of these patients (33.5%) having type 2 diabetes mellitus (T2DM). Mean glycated haemoglobin (HbA1c) among patients with diabetes was 58.6 mmol/mol. Mean time since diagnosis of diabetes was 17.8 years. Reported frequency of insulin use in the UK cohort was 192 cases, corresponding to 48% of patients with diabetes. 758 patients (66.9%) received lipid modifying therapy at the baseline. 80 patients (7.1%) identified themselves as active smokers and 477 (42.1%) no longer smoke regularly. Information about hypertension wasn't prespecified as a comorbidity in the EMPA-KIDNEY trial case report form (CRF), mean systolic blood pressure (SBP) was 137.3 (SD 18.0) mmHg, 65.5% of patients had SBP above 130 mmHg, mean diastolic blood pressure (DBP) was 78.0 (SD 11.1) mmHg and 29.0% of patients had DBP above 85 mmHg. 840 patients (83%) were treated with renin-angiotensin system (RAS) inhibitors at the baseline and 358 patients (31.6%) received diuretics therapy. Further details are available in 'A1_EMPA-KIDNEY_Baseline-Demographics_UK' and 'A1_EMPA-KIDNEY_Baseline-Demographics_Europe-UK_Diabetes' included.

Of the 2,648 patients in the Western European region (herein referred to as European) randomised in EMPA-KIDNEY, 1,051 patients (39.7%) had a diabetes diagnosis at baseline with 1,010 of these patients (38.1% of the European subgroup) having T2DM. Mean HbA1c among patients with diabetes was 54.8 mmol/mol. Mean time since diagnosis of diabetes was 17.4 years. Reported frequency of insulin use in the European subgroup was 617 cases,

corresponding to 58.7% of patients with diabetes. 1,839 patients (69.4%) received lipid modifying therapy at the baseline. 256 patients (9.7%) identified themselves as active smokers and 1,089 (41.1%) no longer smoke regularly. Information about hypertension wasn't prespecified as a comorbidity in EMPA-KIDNEY, mean SBP was 136.7 (SD 18.5) mmHg, 65.2% of patients had SBP above 130 mmHg, mean DBP was 78.2 (SD 11.5) mmHg and 30.2% of patients had DBP above 85 mmHg. 2,302 patients (86.9%) were treated with RAS inhibitors at the baseline and 1,383 patients (52.2%) received diuretics therapy. Further details are available in the PDFs 'A1_EMPA-KIDNEY_Baseline-Demographics_Europe' and 'A1_EMPA-KIDNEY_Baseline-Demographics_Europe-UK_Diabetes' included.

A2. For the EMPA-KIDNEY subset with T2DM at baseline, the EMPA-REG population, and the EMPA-REG subgroup of M.2.2 what proportions were receiving:

- **Monotherapy metformin**
- **Other monotherapy OAD**
- **Dual therapy OAD**
- **Triple therapy OAD**
- **Insulin therapy**

Company response: The following tables show the proportions of antidiabetic medication used by the EMPA-KIDNEY subpopulation with T2DM at baseline (Table 1), the EMPA-REG OUTCOME chronic kidney disease (CKD) subpopulation at baseline (Table 2), and the EMPA-REG OUTCOME subgroup of M.2.2 (CKD patients with estimated glomerular filtration rate [eGFR] ≥45 <90 ml/min/1.73m^2 but without albuminuria (urine albumin-creatinine ratio [uACR] <200 mg/g [22.6mg/mmol]) at baseline (Table 3).

Table 1: Antidiabetic medication use at baseline in EMPA-KIDNEY patients with T2DM – RS

	Placebo N (%)	Empa 10mg N (%)	Total N (%)
Number of patients	1,466 (100.0)	1,470 (100.0)	2,936 (100.0)
Insulin therapy with or without OADs	800 (54.6)	779 (53.0)	1,579 (53.8)
Monotherapy metformin	84 (5.7)	69 (4.7)	153 (5.2)
Other monotherapy OAD	206 (14.1)	199 (13.5)	405 (13.8)
Dual therapy OAD	148 (10.1)	188 (12.8)	336 (11.4)
Triple therapy OAD	41 (2.8)	36 (2.4)	77 (2.6)

Abbreviations: N, number of patients; OAD, oral antidiabetic medication; RS, randomised set; T2DM, type 2 diabetes mellitus

Table 2: Antidiabetic medication use at baseline in EMPA-REG OUTCOME CKD patients – RS

	Placebo N (%)	Empa 10mg N (%)	Total N (%)
Number of patients	2,337 (100.0)	2,347 (100.0)	4,684 (100.0)
Insulin therapy with or without OADs	1,135 (48.6)	1,132 (48.2)	2,267 (48.4)
Monotherapy metformin	246 (10.5)	274 (11.7)	520 (11.1)
Other monotherapy OAD	128 (5.5)	122 (5.2)	250 (5.3)
Dual therapy OAD	581 (24.9)	589 (25.1)	1,170 (25.0)
Triple therapy OAD	179 (7.7)	156 (6.6)	335 (7.2)

Abbreviations: CKD, chronic kidney disease; N, number of patients; OAD, oral antidiabetic medication; RS, randomised set

Table 3: Antidiabetic medication use at baseline in EMPA-REG OUTCOME patients with eGFR ≥45 <90 ml/min/1.73m^2 but without albuminuria (uACR < 200 mg/g [22.6mg/mmol] at baseline – RS

	Placebo N (%)	Empa 10mg N (%)	Total N (%)
Number of patients	1,298 (100.0)	1,286 (100.0)	2,584 (100.0)
Insulin therapy with or without OADs	616 (47.5)	601 (46.7)	1,217 (47.1)
Monotherapy metformin	145 (11.2)	141 (11.0)	186 (11.1)
Other monotherapy OAD	80 (6.2)	77 (6.0)	157 (6.1)
Dual therapy OAD	319 (24.6)	329 (25.6)	648 (25.1)
Triple therapy OAD	94 (7.2)	89 (6.9)	183 (7.1)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; number of patients; OAD, oral antidiabetic medication; RS, randomised set; uACR, urine albumin-creatinine ratio

A3. Priority: It appears that the economic model *Other_Default_Data* F123:O132, F171:F172, F201:O203 and F215:O215 includes a number of clinical effect estimates that may not have been presented in the clinical effectiveness section or in the consideration of the equivalence of empagliflozin with the other SGLT2s. Please highlight where these clinical effect estimates are presented in the clinical effectiveness section, or provide an addendum to the clinical effectiveness section addressing these clinical effect estimates for EMPA-KIDNEY and to the extent possible for the M.2.2 subset of EMPA-REG. Please also clarify within the economic model which are one off effects that are applied once to baseline values and which are ongoing effects that are applied repeatedly every year while the patient remains on treatment

Company response: The treatment effect estimates outlined in this question were obtained from EMPA-KIDNEY trial outputs and used in the model, but were not detailed in the clinical effectiveness section in Document B. These treatment effects are now presented in Table 4, Table 5 and Abbreviations: AKI, acute kidney injury; HHF, hospitalisation for heart failure; HR, hazard ratio; SE, standard error

Source: EMPA-KIDNEY trial output. Data on File.

Table 6 below. They are measured from baseline until the last available time point (up to 36 months). Treatment effects are applied to baseline patients and repeated in the next cycle while patients are on treatment. Treatment discontinuation (Source: EMPA-KIDNEY trial output. Data on File.

Table 7) is defined based on discontinuation rates, death, or initiation of renal replacement therapy (RRT).

Table 4: Incremental treatment effect per risk factor in EMPA-KIDNEY for the full cohort

Risk factor	Empagliflozin 10mg				Placebo			
	Mean	SE	Lower min	Upper max	Mean	SE	Lower min	Upper max
HbA1c (mmol/mol)	-0.56	0.14	-0.83	-0.29	-0.15	0.14	-0.41	0.12
Weight (kg)	-1.55	0.09	-1.74	-1.37	-0.68	0.09	-0.86	-0.49

BMI (calculated)	-0.55	-	-	-	-0.24	-	-	-
Hb (g/dL)	0.60	0.06	0.49	0.71	-0.14	0.06	-0.26	-0.02
SBP (mmHg)	-3.92	0.21	-4.32	-3.51	-1.29	0.21	-1.70	-0.88
DBP (mmHg)	-1.64	0.12	-1.88	-1.40	-1.22	0.12	-1.47	-0.98

Abbreviations: BMI, body-mass index; DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, glycated haemoglobin; max, maximum; min, minimum; SBP, systolic blood pressure; SE, standard error
Source: EMPA-KIDNEY trial output. Data on File.

Table 5: Incremental treatment effect on event rates HHF and AKI in EMPA-KIDNEY for the full cohort

Treatment effect on event rate	Empagliflozin 10mg vs Placebo			
	HR	SE	Lower	Upper
HHF	0.80	0.117	0.60	1.06
AKI	0.78	0.102	0.60	1.00

Abbreviations: AKI, acute kidney injury; HHF, hospitalisation for heart failure; HR, hazard ratio; SE, standard error
Source: EMPA-KIDNEY trial output. Data on File.

Table 6: Mean amputation rate per 100-patient-years in EMPA-KIDNEY for the full cohort

Mean rate per 100-patient-year	Empagliflozin 10mg	Placebo
Leg Amputation	0.12	0.02
Toe Amputation	0.25	0.15
Foot Amputation	0.08	0.02

Source: EMPA-KIDNEY trial output. Data on File.

Table 7: Annual treatment discontinuation rate in EMPA-KIDNEY for the full cohort

	Empagliflozin 10mg	Placebo
Annual discontinuation rate	12.56	14.16

The EMPA-REG OUTCOME trial reported incremental treatment effect per risk factor, measured as the mean change from baseline until the last available time point. See Table 8 for these treatment effects specifically for the M2.2. subgroup of the EMPA-REG OUTCOME population. The time points available for EMPA-REG OUTCOME (up to 220 weeks) are not comparable to the time points available for EMPA KIDNEY (up to 157 weeks). Incremental treatment effect on event rate on hospitalisation for heart failure (HHF) and AKI, mean amputation rate per 100-patient years and annual treatment discontinuation rate are not available for the M2.2. subset of EMPA-REG OUTCOME trial population.

Table 8: Incremental treatment effect per risk factor in EMPA-REG OUTCOME M2.2 subgroup

Risk Factor	Empagliflozin 10mg		Placebo	
	Mean	SE	Mean	SE
HbA1c (%)	-0.15	0.07	0.02	0.08
Weight (kg)	-2.14	0.25	-1.36	0.27
Hb (g/dL)	0.65	0.08	-0.07	0.09
SBP (mmHg)	-0.76	1.07	0.77	1.23
DBP (mmHg)	-1.79	0.61	-3.13	0.70

Abbreviations: BMI, body-mass index; DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; SE, standard error

A4. Priority: If EMPA-REG recorded eGFR, for the subgroup of appendix M.2.2 please provide the equivalents of Document B Figure 18 and Table 29. The ERG understands that it may not be possible to populate all cells of Table 19 but those for the KDIGO position sought for those with T2DM of Document Figure 1 would be of particular interest.

Company response: Annual eGFR was recorded in EMPA-REG OUTCOME. Table 9 provides the equivalent of Table 29 from Document B, populated where possible, for the M2.2. subgroup of EMPA-REG OUTCOME, (specifically patients with eGFR ≥45 <90 ml/min/1.73m^2 but without albuminuria (uACR < 200 mg/g [22.6mg/mmol]). 'Table 19' is also referred to in the question, but this is believed to be a typo.

Table 9: Annual eGFR change in EMPA-REG OUTCOME (M2.2.) patients receiving empagliflozin and SoC, Total slope (baseline to week 234)

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)							
	Empagliflozin 10 mg on top of SoC				**Placebo on top of SoC**			
	A1	A2 (<22.6 mg/mmol)	A2 (≥22.6)	A3	A1	A2 (<22.6 mg/mmol)	A2 (≥22.6)	A3
G2	−0.19 (-0.38,0.00)		NA	NA	-1.49 (-1.69, -1.30)		NA	NA
G3a			NA	NA			NA	NA
G3b	NA	NA		NA	NA			NA
G4	NA	NA		NA	NA	NA		NA
All								

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA, not available; SoC, standard of care

Figure 1 below is the equivalent of Document B Figure 18 for the M2.2. subgroup of EMPA-REG OUTCOME.

As per the explanation in the response to question B1, Document B Figure 18 (and so Figure 1 here also) plots the average eGFR (mL/min/1.73m^2) per visit and treatment group estimated using a mixed-model-repeated measure.

Figure 1: Change from Baseline in the eGFR, for M2.2. subgroup of EMPA-REG OUTCOME

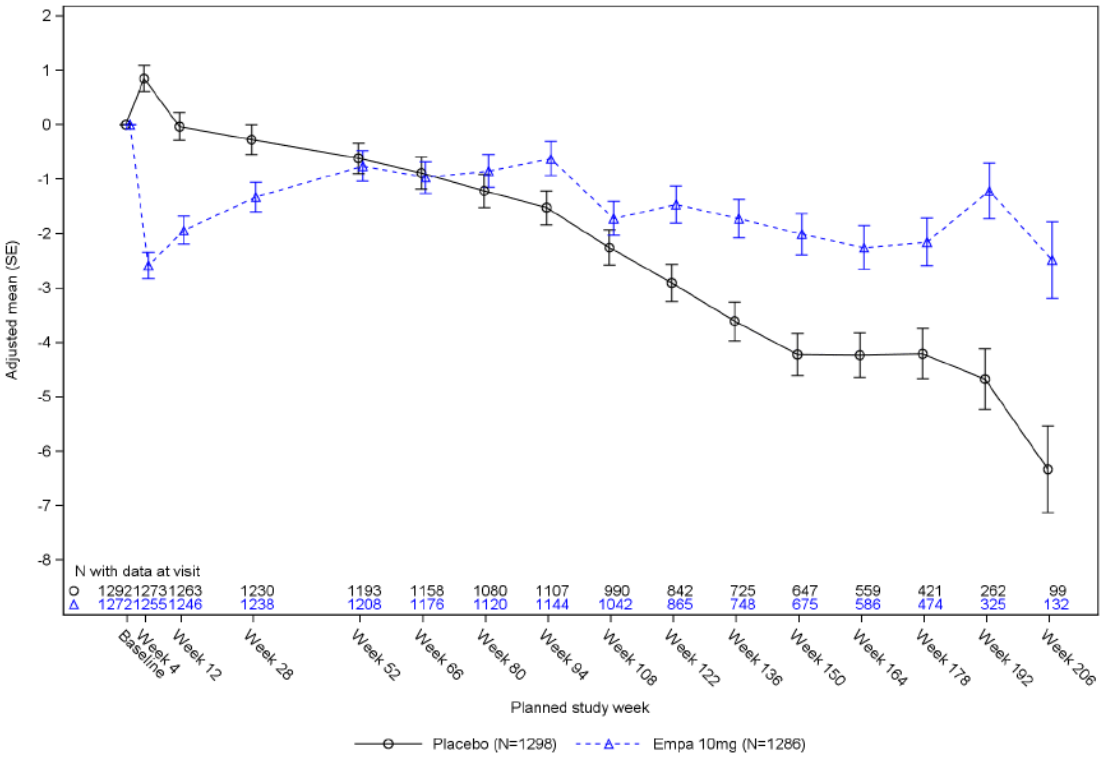


Figure 14.1.1 eGFR (CKD-EPI) [mL/min/1.73m²] change from baseline MMRM results over time in patients with eGFR (CKD-EPI) >= 45 < 90 mL/min/1.73 m² and uACR < 200 mg/g (<=22.6mg/mmol) at baseline - TS (OC-AD)

r2241\fcot1001.sas 27JUL2023

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MMRM. Mixed model with repeated measurements; N, number of patients; OC-AD, Observed Case-All Data; SE, standard error; TS, treated set; uACR, Urine albumin-to-creatinine ratio

A5. Please provide a spreadsheet of the OC-AD Kaplan Meier data for all cause deaths, separately by arm. Please also provide this for the T2DM at baseline subset. (4 tables)

Day	N at risk	Deaths	Censored	S(t)
0	N = ???			100%
1	N = ???	N = ???	N = ???	???%
2	N = ???	N = ???	N = ???	???%
3	N = ???	N = ???	N = ???	???%
Etc.				

Company response: The confidential Excel file 'A5_Time to ACM' included as an attachment includes separate sheets for the Observed Case-All Data (OC-AD) Kaplan Meier data for all cause deaths, separately by arm, for both the whole cohort and the T2DM subset (4 sheets in the workbook).

A6. Priority: Please provide the OC-AD Kaplan-Meier data for remaining on study treatment separately by arm treating death from any cause as a competing risk (C.R.). Please also provide this for the T2DM at baseline subset (4 tables).

Day	N at risk	Discontinued	C.R.: Any death	Censored	S(t)
0	N = ???	..	..	..	100%
1	N = ???	N = ???	N = ???	N = ???	???%

2	**N = ???**	**N = ???**	**N = ???**	**N = ???**	**???%**
3	**N = ???**	**N = ???**	**N = ???**	**N = ???**	**???%**
Etc.					

Company response: The confidential Excel file 'A6_TTD with ACM as CR' sent as an attachment includes separate sheets for the OC-AD Kaplan Meier data for remaining on study treatment, separately by arm, treating death from any cause as a competing risk for both the whole cohort and the T2DM subset (8 sheets in the workbook).

A7. Priority: Please provide a plot of the distribution of uACR baseline values, by mg/g rather than by A1, A2, A3, together with the number of observations underlying the distribution, its mean, its standard deviation and any higher moments felt necessary to adequately describe the distribution should it be notably asymmetric, or the log of these quantities if this is felt to better describe the distribution. Similar concerns apply to the modelled baseline eGFR distribution. Please similarly provide a plot and parameterisation of the distribution of the eGFR baseline values (ml/min/1.73m^2).

Company response: Table 10 tabulates the baseline characteristics for eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and log transformed uACR used to create the distribution of baseline eGFR as a histogram and density curve (Figure 2), and the distributions of log-transformed baseline uACR as histograms and density curves by mg/g, for: all patients (Figure 3), all patients except those with baseline values too low to quantify (Figure 4), patients with uACR <30 mg/g (Figure 5), patients with uACR ≥30 and ≤300 mg/g (Figure 6), and patients with uACR >300 mg/g (Figure 7).

Table 10: Baseline characteristics for eGFR (CKD-EPI) [mL/min/1.73m^2] and log-transformed uACR - RS

	uACR <30 mg/g	**uACR ≥30 and ≤300 mg/g**	**uACR >300 mg/g**	**Total**
Number of patients (%)	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (CKD-EPI) [mL/min/1.73m^2]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Q1	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
Log-transformed uACR [mg/g]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Q1	[redacted]	[redacted]	[redacted]	[redacted]

Median	[redacted]		[redacted]		[redacted]		[redacted]	
Q3	[redacted]		[redacted]		[redacted]		[redacted]	
Max	[redacted]		[redacted]		[redacted]		[redacted]	
Log-transformed uACR ('too low to quantify' values excluded) [mg/g]								
N	[redacted]		[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]		[redacted]	
SE	[redacted]		[redacted]		[redacted]		[redacted]	
Min	[redacted]		[redacted]		[redacted]		[redacted]	
Q1	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
Q3	[redacted]		[redacted]		[redacted]		[redacted]	
Max	[redacted]		[redacted]		[redacted]		[redacted]	

If central eGFR or uACR value missing, most recent local value on or prior to randomisation used. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; max, maximum; min, minimum; N, number of patients; Q, quarter; RS, randomised set; SD, standard deviation; SE, standard error; uACR, urine albumin-creatinine ratio

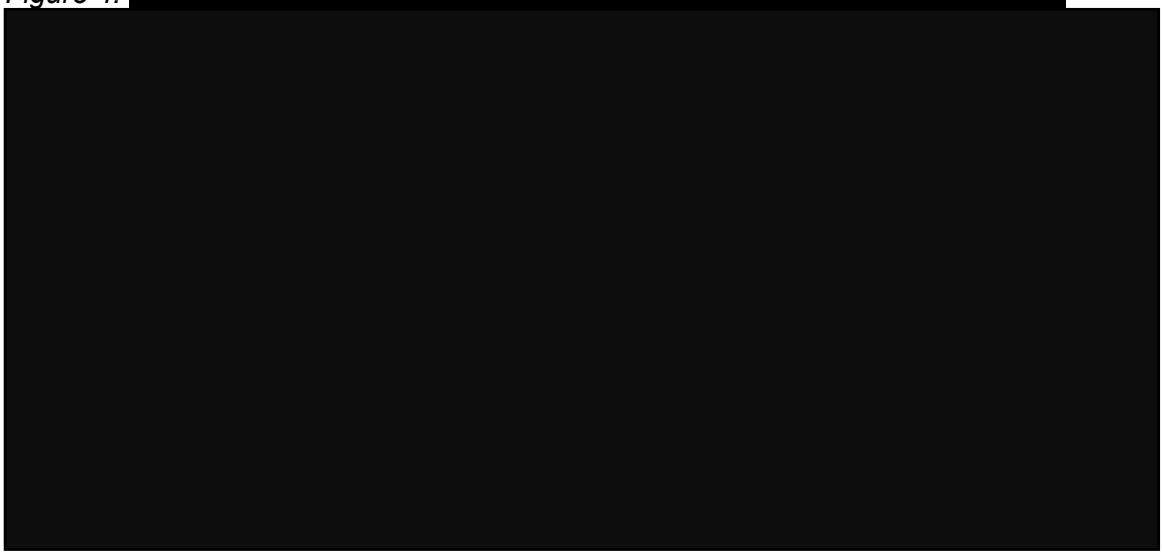
Figure 2: [redacted]

If central eGFR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted] Skewness: [redacted] Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; N, number of patients; RS, randomised set

Figure 3: [redacted]

If central uACR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted]. *Skewness:* [redacted].
Abbreviations: N, number of patients; RS, randomised set; uACR, urine albumin-creatinine ratio

Figure 4: [redacted]



If central uACR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted]. *Skewness:* [redacted].
Abbreviations: N, number of patients; RS, randomised set; uACR, urine albumin-creatinine ratio

Figure 5: [redacted]

If central uACR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted]. Skewness: [redacted].
Abbreviations: N, number of patients; RS, randomised set; uACR, urine albumin-creatinine ratio

Figure 6: [redacted]

If central uACR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted]. Skewness: [redacted].
Abbreviations: N, number of patients; RS, randomised set; uACR, urine albumin-creatinine ratio

Figure 7: [redacted]

If central uACR value missing, most recent local value on or prior to randomisation used. Kurtosis: [redacted]. Skewness: [redacted].
Abbreviations: N, number of patients; RS, randomised set; uACR, urine albumin-creatinine ratio

A8. Priority: Please provide the 8x8 variance-covariance matrix for baseline age (years), baseline uACR (mg/g), baseline eGFR (ml/min/1.73m^2), baseline weight (kg), baseline height (m), baseline SBP (mmHG), baseline DBP (mmHG) and baseline HbA1c (%).

Company response: The 8x8 variance-covariance matrix, as requested, is provided in Table 11.

Table 11: Covariance matrix between selected baseline covariates

Variable	Baseline Age [years]	Log-transformed Baseline uACR [mg/g]	Baseline eGFR (CKD-EPI) [mL/min/1.73m^2]	Baseline Weight [kg]	Baseline Height [m]	Baseline SBP [mmHg]	Baseline DBP [mmHg]	Baseline HbA1c [%]
Baseline Age [years]	[redacted]							
Log-transformed Baseline uACR [mg/g]	[redacted]							
Baseline eGFR (CKD-EPI) [mL/min/1.73m2]	[redacted]							
Baseline Weight [kg]	[redacted]							
Baseline Height [m]	[redacted]							
Baseline SBP [mmHg]	[redacted]							
Baseline DBP [mmHg]	[redacted]							
Baseline HbA1c [%]	[redacted]							

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; uACR, urine albumin-creatinine ratio; SBP, systolic blood pressure

A9. Priority: Please tabulate the number of patients the number of patients with (A) CV Disease, (B) Hypertension, (C) CHF, (D) family history of diabetes, (E) smoking at baseline and (F) NGT for those with baseline age 20-40, 41-50, 51-60, 61-70, 71-80 and 80+ separately for all patients and the subset with T2DM at baseline (2 tables).

Company response: Two tables displaying the requested baseline characteristics by age are provided in Table 12 for all patients and in Table 13 for the subset with T2DM at baseline.

Table 12: Selected baseline characteristics by age (6 cat.) – RS

	Baseline Age					
All patients	**≤ 40**	**41-50**	**51-60**	**61-70**	**71-80**	**≥ 81**
Number	N=529	N=705	N=1151	N=1837	N=1982	N=405
Prior CVD*	N=21	N=46	N=198	N=551	N=760	N=189
HT[#]**	N=474	N=631	N=1028	N=1562	N=1632	N=301
Prior HF*	N=5	N=11	N=75	N=196	N=298	N=73
Fam. T2DM[±]**	-	-	-	-	-	-
Smoking[¥]**	N=150	N=228	N=479	N=882	N=1029	N=181
NGT[$]**	N=463	N=506	N=549	N=534	N=504	N=126

*Evaluated at screening
**Evaluated at baseline
[#]Number of patients with hypertension was not collected by EMPA-KIDNEY trial. Number of patients on RAS-inhibitor at baseline is provided as a proxy
[±]Not collected by EMPA-KIDNEY trial
[¥]Total number of patients who answered 'Yes, still smokes regularly' and 'Yes, but no longer smokes regularly' against 'No' or 'Missing'
[$]NGT was not collected in EMPA-KIDNEY trial. Number of non-diabetic patients with HbA1c <39 mmol/ml provided as a proxy
Abbreviations: CVD, cardiovascular disease; HF, heart failure; HT, hypertension; N, number of patients; NGT, normal glucose tolerant; RAS, renin-angiotensin system;RS, randomised set; T2DM, type 2 diabetes mellitus

Table 13: Selected baseline characteristics by age (6 cat.) in patients with diabetes at baseline – RS

	Baseline Age					
T2DM patients	**≤ 40**	**41-50**	**51-60**	**61-70**	**71-80**	**≥ 81**
Number	N=49	N=114	N=450	N=1053	N=1172	N=202
Prior CVD*	N=5	N=14	N=117	N=378	N=492	N=99
HT[#]**	N=42	N=100	N=396	N=899	N=991	N=163
Prior HF*	N=2	N=4	N=49	N=141	N=199	N=37
Fam. T2DM[±]**	-	-	-	-	-	-
Smoking[¥]**	N=14	N=37	N=201	N=488	N=618	N=88
NGT[$]**	-	-	-	-	-	-

*Evaluated at screening
**Evaluated at baseline
[#]Number of patients with hypertension was not collected by EMPA-KIDNEY trial. Number of patients on RAS-inhibitor at baseline is provided as a proxy
[±]Not collected by EMPA-KIDNEY trial
[¥]Total number of patients who answered 'Yes, still smokes regularly' and 'Yes, but no longer smokes regularly' against 'No' or 'Missing'
[$]Not applicable for patients with T2DM
Abbreviations: CVD, cardiovascular disease; HF, heart failure; HT, hypertension; N, number of patients; NGT, normal glucose tolerant; RS, randomised set; T2DM, type 2 diabetes mellitus

A10. Priority: Please provide the anonymised individual patient Kaplan-Meier data in order to accurately replicate the Cox proportional hazards survival analysis provided in the Company Submission Document B section B.2.6. Please see below example of formatting for the primary outcome of kidney disease progression or adjudicated CV death:

ID	Treatment group	Time to event (days)	Status	Age	Sex	DM Status	eGFR	uACR	Region
1	0	512	2	-	-	-	-	-	-
2	1	2	2	-	-	-	-	-	-
3	1	594	1	-	-	-	-	-	-
4	0	291	2	-	-	-	-	-	-
5	0	469	0	-	-	-	-	-	-
6	1	95	2	-	-	-	-	-	-
7	0	120	1	-	-	-	-	-	-
8	1	418	0	-	-	-	-	-	-
9	0	558	0	-	-	-	-	-	-
10	1	654	2	-	-	-	-	-	-
Where 0 = event free, 1 = kidney disease progression or adjudicated CV death, and 2 = non-CV/renal death (competing risk)									

Company response: The confidential Excel file 'A10_Anonymised individual KM data' sent as an attachment provides the requested anonymised individual patient Kaplan-Meier data in order to accurately replicate the Cox proportional hazards survival analysis provided in the Company Submission Document B Section B.2.6.

A11. Priority: Please provide the raw data and code used in the network meta-analysis to allow the EAG to accurately replicate the NMA, for:

1. **The overall population**
2. **The CKD+T2D subgroup**
3. **Those not in the CKD+T2D subgroup**

Company response: The original network meta-analysis conducted did not include a subgroup of patients with CKD without T2D. Only two trials to date have published outputs in the subgroup of patients with CKD without T2D – EMPA-KIDNEY and DAPA-CKD – and so there are no further datapoints from the extended network to support an analysis. Further, as discussed in the response to question A13, baseline characteristics substantially vary across trials, therefore meaningful comparison is not possible (Table 14). Importantly, baseline risk among patients without T2D in DAPA-CKD could not be identified in publicly available resources, and so cannot be compared with absolute risk among patients in EMPA-KIDNEY. Nonetheless, an attempt to conduct a network meta-analysis for this subgroup was performed and the code is supplied. The results are presented in a confidential addendum to Appendix N (ID6131_EMPAGLIFLOZIN_Addendum to Appendix N_[CIC]).

Table 14: Baseline characteristics of patients with T2DM in EMPA-KIDNEY and DAPA-CKD trials

	EMPA KIDNEY without T2D	DAPA-CKD without T2D
No. of patients (n)	3569	1398
Age, years, mean ± SD	59.3±15.4	56.4±14.6
Sex male, n(%)	2373 (66.5)	938 (67.1)
BMI, kg/m^2, mean± SD	28.0±5.9	27.9
Race or ethnic group (%)		
White	57.4	53.6
Asian	38.8	38.3
Black	2.5	3.9
History of CVD (%)	18.5	23.5
Primary cause of kidney disease		
Hypertensive/ renovascular disease, %	29.2	34.8
Glomerular disease, %	41.9	42.8
Other known, %	28.8	12.5
SBP, mmHg, HbA1c, mean± SD	134.3±17.5	132.6±16.7
DBP, mmHg, mean ± SD	80.2±11.7	79.6±10.9
eGFR, mL/min/1.73m^2, mean ± SD	38.62±15.16	41.7±11.7
eGFR category, mL/min/1.73m^2, %		
>60, %	9.5	7.6
≥45 to <60, %	15.2	29.3
≥30 to <45, %	43.6	47.1
<30, %	31.7	16
uACR, mg/g, median (IQR)	379	861
uACR category, mg/g, %		
<30, %	19.1	0
≥30 to <300, %	25.8	9.7
≥300, %	55.1	90.3

Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR; estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes; uACR, urine albumin-to-creatinine ratio

The raw data and code used in the network meta-analysis are provided in the Word document 'A11_CKD R code'. That document includes 6 sections, as follows:

- Section 1 contains the code required to set up the working directory and install all the necessary packages
- Section 2 contains the code required to run the network meta-analysis (NMA) for all binary outcomes across the overall population dataset, which is titled "A11_Overall_population_binary_outcome_data.xlsx"
- Section 3 contains the code required to run the NMA for all rates outcomes across the overall population dataset, which is titled "A11_Overall_population_rates_outcome_data.xlsx"
- Section 4 contains the code required to run the NMA for all binary outcomes across the CKD + T2DM dataset, which is titled "A11_ckd_t2dm_binary_outcome_data.xlsx"
- Section 5 contains the code required to run the NMA for all rates outcomes across the CKD + T2DM dataset, which is titled "A11_ckd_t2dm_rate_outcome_data.xlsx"
- Section 6 contains the code required to run the NMA for all binary outcomes across the CKD without T2DM dataset, which is titled "A11_ckd_not2dm_binary_outcome_data.xlsx"]

Due to inherent limitations in ITC methodology when there are limited trials with populations that cannot be matched and all prognostic factors and effect modifiers cannot be adjusted for, the NMA results must be interpreted with caution.

Clinical expert opinion indicates there is no difference in treatment effect between empagliflozin and dapagliflozin in similar eligible populations. This is further supported by the entirety of the evidence which has been generated over the years for SGLT2 inhibitors that supports a consistent kidney protective effect across several compounds and in various disease populations and clinical CKD phenotypes. A recent meta-analysis systematically investigated outcomes from 13 trials with SGLT2 inhibitors, which included patients with DM (n = 74,804) and without DM (n = 15,605); trial-level mean baseline eGFR ranged from 37 mL/min/1.73m2 to 85 mL/min/1.73m^2 (1). As described already in Document B.2.9.7, overall, SGLT2 inhibitors reduced the risk of kidney disease progression by 37% (RR 0.63, 95% CI 0.58, 0.69), with similar effects in patients with DM (RR 0.62, 95% CI 0.56,0.68) and without DM (RR 0.69, 95% CI 0.57, 0.82), (heterogeneity by DM status p = 0.31) and consistency across baseline eGFR levels. Likewise, consistent treatment effects on kidney disease progression were observed in both DM and non-DM patients across a broad range of baseline uACR values (1).

Reference:

Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-801.

A12. Figure 41 of Appendix N is a copy of Figure 40. Please provide the corrected figure which should be the assessment of heterogeneity for the all-cause mortality outcome for empagliflozin vs placebo. Similarly, figure 46 is a copy of figure 45, however this should be the assessment of heterogeneity for finerenone. Can you please ensure other figures are correct too (for example, figure 59 also appears to be incorrect).

Company response: An amended Appendix N with corrected figures has been provided as a confidential attachment ID6131_EMPAGLIFLOZIN_Appendix N_CIC__v2.

A small number of figures were updated. All conclusions remain the same, aside from the composite renal outcome definition 2 (50% threshold) and the all-cause hospital admission rates.

For the composite renal outcome definition 2 (50% threshold), it was noted that the random effects (RE) model cross table was incorrectly copied instead of the fixed effects (RE) model figure. Both RE and FE model results are now shown for all outcomes. In the FE model (Figure 53 of the corrected Appendix N), [redacted] (Figure 155 of the corrected Appendix N). It should be noted that this is an exploratory analysis of a non-EMPA-KIDNEY outcome and differences in the patient populations of the two trials and in follow up time contribute to the uncertainty on this outcome. Furthermore, the limited number of studies in the ‘network’ for this outcome prevents accurate estimation of the heterogeneity parameter, so uncertainty in

the heterogeneity parameter shows up as uncertainty in the CrIs for the relative treatment effects.

For the all-cause hospital admission, there is no longer a difference between empagliflozin and finerenone. This change is due to a correction following the incorrect use of the table for OR instead of RR (the latter is the correct outcome measure for rates).

A13. Please provide the full assessment of the feasibility of performing a matching-adjusted indirect comparison (MAIC) that was performed by the company. This includes:

1. **Identification and justification of the key variables that are to be matched.**
2. **Statistical methods including matching algorithm, adjustment techniques, and models used to estimate treatment effects.**
3. **A summary and comparison of the key variables across all the studies considered in the MAIC feasibility assessment.**

Company response: In the presence of a connected network of RCTs, an NMA is the gold standard for indirect treatment comparisons. An anchored NMA was selected as there is a connected network of interventions with a common comparator, and the use of NMA preserves randomization by using relative versus absolute effects. As an NMA preserves randomization, both reported and unreported sources of heterogeneity are accounted for. A MAIC is more sensitive to differences in prognostic factors, and there are known differences between EMPA-KIDNEY and DAPA-CKD in terms of baseline patient characteristics, such as history of CVD, T2D, CKD cause (glomerular disease, diabetic nephropathy, other causes of CKD, distribution of eGFR and UACR categories, differences in HbA1c. In addition, the population of interest corresponded to that of the full population of EMPA-KIDNEY, which means; a MAIC would weight outcomes to match that of DAPA-CKD by down-weighting (to zero) patients with eGFR 20-45 ml/min/1.73m^2 with UACR <200 mg/g, who were explicitly permitted in EMPA-KIDNEY but excluded from DAPA-CKD. Furthermore, a MAIC ignores correlations between covariates, which may affect the performance of the method as correlations deemed to differ between studies. As the correlation of covariates within DAPA-CKD is unknown, it was not possible to assess how it may differ from that of EMPA-KIDNEY. Finally, event rates in the comparator arms of DAPA-CKD and EMPA-KIDNEY differ, suggesting differing underlying absolute risk of outcomes of interest that is not due to CKD status alone; an analysis of relative effects via an NMA accounts for differences in placebo effects between studies while a MAIC may be biased unless all prognostic factors and effect modifiers are adjusted for. Based on the above limitations, the conduct of a reliable MAIC was deemed not feasible.

Table 15 shows a comparison of key characteristics of patients in DAPA-CKD and EMPA-KIDNEY, including a subset of EMPA-KIDNEY patients who would have met the eGFR and uACR inclusion criteria for DAPA-CKD (the ‘DAPA-CKD eligible’ column). Reported event rates from the placebo arms of each trial (and the DAPA-CKD eligible patients of EMPA-KIDNEY) are also presented.

Table 15: Patient characteristics and event rates in EMPA-KIDNEY and DAPA-CKD

	EMPA-KIDNEY	**DAPA-CKD Eligible (EMPA-KIDNEY)**	**DAPA-CKD**
SGLT2 inhibitor	**Empagliflozin**	**Empagliflozin**	**Dapagliflozin**
No. of patients (n)	6,609		4,304
Age, years, mean ± SD	63.8±3.9		61.8±12.1
Sex male, n(%)	4,417 (67)		2879 (67)
BMI, kg/m^2, mean± SD	29±6.8		29.5
Race or ethnic group (%)			
White	58		53
Asian	36		34
Black	4.0		4.4
History of CVD (%)	27		37
Primary cause of kidney disease			
Diabetic nephropathy or diabetic kidney disease*, %	31		58
Hypertensive/ renovascular disease, %	22		16
Glomerular disease, %	25		16
Other known, %	12		5
DM, %	46		68
T1DM*, %	1		n/a
T2DM, %	44		68
Other/unknown n,%	1		n/a
HbA1c, %, mean ± SD	6.3± 3.4		7.1±1.7
HbA1c, mmol/mol, mean ± SD	45±13.6		54±19
SBP, mmHg, HbA1c, mean± SD	136±18.3		137.1±17.4
DBP, mmHg, mean ± SD	78.1± 1.8		77.5±10.5
eGFR, mL/min/1.73m^2, mean ± SD	37.5±14.8		43.1±12.4
eGFR category, mL/min/1.73m^2, %			
>60, %	7.7		11
≥45 to <60, %	21.2		31
≥30 to <45, %	44.3		44
<30, %	34.5		15

uACR, mg/g, median (IQR)	329.35 (48.53, 1068.93)	[redacted]	949 (477-1885)
uACR category, mg/g, %			
<30, %	20.1	[redacted]	0
≥30 to <300, %	28.2	[redacted]	10
≥300, %	51.7	[redacted]	90
Event rates in the placebo arm (Incidence rate [patients with events per 100 patient years at risk])			
	EMPA-KIDNEY	**DAPA-CKD Eligible (EMPA-KIDNEY)**	**DAPA-CKD**
HHF or CV death	2.37	[redacted]	3.0
All-cause mortality	2.58	[redacted]	3.1
CV death	1.06	[redacted]	1.7
Dapa-like primary endpoint (50% eGFR decline cut off)	6.14 (5.54-6.77)	[redacted]	7.5 (95% CI not reported)

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR; estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; uACR, urine albumin-to-creatinine ratio

A14. Please tabulate the data, n, and N separately by arm, of Appendix E Figures 1, 2, 3, 4, 5 and 6. Additionally, please tabulate this data for the subgroup with diabetes at baseline.

Company response: The requested data from Appendix E had been tabulated in Table 16 for all patients and in Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; HR, hazard ratio

Table 17 for the subset of patients with T2DM at baseline.

Table 16: Compilation of time to first event/occurrence and annual rate of change in eGFR data for overall population in EMPA-KIDNEY trial

	Empagliflozin (n/N)	**Placebo (n/N)**	**HR (95% CI)**
Time to the first event of kidney disease progression or adjudicated CV death	432/3304	558/3305	0.72 (0.64 – 0.82)
Time to occurrence of all-cause hospitalisation	1611/3304	1895/3305	0.86 (0.78 – 0.95)
Time to first occurrence of HHF or CV death	131/3304	152/3305	0.84 (0.67 – 1.07)
Time to adjudicated death from any cause	148/3304	167/3305	0.87 (0.70 – 1.08)
	Empagliflozin (N)	**Placebo (N)**	**Estimate (95% CI)**
Annual rate of change in eGFR from 2 months to final follow-up- (chronic slope), allowing for events of ESKD or death (ml/min/year/1.73m^2)	3219	3218	1.37 (1.16 – 1.59)

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; HR, hazard ratio

Table 17: Compilation of time to first event/occurrence and annual rate of change in eGFR data for subgroup of patients with T2DM in EMPA-KIDNEY trial

	Empagliflozin (n/N)	**Placebo (n/N)**	**HR (95% CI)**
Time to the first event of kidney disease progression or adjudicated CV death	218/1525	252/1790	0.82 (0.68 – 0.99)
Time to occurrence of all-cause hospitalisation	956/1525	1114/1515	0.86 (0.75 – 0.98)
Time to first occurrence of HHF or CV death	96/1525	118/1515	0.78 (0.60 – 1.03)
Time to adjudicated death from any cause	101/1525	123/1515	0.80 (0.61 – 1.04)
	Empagliflozin (N)	**Placebo (N)**	**Estimate (95% CI)**
Annual rate of change in eGFR from 2 months to final follow-up- (chronic slope), allowing for events of ESKD or death (ml/min/year/1.73m^2)	1500	1476	1.68 (1.36 – 2.00)
Annual rate of change in eGFR from baseline to final follow-up (total slope), allowing for events of ESKD or death (ml/min/year/1.73m^2)	1525	1515	0.90 (0.59 – 1.21)

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; HR, hazard ratio

Section B: Clarification on cost-effectiveness data

General

B1. The means of Document B Table 29 do not correspond with the means of Document B Figure 18. Please provide an account of this

Company response: Document B Figure 18 plots the average eGFR (mL/min/1.73m^2) per visit and treatment group estimated using a mixed-model-repeated measure. The mean total and chronic slopes for each treatment annotated to Document B Figure 18 are based on the shared parameter model (RS, OC-AD), the main analysis model in EMPA-KIDNEY for the annual rate of change (slopes) in eGFR that accounts for ESKD or CV death as competing risks. Document B Table 29 tabulates the annual rate of change in eGFR (mL/min/1.73m^2) from baseline to final follow-up for each treatment group by baseline Kidney Disease Improving Global Outcomes (KDIGO) categories.

Due to the complexity and frequency of convergence issues when using shared parameter models in small subgroups, random slope, and intercept models (RS, OC-AD) were used instead for this table, which do not take account of potential competing risks. The random slope and intercept model was also used as a sensitivity to the EMPA-KIDNEY main analysis of annual rate of change in eGFR and the total row displayed in Document B Table 29 corresponds to this sensitivity analyses (Table 18 shown below; Table 15.2.4.3.2: 3 in clinical trial report [CTR]). The results of the shared parameter and random slope and intercept models for the EMPA-KIDNEY main analysis were consistent with one another.

Table 18: Random slope and intercept model for annual rate of change in eGFR (centrally assessed) from baseline to final follow−up (total slope) − RS (OC−AD)

Factor Comparison	N analysed	Estimate	SE	95% CI		P value
				LL	UL	
Intercept						
Placebo intercept	3,218	37.05	0.23	36.60	37.51	<0.0001
Empa 10mg intercept	3,219	36.00	0.23	35.54	36.45	<0.0001
Time						
Placebo slope [/year]		−2.68	0.07	-2.82	-2.53	<0.0001
Empa 10mg slope [/year]		−1.96	0.07	-2.11	-1.82	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		0.71	0.10	0.51	0.91	<0.0001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LL, lower limit; N, number of patients; OC−AD, Observed Case-All Data; RS, randomised set; SE, standard error; UL, upper limit

B2. For Document B Table 29 please clarify whether the data uses all the trial eGFR change data or only the "chronic" phase, whether all eGFR follow-up data was used rather or an arbitrary cut-off such as the 18-month cut-off as applied in the uACR analysis and whether the analysis was OC-AD or OC-OT. Why was it necessary to "match" SoC to empagliflozin and what did this involve? Please provide any internal report on this matching analysis. Please also clarify how a normal distribution was fitted to the data rather than using the raw data: is this just imposing a normal distribution to the individual health state eGFR declines after the raw data has been calculated (the stated means being very close to the means of the 95% Cis) or is this something more complicated like a joint normal over eGFR and uACR and if so what did this involve? To further clarify how the eGFR change data has been analysed please assume for the following that all patients are in the empagliflozin arm, remain in A2 throughout, and, aside from the last bullet, remain on empagliflozin treatment throughout. For the following it would be appreciated if the worked examples could be provided within excel. Ignoring the fitting of the normal distribution and matching to SoC:

1. **Patient A has an eGFR 59 at baseline, 55 at 2 months, 54 at 6 months, 53 at 12 months, 52 at 18 months and 51 at 24 months, after which they are LTFU. How is the annual rate of eGFR change calculated for this patient? Or if more than one annual rate is calculated; e.g. two annual rates, baseline to 12 months and 12 months to 24 months, or four six monthly rates with these then being doubled to annualise them or even 5 rates of duration 2, 4, 6, 6 and 6 months which are then annualised, please outline how these are calculated and what the resulting values are.**

2. **Patient B has an eGFR 55 at baseline, 54 at 2 months, 50 at 6 months, 47 at 12 months, 43 at 18 months, 40 at 24 months, 37 at 30 months and 35 at 36 months, after which they are LTFU. Noting that this patient changes from G3a to G3b at an indeterminate point between 12 months and 18 months, how are this patient's**

annual rate(s) of eGFR change calculated, how are they attributed to G3a and G3b health states and what are the resulting values for G3a and G3b.

3. **Patient C has an eGFR of 40 at baseline, 43 at 2 months, 41 at 6 months, 43 at 12 months, 48 at 18 months, 49 at 24 months and 55 at 30 months, after which they are LTFU. How are this patient's annual rate(s) of eGFR calculated and what are the resulting values.**

4. **How are the annual rates of eGFR change of Patients A, B and C combined to give pooled rates of decline for G3a and G3b and what are the resulting values?**

5. **How would the calculations change if Patient A discontinued empagliflozin treatment at 12 months but remained followed up for eGFR throughout.**

Company response: Document B Table 29 tabulates the annual rate of change in eGFR [mL/min/1.73m^2] from baseline to final follow-up (total slope – RS, AD) by treatment group overall and in the KDIGO baseline categories estimated from a random slope and intercept model. The random slope and intercept model provides a single estimate (one annual rate) reflecting the decline over time and includes all eGFR data from baseline to final follow-up. The subgroup analysis displayed in Document B Table 29 is based on KDIGO categories at baseline only, no transitions between KDIGO categories during the trial are considered in the random slope and intercept model. Patients were allocated to KIDIGO categories as randomised; no matching was performed. The word 'matched' was used inappropriately to describe 'corresponding' patients in the placebo arm.

The model estimates the average annual rate of change in eGFR [mL/min/1.73m^2] per treatment group as fixed effects and in addition includes random effects that allow for patient-specific deviations in intercept and slope from the group averages. As these random effects cannot be estimated down to a specific patient level the random slope and intercept model used in Document B Table 29 cannot be used to calculate annual rates as asked for in 1 to 5 above. As an alternative the excel file "B2 worked example simplified" has fitted ordinary least squares slope estimates to the eGFR values of the patients detailed in 1), 2), 3). The monthly slope estimates are re-scaled to provide annual rates of change in eGFR to align with the presentation in Document B Table 29. A summary is provided below:

1. Fitted by the simplified ordinary least squares regression and ignoring any random effects of the random slope and intercept model, this patient's annual rate of change in eGFR is estimated to be -3.19 mL/min/1.73m^2.

2. Fitted by the simplified ordinary least squares regression and ignoring any random effects of the random slope and intercept model, this patient's annual rate of change in eGFR is estimated to be – 6.82 mL/min/1.73m^2. This regression model and the random slope and intercept model used for Document B Table 29 assume constant annual rates of change over the complete follow-up period. Changes in KDIGO risk category over time are not considered in the modelling, Patient B would appear in Document B Table 29 according to his/her baseline KDIGO risk category.

3. All values until a patient is lost to follow-up have been included in the random slope and intercept model in Document B Table 29 (RS, OC-AD). Fitted by the simplified

ordinary least squares regression and ignoring any random effects of the random slope and intercept model, this patient's annual rate of change in eGFR is estimated to be 5.35 mL/min/1.73m^2.

4. In this case the random slope and intercept model in Document B Table 29 considers that measurements taken from the same patient over time are more correlated than measurements taken from different patients by including patient-specific random slopes and intercepts in the model. Similarly, to the worked example above, the random slope and intercept model assumes constant annual rates of change over the complete follow-up period. However, by including the subject-specific random-effects, this model allows for adjustment for subject-specific random deviation from the estimated treatment group-specific average annual rates of changes.

5. Document B Table 29 is based on RS, OC-AD. The calculation would not change in case 5.

B3. Please clarify if the EMPA-KIDNEY 18-month uACR changes in Document B Table 31 have been annualised or if they remain 18-month changes. Please clarify to what extent the same calculations for uACR annual changes matched the calculations for eGFR, as queried in the question B2 above. Please clarify why the uACR data was arbitrarily cut-off at 18 months and the effect of extending this analysis to an OC-AD of all trial data, i.e., to 36 months. If it is felt appropriate, please also provide an OC-OT analysis of all trial data

Company response: Document B Table 31 presents the relative changes from baseline to Month 18 for each treatment group (overall and by baseline KDIGO category) in the form of a ratio of the adjusted geometric means; they have not been annualised. The methods of analysis and estimates presented in Document B for Tables 31 and 29 are very different and not comparable.

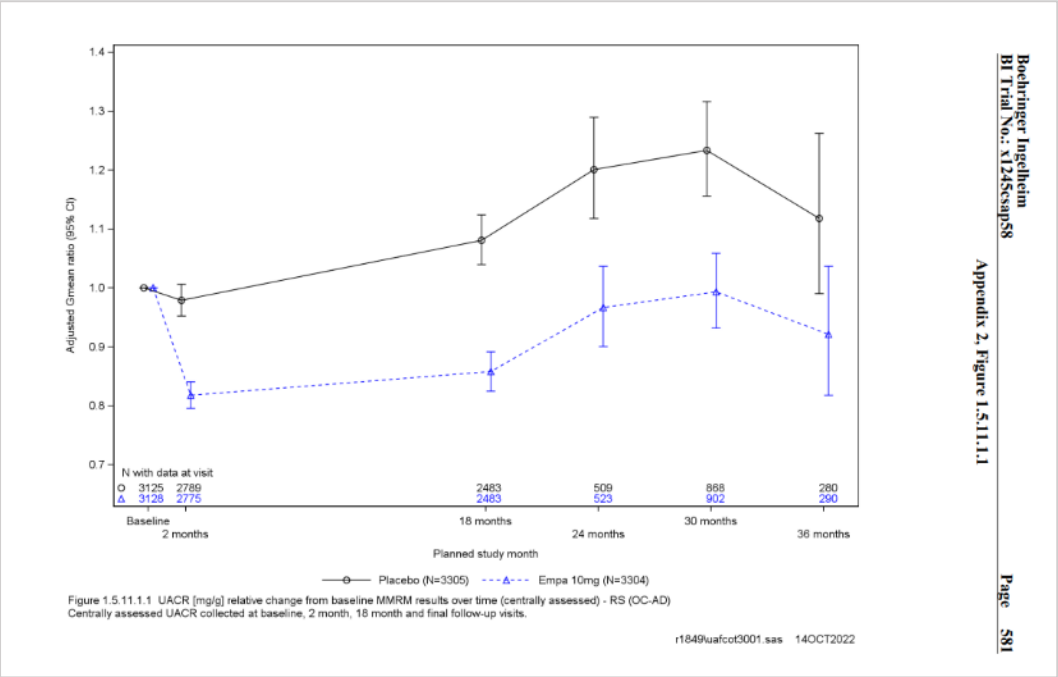
uACR was only scheduled for collection post-baseline at 2 months, 18 months, and the final follow-up visit (slotted to pre-defined visit windows); hence the 18-month analysis and summary presented. A mixed-model-repeated-measures analysis was performed on the uACR data, providing geometric mean values at each scheduled time-point along with the ratios relative to baseline (a value <1 indicating a reduction from baseline and a value >1 an increase from baseline). There was insufficient data to warrant a slope analysis as performed on the eGFR data (refer to responses to B1 and B2 for more detail on the eGFR analysis).

The ratio of the uACR geometric means at each scheduled visit relative to baseline are presented in Figure 8 (OC-AD) (R1849, 1.5.11.1.1) and Figure 9 (Observed Case-On Treatment [OC-OT]) and are largely consistent over time. Given this, utilising 18 months values as a proxy for values at 12 months was deemed plausible from a disease state perspective.

In the submitted base case, the treatment effect of empagliflozin on uACR applied at 12 months (derived using 18-month values) is repeated each year on treatment. A scenario was conducted in which the treatment effect only applies for the first 12 months on treatment, keeping the value unchanged for the remaining time on treatment. In this scenario, empagliflozin is dominant (less cost, more quality adjusted life years [QALYs]) vs standard of

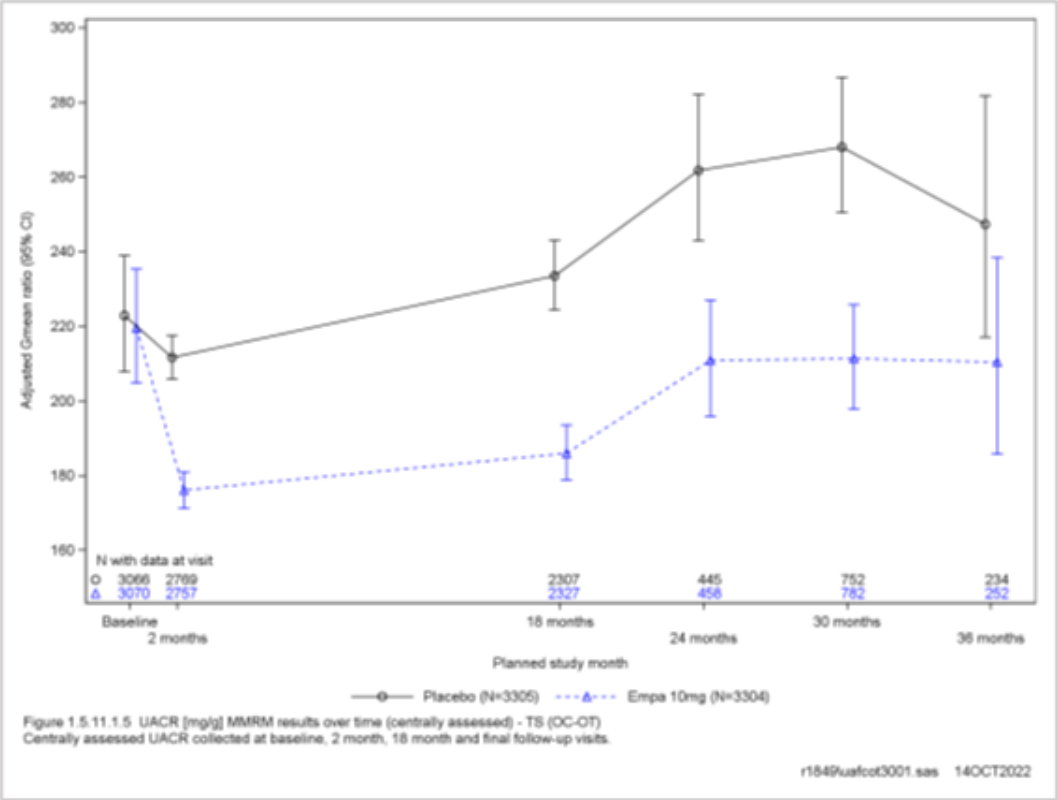
care (SoC) alone, with a net monetary benefit of £14,214. The full results are presented in “B3 model scenario results”. This scenario may be regarded as extreme, as treatment effects on uACR are expected to extend beyond 12 months on treatment.

Figure 8: uACR (mg/g) relative change from baseline MMRM results over time - RS (OC-AD)



Abbreviations: CI, confidence interval; MMRM. Mixed model with repeated measurements; N, number of patients; OC-AD, Observed Case-All Data; SE, standard error; TS, treated set; UACR, Urine albumin-to-creatinine ratio

Figure 9: uACR (mg/g) relative change from baseline MMRM results over time - TS (OC-OT)



Abbreviations: CI, confidence interval; MMRM. Mixed model with repeated measurements; N, number of patients; OC-OT, Observed Case- On Treatment; TS, treated set; UACR, Urine albumin-to-creatinine ratio

B4. Priority: Please provide equivalents of Document B Table 29 separately for the OC-AD data and the OC-OT data (12 Tables, one presumably being as per Table 29):

1. **For all patients**
2. **For the subset of patients with T2DM at baseline**
3. **For the subset of patients without T2DM at baseline**
4. **Without matching to SoC or fitting a normal distribution to the data supply the mean values and s.e. values (rather than fitted normal C.I.), i.e., the nearest to the raw trial data as possible:**
    a) **For all patients**
    b) **For the subset of patients with T2DM at baseline**
    c) **For the subset of patients without T2DM at baseline**

Company response: Please note, as explained in the company response to question B2, patients were analysed as randomised, there was no additional matching performed, the word “matched” was incorrectly used, meaning “corresponding “values. Therefore, a total of 6 tables are presented in response to this question, rather than the 12 requested.

Table 19 and Table 22 provide the equivalent of Document B Table 29 – annual change in eGFR across KDIGO categories – for all patients for the OC-AD and OC-OT data, respectively.

Further split of patients with and without diabetes per KDIGO category analyses have inherent limitations. For the subgroups of patients with and without T2DM at baseline, annual change in eGFR is presented across uACR categories rather than KDIGO categories due to

convergence issues with small subgroup sizes. The analyses are not adjusted for multiple testing, and outputs reported in small subgroups are prone to random variation and might not be representative of the true treatment effect. Table 20 and Table 21 present OC-AD data for patients with and without T2DM, respectively, and Table 23 and Table 24 present OC-OT data for patients with and without T2DM.

For the CEA, treatment effect in the overall population was applied in all scenarios for patients while on treatment rather than subgroup's specific treatment effect, this assumption was driven by limitation of the size of the dataset and supported by the evidence of T2DM not being a treatment effect modifier (1). Upon treatment discontinuation, differential annual eGFR decline rates are used for patients with and without T2DM (based on published literature supporting faster CKD progression among patients with T2DM).

Table 19: Annual eGFR change in patients receiving empagliflozin and SoC – RS (OC-AD) all patients

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3a	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA: not available; OC-AD, Observed Case-All Data; RS, randomised set; SoC, standard of care

Table 20: Annual eGFR change in patients receiving empagliflozin and SoC – RS (OC-AD) patients with diabetes at baseline

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OC-AD, Observed Case-All Data; RS, randomised set; SoC, standard of care

Table 21: Annual eGFR change in patients receiving empagliflozin and SoC – RS (OC-AD) patients without diabetes at baseline

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OC-AD, Observed Case-All Data; RS, randomised set; SoC, standard of care

Table 22: Annual eGFR change in patients receiving empagliflozin and SoC – TS (OC-OT) all patients

	Mean annual eGFR change – mL/min/1.73m² (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3a	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA, not available; OC-OT, Observed Case-On Treatment; TS, treated set; SoC, standard of care

Table 23: Annual eGFR change in patients receiving empagliflozin and SoC – TS (OC-OT) patients with diabetes at baseline

	Mean annual eGFR change – mL/min/1.73m² (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OC-OT, Observed Case-On Treatment; TS, treated set; SoC, standard of care

Table 24: Annual eGFR change in patients receiving empagliflozin and SoC – TS (OC-OT) patients without diabetes at baseline

	Mean annual eGFR change – mL/min/1.73m² (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OC-OT, Observed Case-On Treatment; TS, treated set; SoC, standard of care

Reference:

1. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-801

Modelling

B5. It appears that the model estimates, particularly net costs, do not converge for a deterministic model run over 1,000 patients. The only means of addressing this within the current model appears to be to rerun the model a number of times with a random seed as per the enclosed model: ID6131 ERG Multi Run Random Seed- Disagg – 2023-07-06 – Run Company Base Case.xlm: see within it the ERG_Multi_Run worksheet and the ERG submodule within the Excel VBA. Does this provide a correct multirun of the model; i.e. 50 multiruns is equivalent to modelling 50,000 patients? What number of patients need to be run through the deterministic model for net costs, net QALYs and NHBs to all converge? Is there a simpler means of increasing the number of patients run through the deterministic model towards 20 thousand or so and can such a model be supplied, changing only this aspect of the model from that originally submitted? Also in this regard, to avoid the variability caused by patient heterogeneity and to only sample the "average" patient repeatedly is it sufficient in the model VBA in Getrand_patient() to revise Arr_patient(i, 1) = Rnd to Arr_patient(i, 1) = 0.5, or would other changes have to be made and if so, what?

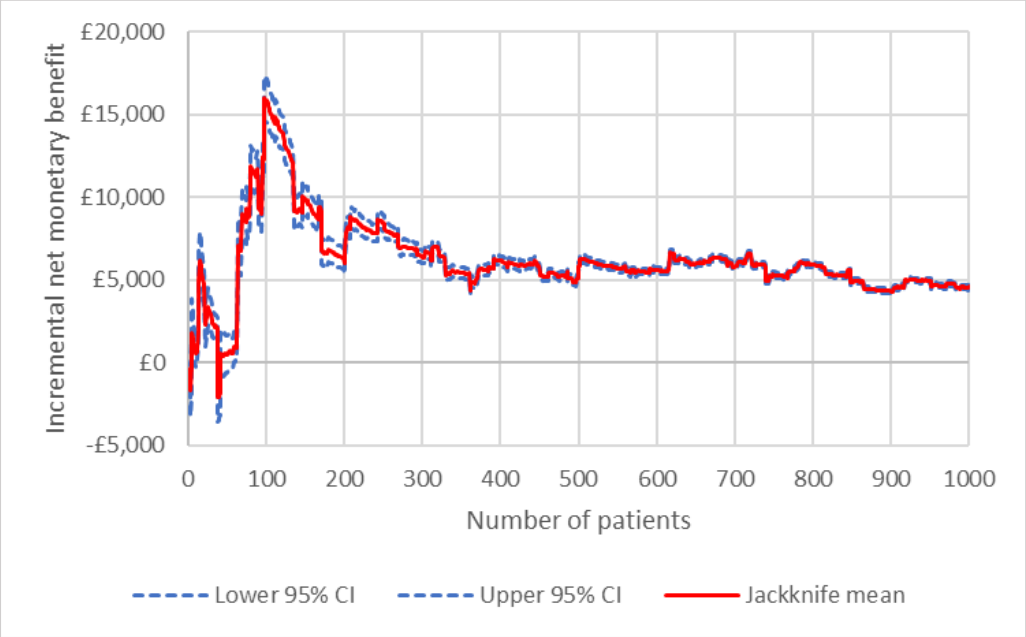
Company response: The CKD progression model (CKD-PM) presented in this submission was designed to accommodate a maximum of 1,000 patients per simulation run. This maximum limit was determined as a result of need to balance between sufficient convergence of net monetary benefit (NMB) value in the base case (cf. Figure 10, Figure 11, Figure 12, and Figure 13) and model performance/ability to produce results with scenarios and sensitivity analysis within a reasonable timeframe. 50 multi-runs of the model are equivalent to 50,000 patients provided the seed is kept random for each run. We added a user-defined seed option to enable a repeatable base case. The external assessment group (EAG) should note that as per convention, the seed must be fixed in order for convergence testing. This is the approach taken in the CKD-PM, as well as the IQVIA Core diabetes model. If the seed is not fixed, for each chance node the seed is different, and so an additional and inappropriate level of variability is added to the model. Fixed seeds are necessary to preserve patient randomisation and so patients in each model arm are comparable. With random seed, unnecessary heterogeneity is introduced between samples, precluding meaningful comparison of treatment effect between cohorts.

A series of scenarios were run in the model, using Seed 0.7, Seed 1, Seed 5, Seed 10 and Seed 23. Each of these are presented in the file "B5_model scenario results". In each scenario, empagliflozin is dominant (less cost, more QALYs) vs SoC alone, with net monetary benefit being relatively stable across the scenarios (ranging from £18,842 to £23,916).

Figure 10, Figure 11, Figure 12, and Figure 13 below indicate a good convergence of the mean totals and incremental costs and net monetary benefit (NMB) with 1,000 patients. Simulating several thousands of patients per run is not necessary as the model does converge well with 1,000 patients. In addition, this would lead to computation times exceeding 10-15 minutes per simulation run, making it impossibility to perform the full range of validity tests with each model option, within a reasonable time. Using an alternative modelling software was opted out, because an Excel-based model with limited use of Visual Basic for Applications (VBA) macros remains preferred modeling platform by most of HTA bodies due to its transparency and relatively easy review process.

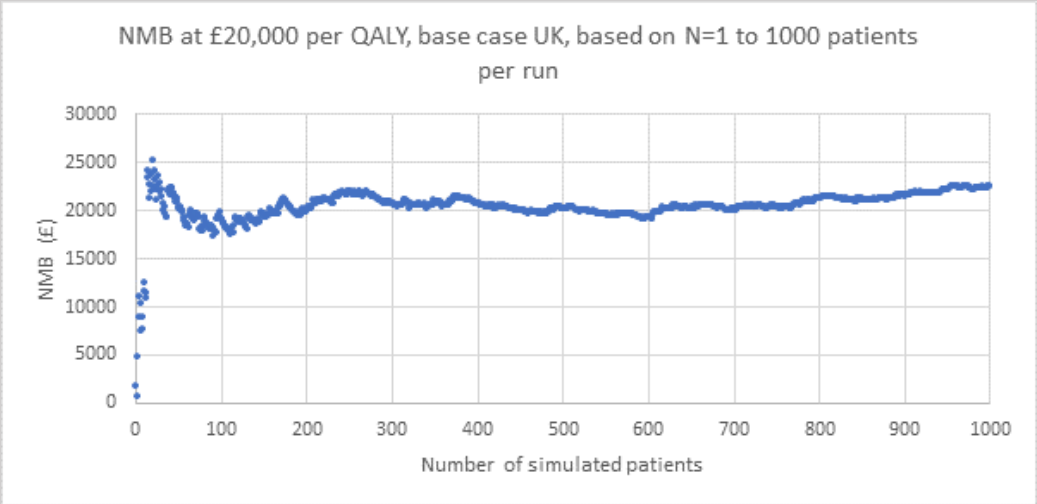
The simulation based on a “fixed” patient profile was not considered because it would be against the concept behind the CKD model: aiming to capture heterogeneity of the CKD patient population. In addition, most risk equations used in the model would not provide exact results if binary risk factors (such as sex, diabetes, or smoking status) are replaced with their average prevalence.

Figure 10: Convergence of NMB in the company model



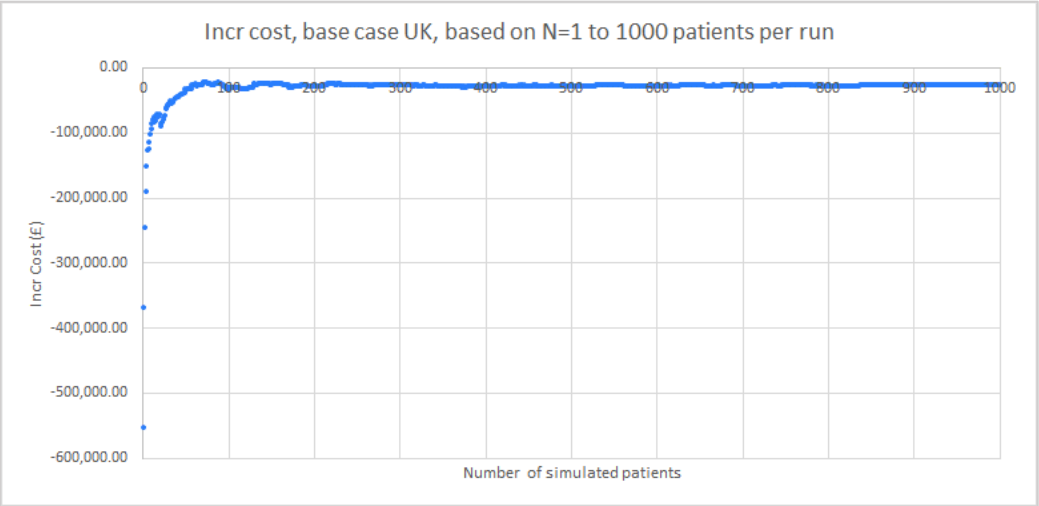
Abbreviations: CI, confidence interval; NMB, net monetary benefit

Figure 11: Convergence of NMB in the company model



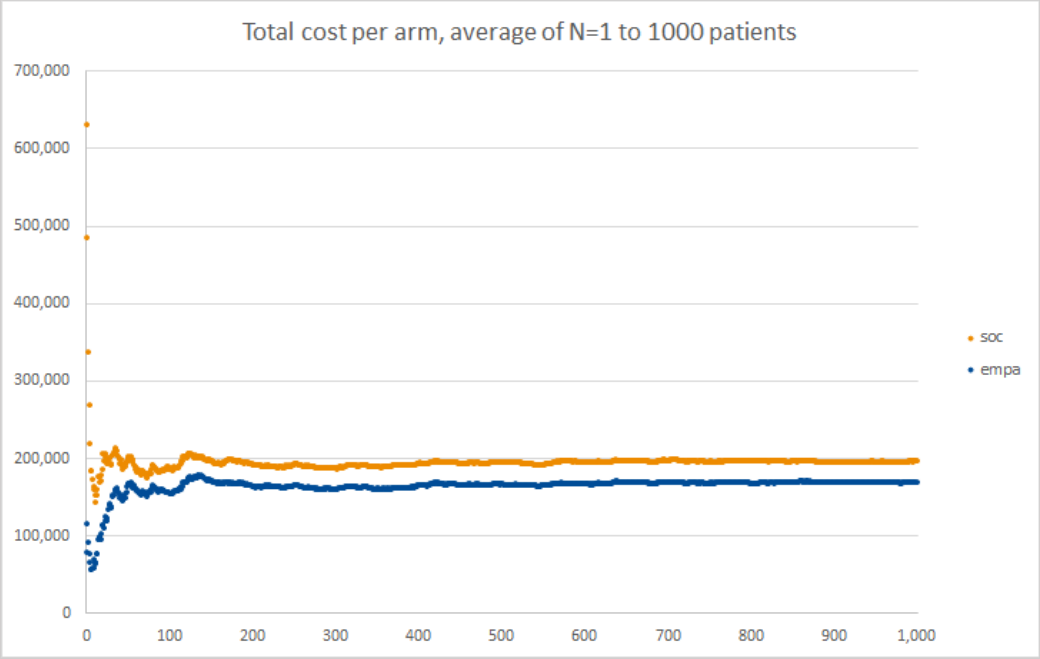
Abbreviations: N, number of simulated patients; NMB, net monetary benefit; QALY, quality adjusted life years

Figure 12: Convergence of mean incremental cost in the company model



Abbreviations: Incr, incremental; N, number of simulated patients

Figure 13: Convergence of mean total cost in the company model



Abbreviations: N, number of simulated patients, soc, standard of care

B6. Please provide the equivalent of *Other_default_data* F119:F172, F201:F203, F215, L119:L172, L201:L203, and L215 separately for (A) the subset of EMPA-KIDNEY with T2DM at baseline and (B) the subset of EMPA-KIDNEY without T2DM at baseline.

Company response: The requested data, where available, are presented below in Table 25, Table 26, Table 27 and Table 28.

Table 25: Incremental treatment effect per risk factor in EMPA-KIDNEY for patients with DM

Incremental treatment effects for the full cohort	Empagliflozin 10mg	Placebo

HbA1c	-0.2	-0.8
Weight	-3.47	-2.83
Hb	0.75	-0.14
SBP	-6.7	-3.3
DBP	-3.0	-0.9

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; Hb, haemoglobin; HbA1c, glycated haemoglobin; SBP, systolic blood pressure

Table 26: Incremental treatment effects per health state for patients with diabetes at baseline

Incremental treatment effects per health state	Empagliflozin 10mg	Placebo
eGFR annual change		
eGFR: G2A2	0.81	-3.05
eGFR: G2A3	-3.73	-5.63
eGFR: G3aA1	NR	NR
eGFR: G3aA2	-1.89	-3.22
eGFR: G3aA3	-3.15	-5.55
eGFR: G3bA1	-0.46	-0.61
eGFR: G3bA2	-0.91	-1.78
eGFR: G3bA3	-3.12	-4.17
eGFR: G4A1	0.15	-0.10
eGFR: G4A2	-0.25	-0.57
eGFR: G4A3	-2.33	-3.84
uACR ratio change*		
uACR: G2A2	0.94	0.80
uACR: G2A3	0.53	0.67
uACR: G3aA1	NR	NR
uACR: G3aA2	0.62	0.89
uACR: G3aA3	0.39	0.59
uACR: G3bA1	1.65	1.69
uACR: G3bA2	0.77	1.09
uACR: G3bA3	0.55	0.77
uACR: G4A1	1.93	2.55
uACR: G4A2	0.93	1.34
uACR: G4A3	0.64	0.90

*For patients without diabetes change from baseline uACR is reported for 18 months. Abbreviations: eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio

Table 27: Incremental treatment effect per risk factor in EMPA-KIDNEY for patients without DM

Incremental treatment effects for the full cohort	Empagliflozin 10mg	Placebo
HbA1c	0.2	0.4
Weight	-1.79	-0.71
Hb	0.52	-0.14
SBP	-1.4	-1.3
DBP	-2.2	-2.3

Abbreviations: DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, glycated haemoglobin; SBP, systolic blood pressure

Table 28: Incremental treatment effects per health state for patients without diabetes at baseline

Incremental treatment effects per health state	Empagliflozin 10mg	Placebo
eGFR annual change		
eGFR: G2A2	-2.96	-2.60
eGFR: G2A3	-3.19	-4.88
eGFR: G3aA1	NR	NR
eGFR: G3aA2	-1.29	-1.19
eGFR: G3aA3	-3.63	-4.19
eGFR: G3bA1	-0.68	-1.07
eGFR: G3bA2	-1.17	-1.34
eGFR: G3bA3	-2.72	-4.07
eGFR: G4A1	-0.81	-0.22
eGFR: G4A2	-1.07	-1.20
eGFR: G4A3	-3.20	-3.71
uACR ratio change*		
uACR: G2A2	1.58	1.16
uACR: G2A3	0.67	0.82
uACR: G3aA1	NR	NR
uACR: G3aA2	1.08	1.05
uACR: G3aA3	0.73	0.80
uACR: G3bA1	1.60	1.73
uACR: G3bA2	1.03	1.16
uACR: G3bA3	0.80	0.77
uACR: G4A1	3.01	2.06
uACR: G4A2	1.97	1.97
uACR: G4A3	0.65	0.95

*For patients without diabetes change from baseline uACR is reported for 30 months. Abbreviations: eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio

B7. For *Risk_Factors_Inputs* the Sumproduct(I66:I75,J66:J75) = -0.24 and the Sumproduct (I66:I75,K66:K75) = -0.73. Please provide an account of this and their relation to Document B B.3.3.2.1 and the stated fitted mean of -0.60. Please clarify if this value is sampled within the deterministic (i.e., non-PSA) modelling and if so, why this value is sampled. Please tabulate the effect upon the deterministic total costs in each arm and total QALYs in each arm of (1) sampling this value based upon the actual *Risk_Factors_Inputs* I66:I17 distribution, (2) not sampling this value and applying -0.24 throughout, (3) not sampling this value and applying -0.60 throughout, and (4) not sampling this value and applying -0.73 throughout. Please ensure that the model has converged when reporting this.

Company response: In preparing this response, we have noted a misstatement in Document B, Section B.3.3.2.1 whereby Naimark et al. (2016) is referred to as used in the base-case for modelling eGFR progression post treatment discontinuation. This is incorrect and due to mis-transposition of the technical model report only. The analyses presented in this submission do not use Naimark et al. (2016), but instead use Grams et al. 2020[1] data to model the progression of eGFR in CKD. Naimark et al. (2016) is a modelling option that was not selected in the cost-effectiveness analysis (CEA). The utilized Grams et al. 2020 data can be seen in CKD-PM tab *Risk_Factors_Inputs G51:I54* and *G56:I59*. Therefore, this question is linked to a model option that was not used in the CEA.

Grams et al. (2020) reports eGFR decrements per KDIGO categories as observed in the CRIC registry. This approach was chosen as it allows to reflect different rate of eGFR decline over time depending on CKD disease stage and presence of markers of kidney damage.

Table 29: eGFR annual change per Grams et al. 2020 (mL/min/1.73m^2)

eGFR annual slope	Patients with DM			Patients without DM		
	A1	A2	A3	A1	A2	A3
G1/2	-0.8	-2.2	-4.6	-0.1	-1.0	-3.1
G3a	-0.3	-2.1	-4.6	-0.2	-1.5	-4.0
G3b	-0.3	-1.5	-4.5	-0.2	-1.4	-3.2
G4/5	-0.1	-1.1	-3.6	-0.2	-1.2	-2.8

Source: Grams et al. 2020. Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate

The option described in Table 30 of Document B B.3.3.2.1 uses data from the chronic kidney disease - peritoneal dialysis (CKD-PD) registry reported in Naimark et al. This study reports the distribution of eGFR decrements for a CKD population, independently of the health state, but it allows inclusion of different CKD patient profiles with improvements and declines in eGFR, and it also represents fast and slower progressor patients in CKD. The shape of this curve is irregular, and it was fitted to a standard Microsoft Excel® distribution by visual inspection. This curve is used to select a different eGFR decrement or increment for each individual patient per cycle through random sampling.

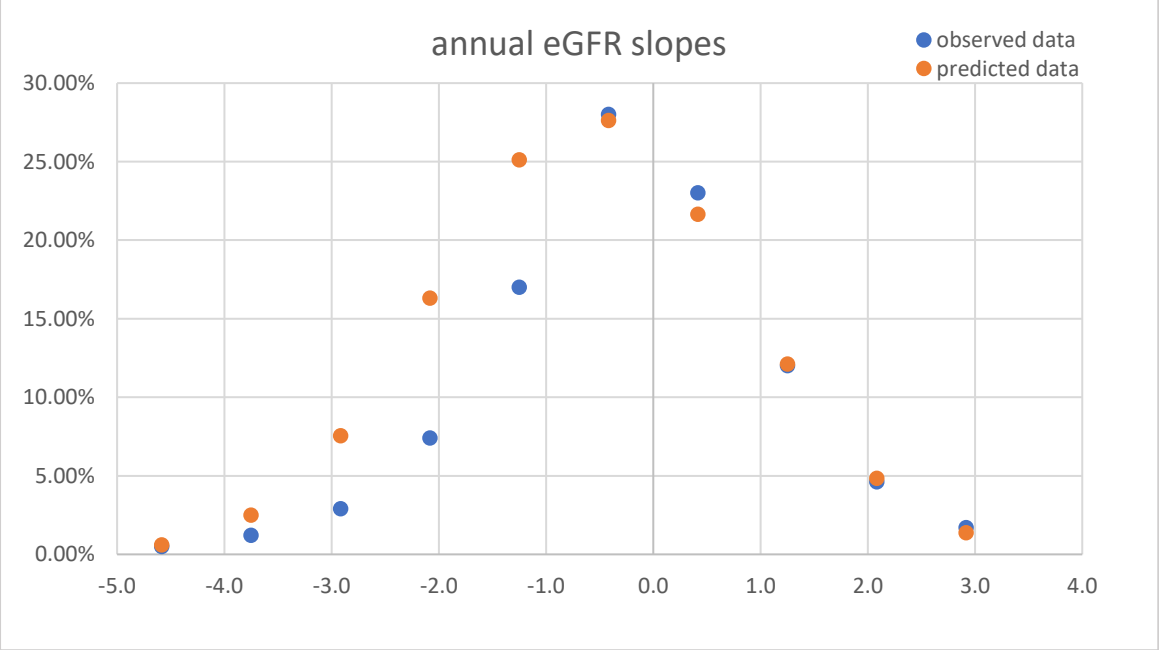
The value -0.60 was found by visually fitting the two curves (*observed* and *predicted*) as best as possible with the standard Excel statistical distributions (see Figure 14). For eGFR

[1] Grams, M.E., et al., Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 2021. 36(9): p. 1685-1693. [Supplementary appendix gfaa364, Table 3]

progression, a Normal inverse distribution was used, with mean and SD of -0.6 and 1.43, respectively. Looking at the extremes of the distribution shape, and comparing with those reported by Grams et al. 2020, they seem to be aligned and not exceeding decline of -5.0ml/min/1.73m^2. Fixing the eGFR increments for all health states to -0.27, -0.6, and -0.73 will not reflect the CKD disease progression, thus deemed not plausible modeling assumption.

Further, patients in EMPA-Kidney are at advanced stage of the disease: For example, 50% of patients are in level A3, for which the eGFR decrement is between -3.1 and -4.6 ml/min/1.73m^2 per Grams et al (2020) (Table 29). These scenarios with fixed and uniform eGFR decline across KDIGO categories wouldn't add value for the assessment, as this assumption contradicts to current knowledge of CKD progression. 'B7_Document B_B3321 addendum' updates section B.3.3.2.1 of Document B to provide clarify to the EAG on the usage of Grams et al. (and not Naimark et al. 2016) in the base-case scenario for modelling of eGFR progression post treatment discontinuation. Independent of the options selected by the user, both approaches are run for deterministic and probabilistic analyses.

Figure 14: Annual eGFR slopes



Source: Derived from Naimark et al. (2016)[2]. Abbreviations: eGFR, estimated glomerular filtration rate

B8a. Please clarify how the data in *Risk_Factors_Inputs* G51:I54 and G56:I59 relates to the account provided in Document B B.3.3.2.1 and in particular to that of Table 29 and Table 30, whether this data is used in the modelling and if so how.

Company response: As per question B7, *Risk_Factors_Inputs G51:I54* and *G56:I59* displays annual eGFR changes in patients with or without diabetes as reported for the Chronic Renal Insufficiency Cohort (CRIC) cohort of patients with CKD with and without diabetes per Grams et al. 2020. Table 29 in the Document B B.3.3.2.1 tabulates the annual rate of change in eGFR [mL/min/1.73m^2] from baseline to final follow-up (total slope) per the KDIGO categories (RS,

[2] Naimark DM, Grams ME, Matsushita K, Black C, Drion I, Fox CS, et al. Past Decline Versus Current eGFR and Subsequent Mortality Risk. J Am Soc Nephrol. 2016;27(8):2456-66.

OC-AD) estimated from a random slope and intercept model in EMPA-KIDNEY trial. These values apply in the model to describe progression of individual patients in the simulated cohort over time depending on the eGFR and uACR values at the end of each cycle in the model, while patients remain on treatment i.e., empagliflozin or SoC in the modelling horizon.

Following treatment discontinuation, annual eGFR changes in patients with or without diabetes as reported for the CRIC cohort of patients with CKD with and without diabetes per Grams et al. 2020 are used in the model as per question B7 above (Table 29). The value applied in the next cycle of the model, depends on the patient's KDIGO class in the previous cycle of the simulation. Previous eGFR value and KDIGO-specific slope are summed to generate the new eGFR in the next cycle.

Table 30 in the Document B, Section B.3.3.2.1 tabulates percentage of patients reporting specific eGFR slopes depicted on Figure 23 in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) cohort per Naimark et al. 2016. This is an alternative data source to describe CKD progression in the model. As per the response to question B7, this data source was not used in the current submission, and instead Grams et al. 2020 was used in the base-case CEA. Grams et al 2020 (CRIC cohort) was prioritised over Naimark et al. 2016 (CKD-PC cohort) as it provides change in eGFR per KDIGO categories and for patients with or without diabetes, details of which are not available from Naimark et al. 2016 (CKD-PC cohort). Addendum document B7 updates section B.3.3.2.1 of Document B to provide clarify to the EAG on the usage of Grams et al. (and not Naimark et al. 2016) in the base-case scenario for modelling of eGFR progression post treatment discontinuation.

B8b. Please clarify the mean annual uACR changes implied by Fig 24 at midpoint values, Fig 25 observed and Fig 25 predicted. How is this variable handled within the deterministic modelling. If it is sampled within the deterministic modelling, how can this sampling be turned off so as to apply the central estimate and what effect does this have upon the deterministic net costs and net QALYs? Please ensure that the model has converged when reporting this.

Company response: In Document B, Figure 24 is a copy of the original figure from the Coresh et al. 2019[3] paper (CKD-PC data), in which 3-year albumin-to-creatinine ratio (ACR) fold change from baseline were reported. This was the only source available in the literature reporting uACR changes in the CKD population. The data available illustrates the variations in uACR changes that was observed in CKD patients. *Risk_factors_inputs C79:AA123* details how the following options were derived from the data: annual uACR change per albuminuria class; LogNormal distribution uACR fold; and annual uACR fold change per distribution in CKD-PC Cohort. The 'observed' slope of Figure 25 shows the same data as Figure 24 from Coresh et al. 2019.

The 'predicted' slope of Figure 25 shows the shape of the visual fit done to the observed curve, using standard excel distributions. The LogNormal distribution was selected for uACR changes. This distribution allows to sample and quantify the ACR fold change typical of a CKD population. These random uACR changes are transformed to annual changes, using the cubic

[3] Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. The Lancet Diabetes & Endocrinology. 2019;7(2):115-27.

root of the value to be applied in annual cycles. This variable is sampled both for the deterministic and probabilistic analyses, for each patient and cycle. Fixing the value to the central point will limit the representation of CKD patients in the model, which are well known for being a very heterogeneous population, and therefore we believe this is not appropriate.

B9. The account of the modelling of deaths within the submission appears to suggest that non-specific mortality rates are applied, these having CVD and renal deaths removed from general life table statistics. Within the model there appear to be four sets of data related to SMRs and mortality: *Mortality_Inputs* D14:D16, D24:D54, D62:D92 and E128:E130 though this may be complicated by BSI deaths as alluded to in Appendix P Section 7.3.

1. **Please provide an account of Mortality_Inputs D14:D16, how this interacts with E128:E130 and if relevant how either or both of these interact with the patient modelling in Patient_Engine**
2. **Please provide an account of any interaction between *Mortality_Inputs* D24:D54 and D62:D92, and also whether D62:D92 is conditional upon having a CV event that year, having had a CV event during the previous year, having had a prior CV event, or something else. Please also provide separate worked examples, with full model cell referencing for the inputs, of the annual risk of death for a 60-year-old man with eGFR 45-59 and A2 with:**
   - **2.1 no history of CV events or prior all-cause hospitalisation.**
   - **2.2 a past history of CV events but no prior all-cause hospitalisation.**
   - **2.3 no history of CV events but prior all-cause hospitalisation.**
   - **2.4 a past history of CV events and prior all-cause hospitalisation.**
   - **2.5 a CV event in the year in question and no prior all-cause hospitalisation.**
   - **2.6 a CV event in the year in question and prior all-cause hospitalisation.**
3. **Please provide a worked example, with full model cell referencing for the inputs, for the annual risk of death for a 60-year-old man with a history of CV events, no CV event during the year in question but prior all-cause hospitalisation on HD**
   - **3.1 on HD with BSI**
   - **3.2 on PD**
   - **3.3 in PD with BSI (if this is possible in the model)**
   - **3.4 in the year of a successful kidney transplant**
   - **3.5 in the year of an unsuccessful kidney transplant**
   - **3.6 eligible for RRT but conservatively managed**

Please provide the worked examples within an excel spreadsheet.

Company response: The EAG should note that the options for modelling mortality are mutually exclusive i.e., only one is used per scenario / is selected at a time. The option selected in the base-case CEA is outlined in Document B, section B.3.3.4.

Table 30: Explanation of mortality inputs used in CKD-PM

Model tab: *Mortality_Inputs*			
Cells	**Parameters**	**When applicable**	**Used or not in the submission**
D14:D16	Death rates associated to	Applicable only if user selects	Used in a scenario analyses only and not in base-case

	having or not a previous ACH.	1) ACH: Tx effect per health state then Schrauben 2020, with: 2) all-cause mortality option 2b); Risk of death after hospitalization (EMPA Kidney trial data on file)	CEA. See section B.3.11.3 of Document B (Table 56, Final row, page 139]. This scenario is valid over a time horizon inferior or equal to EMPA-KIDNEY trial duration (rates are fixed, thus not adjusted to age).
D24:D54	HR for all cause of death from Matsushita 2010	Applicable only if user selects 1) all-cause mortality option 2); Matsushita 2010	Not used in the CEA presented in this submission.
D62:D92	HR for CV death from Matsushita 2010	Applicable only if user selects 1) CVD death + non-specific mortality + Renal death option 2); uses Matsushita 2010 instead of Matsushita 2020	Not used in the CEA presented in this submission.
E128:E130		Background data, not used in the model	

Abbreviations: ACH, all-cause hospitalisation; CEA, cost-effectiveness analyses; CKD-PM, chronic kidney disease- progression model; CV, cardiovascular; CVD, cardiovascular death; HR, hazard ratio; Tx, treatment

As detailed in row (a) of Table 30, *Mortality_Inputs D14:D16* refers to death rates associated with all-cause hospitalisation (ACH). This is a model option not selected in the base-case and only used in scenario analysis. *Mortality_Inputs E128:E130* is not used in the model engine, so there is no interaction between both sets of data. ACH scenario analysis is provided in the submission dossier (Document B, Section B.3.11.3, Table 56). There are no interactions between the risk of death prior to ACH and the risk of CV or CV death; they are independent submodules. The result of the scenario analysis is highly consistent with a base case outcome.

As detailed in row (b) and (c) in Table 30, above, the options to which these data are applicable are not used in the base-case CEA nor in the scenario analyses. If options are selected, *Mortality_Inputs D24:D54* interact with cells *E140:F231* (non-specific mortality taken from UK life tables) when the composite mortality option is selected together with Matsushita 2010. *Mortality_Inputs D62:D92* interact with cells *P140:Q231* (CV mortality taken from UK life tables) when the composite mortality option is selected together with Matsushita 2010. Both Matsushita 2020 and 2010, predict fatal CV events, their predictions are both independent of whether CV or other events occurred or not. Matsushita 2020 engine depends on patient risk factors evolution. Please refer to Table 1 of Appendix P.

The model presented in this submission is a CKD disease progression model (CKD-PM), not a renal replacement therapy (RRT) model. As such it is not feasible to study patients only in haemodialysis (HD), or peritoneal dialysis (PD), etc. The model is not prepared to trace individual cases of fatality in the RRT submodule therefore a worked example has not been created.

B10. For patients with multiple comorbidities please clarify how their disutilities affected overall quality of life. How does this compare with their treatment in other

models, such as the default for the IQVIA Core Diabetes Model? If this is best illustrated with worked examples, please provide one

Company response: The CKD-PM (company submitted) is set up to track the common CKD comorbidities: hypertension and diabetes. Both conditions impact eGFR progression and the risk of other complications in the model (RRT, CVD, mortality). Considering high prevalence of hypertension (in the range of 80%) and challenges in quantifying disutility associated with prevalence of diabetes (due to high heterogeneity of this subgroup [patients with diabetes are in different disease state, treatment lines etc]) it is not appropriate to apply a single disutility value to patients with diabetes. It is assumed that the KDIGO/health state utilities already include the utility and disutilities attributable to hypertension and/or diabetes. This assumption was applied to reduce the risk of double or multiple counting of the disutility of diabetes and so multiplying potential treatment effects on quality of life.

The same applies to other complications that may have varying levels of disutility (hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, metabolic acidosis, hyperkalemia, hyperuricemia/gout) and/or are highly prevalent (e.g., infections). These are all assumed to be included in the health state/KDIGO classes utilities.

For other events and complications not listed above, disutilities are applied in an additive way, similarly to other economic models. The CKD-PM model counts disutilities for CVD, AKI, fractures and cancer events on the top of health state utilities in the year the event occurs. Long-term disutilities associated to CVD events again are not considered in the model, but instead assumed to be reflected in the KDIGO health states utilities (Table 31). In the RRT submodel, once a patient receives RRT therapy, e.g., hemodialysis, peritoneal dialysis or kidney transplant, they have the respective RRT associated utility applied instead of a health state. Patients who receive a transplant move the G3aA1 health state. Disutilities related to specific types of RRT and complications (e.g., immunosuppressive therapies for transplant patients; peritonitis for peritoneal dialysis patients) are applied using an additive method.

Contrary to the IQVIA Core Diabetes Model (CDM), the CKD-PM model has health state utilities related to the severity of the disease – KDIGO classes. Whereas the CDM measures health state utility based on the history of complications as HbA1c varies in response to treatment and thus can't serve as an indicator of health state.

Please consult 'B10_Assumptions Costs and Utilities' to understand better how costs and utilities are applied in the CKD model.

Table 31: Submodule-wise application of utilities and disutilities in the model

Submodule	Health State/ Complication/ Event modelled	How utilities and disutilities are applied in model
Health states	KDIGO classification Albuminuria additional classes	Utility weight applied per health state Add-on disutility per additional 1000+ uACR classes (zero in base case)
ESKD	Conservative management PD HD RT with immuno-suppressive therapy	Utility weight is applied as: • For conservative therapy it is assumed to be same as G5 from the KDIGO classification • For PD, HD and the first year of RT there is a specific utility

		• As patients after RT move to G3A1 the utility of that group is used after year 1, however a disutility is applied to account for the immunosuppressive therapy in the follow-up years
	Peritonitis AV access Thrombosis Bloodstream infections	No disutility is applied as it is assumed to be included in the health state utility
Cardiovascular events	MI Stroke UA TIA HF PAD	For these complications a disutility is applied for the acute event in the cycle it occurs in • For MI, Stroke, TIA and UA; the same value is used for the first and recurrent events • For HF and PAD; multiple occurrences leads to disutilities applied in the cycles they appear in
Acute Kidney Injury	AKI hospitalisation	Disutility is applied for the acute event in the cycle it occurs
BMD	Hyperphosphataemia Hypocalcaemia Hyperparathyroidism	No disutility is applied as it is assumed to be included in the health state utility
	Hip Fractures Other Fractures	Disutility is applied for the acute event in the cycle it occurs. It was assumed that the disutility of fractures published in Sullivan et al. applies to both types of fractures, hip and other.
Infections	Respiratory track Gastrointestinal track Urinary track Skin and soft tissue Nervous system Musculoskeletal system Sepsis	No disutility is applied as it is assumed to be included in the health state utility
Cancers	Renal Cancer Urothelial cancer	Disutility is applied lifelong from the cycle it appears onwards
Diabetes	Diabetes	No disutility is applied as it is assumed that patients with diabetes will have a higher risk of events, therefore differences in utilities are already considered.
Hypertension	Hypertension Not controlled hypertension Resistant hypertension	No disutility is applied
Other events	Metabolic acidosis Hyperkalaemia Hyperuricaemia/Gout Anaemia	No disutility is applied as it is assumed to be included in the health state utility
Adverse events	Leg, foot, or toe amputation Placeholders 4 to 6	Disutility is applied for the acute event in the cycle it occurs in
ACH (Optional)	Disutility of acute events replaced with a disutility upon occurrence of an all-cause hospitalisation	Event disutility turned to zero when ACH module is ticked: peritonitis, BSI, AV access, AKI, infection, fracture, CV events, AE.

Abbreviations: ACH, all-cause hospitalisation; AE, adverse event; AKI, acute kidney injury; AV, arteriovenous; BMD, bone, and mineral disorder; BSI, bloodstream infection; CV, cardiovascular; HD, haemodialysis; HF, heart failure; KDIGO, Kidney Disease

B11. The ERG has not yet had time to review Matsushita et al. (2020), Hennessy et al. (2015) or Goff (2013). Please outline why within the CKD patch risk calculation the expected eGFR and expected logACR are modelled from other inputs rather than using the modelled patient's contemporaneous eGFR and uACR values. Please outline how these three references are used to result in Appendix P Table 1 and Table 29 together with any required assumptions. Please clarify the distinction between Table 29 New risk low and New risk high and how these are applied within the model. How are the 10-year CVD risk and 10-year CVD mortality risks converted to annual risks? Please also provide a worked example of the calculation of PCE within the CKD patch New Risk calculation of Table 1. Please provide the worked example within an excel spreadsheet.

Company response: The CKD-Patch methodology was implemented in the CKD-PM as described by the authors, Matsushita et al. 2020 Supplement Web Tables 13. The 10-year risk for each patient and at each cycle of the model is estimated in three steps as per the below (cf. also worked example in Addendum 2):

1) Calculating the "expected eGFR" (exeGFR) for each individual patient using current patient characteristics (independent factors including age, sex, black ethnicity, SBP value and treatment for hypertension, total and high-density lipoprotein (HDL) cholesterol, diabetes status, smoking status)

2) Calculating the "expected log uACR" (exlogACR) for each individual patient using current patient characteristics (same independent factors as above, plus exeGFR)

3) Using the calculated "expected eGFR" and "expected log uACR" per steps (1) and (2) in the CKD Patch part to correct the risk using the Pooled Cohort Equation (PCE) (for atherosclerotic cardiovascular disease [ASCVD]) or Systematic Coronary Risk Evaluation (SCORE; for CVD mortality).

Therefore, the actual eGFR and uACR values are used to estimate the risk at patient level. Calculating the expected eGFR and uACR for each patient is inherent to the adjustment of PCE and SCORE models, as stated by the authors: "The risk enhancement by CKD Patch was determined by the deviation between individual CKD measures and the values expected from their traditional CVD risk factors and the hazard ratios for eGFR and albuminuria."

The coefficients for ASCVD and cardiovascular mortality (CVM) prediction according to the 'CKD Patch' methodology, as presented in Matsushita 2020 Supplement Web Table 13, are presented in Appendix P Table 1 (ASCVD prediction) and Table 29 (CVD mortality), without any modification, apart from a typo identified in the original publication concerning parentheses. No other options are available to estimate ASCVD occurrence in the model. The risk of CVD mortality can be optionally predicted via hazard ratios by KDIGO class as published by Matsushita et al. 2010 (although this is not used in base case). Further assumptions used in the model:

The predicted risk of ASCVD is independent of the predicted risk of death. It was however assumed that if death occurs during a cycle, no ASCVD event could occur during this same

cycle. In the CKD Patch equations, age parameter was capped at 80 years, and uACR input was capped at 300 mg/g (i.e., risk is not increasing further once patient age, or uACR, reaches the 'capping' value, all other factors being equal). Capping ensures that risk factors input values remain within a valid range. The capping values were determined by looking at mean baseline characteristics and standard deviations of the 35 cohorts used to develop the different risk equations of Matsushita et al. (2010, 2020). Capping ensures that risk factors input values remain within a valid range.

Both types of risk correspond to different background risk of dying from a CV cause, according to country-specific CVD mortality. Both 'low risk' and 'high risk' prediction models were implemented separately in the model. A UK profile is considered a 'low risk of CV death', therefore, the base case analysis is conducted with a "low risk" version of the equation.

The 10-year risk *P10* was converted to an annual risk *P1* using the Miller and Homan (1994) formula: P1 = 1- (1-P10)^(1/10). Reference: Miller, D.K. and S.M. Homan, Determining transition probabilities: confusion and suggestions. Medical Decision Making, 1994. 14(1): p. 52-58.

Cf. attached Excel file with calculation steps for a specific patient profile in Addendum 3.

B12. Please clarify Section P.1.1.1 as to how the first ASCVD is split between MI, TIA, Stroke and Angina.

Company response: From the predicted risk of ASCVD (Matsushita 2020, CKD Patch), the risk of a fatal CV event was removed, as death is projected independently from ASCVD in the model. Then, the risk of non-fatal ASCVD (stroke + myocardial infarction [MI]) was extrapolated to the risk of a CV event including unstable angina (UA), and transient ischemic attack (TIA). These adjustments were applied by multiplying the initial ASCVD risk with the following ratios:

- Proportion of non-fatal events among all ASCVD events: 73.3% (source: distribution of events in EmpaReg trial, 52 fatal CV events out of 195 CV events)
- Ratio number of CV events total per non-fatal ASCVD event: 2.03 (based on Framingham data, there were 51 TIA, 91 angina and 138 non-fatal ASCVD (stroke and MI); source Wolf 1991 and D'Agostino 2000.

The actual split derived from Framingham is presented in the table below (sum is not 100% because only nonfatal events are split; these are then rescaled in the model engine when distributing the risk across the 4 types of events).

	%	%
	Males	Females
p MI	41.56%	29.48%
p all stroke except TIA	14.21%	12.57%
p angina	32.33%	50.65%
p TIA	5.15%	3.90%

B13. Are the risks of recurrent stroke, Appendix P Table 5, reapplied, i.e. If a patient is modelled as having a stroke in Year 3 and in Year 5 is his risk of recurrent stroke in Year 6 6.3% or 13.5%?

Company response: The 'counter' of time since first stroke is not reset to zero when a subsequent stroke occurs (i.e., the index stroke remains the first stroke). In the example above, the risk of recurrent stroke for the patient in year 6 is therefore 6.3%.

B14. Appendix P section 1.2 provides the HRs by KDIGO state for PAD, but the ERG cannot identify the baseline annual risk of PAD for G1, A1 patients. Please state where this is presented. Please ensure that a full account of how the annual PAD risk for G1, A1 patients is derived with full referencing of sources is provided.

Company response: A baseline peripheral arterial disease (PAD) rate of 17.33 per 10,000 patient-year is applied by default. This rate was sourced from Cea-Soriano et al. 2018 who studied the incidence and the prevalence of symptomatic PAD between 2000 and 2014 in the UK using data derived from The Health Improvement Network database in the UK, an electronic medical research database that contains fully anonymized data on approximately 11 million patients from primary care. Findings concluded that the incidence of PAD decreased steadily over time from 38.6 in 2000 to 17.33 per 10,000 person-years in 2014 and this decrease in the incidence over time was observed in all age groups. Patients in A1, G1 states had no increased risk vs. general population (HR=1) (1).

Reference:

1. Cea-Soriano et al. Time trends in peripheral artery disease incidence, prevalence, and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. BMJ Open 2018. 8(1):e018184 (UK data): "The incidence of symptomatic PAD per 10 000 person-years was 17.3 (men: 23.1; women: 12.4) in 2014."

B15. Please clarify which of the risk equations of Appendix P Table 23 are used in the base case and why, and if the equations are not annual risks how these risks were converted to annual risks.

The risk equation used to predict RRT initiation in the base case is the Pooled, 6 variable ("6v") equation by Tangri et al. 2016. This version was based on the most recent data and the largest number of cohorts (pooled North America and non-North America).

The Tangri pooled 6v equation provided a 5-year risk of RRT. The 5-year risk was adjusted to a risk per cycle (annual risk) using the Miller & Homan formula (cf. Question B11.4).

B16. Are all deaths for those in RRT modelled using only the proportions of Appendix P Table 24 or do other factors and inputs come into play and if so, how? Does the model imply that patients will potentially endlessly circle round different types of RRT, i.e., among the 4% switching from HD to PD do 21% of those remaining alive switch back to HD the next year? Are patients limited to one transplant? Are there any switching costs, over and above the annual direct treatment costs, for going between RRTs?

The EAGs interpretation is correct: No other data or links are used to model deaths for patients in RRT beyond the proportions outlined in Appendix P, Table 24.

The EAGs interpretation is correct: The CKD-PM accounts for the possibility of patients switching between different forms of RRT. Given the advance stage of the disease, then patients either receive a form of RRT and move to a G3aA1 (in case of renal transplant) or die.

No limit was placed on how many transplants a patient could receive. In the base case life-long model horizon, a single patient (on empagliflozin) was projected to receive two transplants (out of 1,000 patients) and six patients in the placebo arm were projected to receive two transplants.

There are no switching costs for transitions between different forms of RRT in the CKD-PM. There are only annual health state costs applicable to each therapy, except for kidney transplant, which is an event cost with follow-up costs applied from the first year onwards. If patients are still on treatment with empagliflozin, treatment costs are stopped when patients initiate RRT.

B17. Appendix P Table 24 obviously implies the values of Table 25 for those under 80 and initiating with PD and for those under 80 and initiating with HD. The values of Table 25 for those initiating RT are less obvious. Please outline the calculation of the proportion failing RT, together with any additional references, and provide the arithmetic of the calculation of the other percentages including the proportion of patients surviving and remaining on RT. The ERG is confused by the values for the 80+. Those initiating RRT with HD those less than 80 have an annual 17% chance of dying but this apparently increases to 85% for those aged 80 plus. Please provide an account of this with particular reference to the calculation of the probabilities for those 80 plus. Please also clarify why the mortality for those 80+ initiating RRT with RT is not stated and why the probabilities for this group do not sum to 100%. Please confirm that the percentages in Table 25 are all annual percentages that are reapplied every year, e.g., an HD patient has an annual 34.2% risk of one AV shunt thrombosis every year he is on HD. Please clarify if the RRT percentages of Table 25 are assumed to apply to all patients in eGFR state G5 (other than the percentage that are conservatively managed) or if specific eGFR thresholds within the G5 health state(s. x3, A1, A2, A3), i.e., less that 15ml/min/1.73m^2, are applied for each type of RRT (HD, PD, RT). What proportion(s) of patients are assumed to be conservatively managed for RRT: 5% of those incident G5 under 75 and 16.7% of those incident G5 over 75 and what happens to those who were incident under 75 who live beyond 75? What HCRU inputs does conservative care involve?

Company response:

Calculations for the proportion of patients failing RRT

Patients initiating RT	= 615/(615+1492+5671)
Patients in RT failing RT (go to HD, PD, or death)	2.9%=1.3% (go to HD) + 1.6% (go to death)+ 0% (go to PD)
Proportion of patients surviving and remaining on RT	This is not an output of the model. The model keeps patients in the RT tracker if the failed

	event is not occurring i.e., proportion = 100%-2.9% = 97.1%

Source: Appendix P Table 24. Abbreviations: HD, haemodialysis; PD, peritoneal dialysis; RT, renal transplant; RRT, renal replacement therapy.

The risk of death in patients initiating RRT with HD who are aged 80 plus is 21.8%, not 85%. There was an error on the calculations (the calculated rate was not accounting for the fact that patients aged above 80 years do not get renal transplant). This is now corrected in the new version of the model (see question S3 below).
The following elements were corrected for ages above 80.

- % of PD patients moving to HD
- % of PD patients on PD dying
- % of HD patients moving to PD
- % of HD patients on HD dying

Risk death for patients above and below 80 years initiating RRT with HD

Risk of death for patients < 80 years initiating RRT with HD (%)	17%
Risk of death for patients ≥ 80 years initiating RRT with HD (%)	85% =p_pt_d_RRT_HD_fail_die (17%)/ (p_pt_d_RRT_HD_fail_die (17%)+p_pt_d_RRT_HD_move_PD (3.1%)
Risk of death or RRT failure for patients < 80 years initiating RRT with HD (%)	26%
Those initiating RRT with HD those aged 80 plus, % of dying	=p_pt_d_RRT_HD_fail_die (17%)/ ((p_pt_d_RRT_HD_fail_die (17%)+p_pt_d_RRT_HD_move_PD (3.1%)/26%) =21.8%

Abbreviations: HD, haemodialysis; RRT, renal replacement therapy

Mortality of patients above 80 years initiating RRT with RT

Category	Proportion	Comment
% of patients initiating RRT with RT		
above 80 years old	0%	Assumed that above a certain age threshold no patients initiate kidney transplant
% of patients receiving PD instead of RT	=p_pt_d_RRT_RT (8%)*J405 (21%)	Redistributing the % of patient in RT to HD and PD
above 80 years old	20.83%=p_pt_d_RRT_PD (19%)/ (p_pt_d_RRT_HD (72.9%) + p_pt_d_RRT_PD (19%))	
% of patients receiving HD instead of RT	=J407 (79.17%)*p_pt_d_RRT_RT (8%)	
above 80 years old	79.17%=p_pt_d_RRT_HD(72.9%) / (p_pt_d_RRT_HD (72.9%) + p_pt_d_RRT_PD (19%))	

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; RT, renal transplant

The 8% of patients originally going to RT are redistributed in PD and HD. 20.83% + 79.17% which sums to 100%.

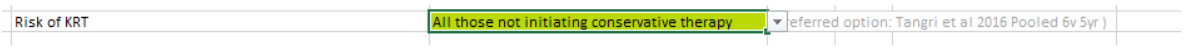
The EAG's interpretation is correct – all proportions are applied annually, inclusive the one described for AV shunt.

A single G5 definition is used defined by an eGFR less than 15ml/min/1.73m^2. The risks available in table 25 are only applicable once eGFR is less than 15ml/min/1.73m^2, and patients initiate RRT.

Conservative management is employed to patients reaching eGFR under 15ml/min/1.73m^2 and are not yet in RRT. This data is only applicable if instead of choosing the option of applying Tangri et al. equations, RRT is initiated for those patients not initiating conservative management. See print screen below. Conservative care in G5 assumes healthcare resource use based on Phair G, et al 2017.

Reference:

Phair G, Agus A, Normand C, et al. Healthcare use, costs and quality of life in patients with end-stage kidney disease receiving conservative management: results from a multi-centre observational study (PACKS). Palliative Medicine. 2018;32(8):1401-1409. doi:10.1177/0269216318775247.



B18. Exploratory work by the ERG suggests that setting discontinuation rates to zero in *Other_Default_Data* cells F215 and L215 somewhat improves life expectancy in both arms and the overall NHB gain from empagliflozin. This seems counterintuitive given that the stated mean off treatment eGFR change of -0.6 ml/min/1.73m^2 is slower, i.e., better, and usually considerably slower than virtually all the values within Document B table 29, other than for some values for those in A1. Please provide an intuitive account of this

Company response: The EAG should note that the stated mean of -0.6mL/min/1.73m^2 for eGFR progression post treatment continuation in Document B, Section 3.3.2.1 is a misstatement. As per the Company's response in question B7, the CKD-PM utilises Grams et al. (2020) data to model eGFR progression post treatment discontinuation and not Naimark et al. (2016) which was a model option not utilised in the CEA presented in this submission.

If discontinuation rates are set to zero, it means all patients receiving empagliflozin remain on treatment until they initiate RRT or die. A comparison of eGFR progression from the EMPA-KIDNEY trial (Table 32) with eGFR progression in Grams et al. 2020 (Table 29) demonstrates that patients on treatment have a slower progression of the disease, whereas the eGFR natural progression per Grams et al. 2020 shows higher decrements for many KDIGO classes.

Table 32: eGFR progression per EMPA-KIDNEY

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			**Placebo on top of SoC**		
	A1	**A2**	**A3**	**A1**	**A2**	**A3**
G2	NA	-2.20 (-3.26, -1.14)	-3.39 (-3.96, -2.81)	NA	-2.76 (-3.92, -1.59)	-5.14 (-5.7, -4.58)
G3a	NA	-1.60 (-2.32, -0.89)	-3.45 (-3.91, -2.98)	NA	-2.29 (-3.04, -1.55)	-4.66 (-5.14, -4.19)
G3b	-0.58 (-0.96, -0.19)	-1.04 (-1.4, -0.67)	-2.90 (-3.2, -2.6)	-0.83 (-1.2, -0.46)	-1.56 (-1.92, -1.2)	-4.11 (-4.42, -3.8)

G4	-0.32 (-0.87, 0.22)	-0.62 (-1.04, -0.19)	-2.76 (-3.08, -2.45)	-0.15 (-0.71, 0.4)	-0.85 (-1.27, -0.43)	-3.76 (-4.09, -3.44)
All	-1.96 (-2.11, -1.82)			-2.68 (-2.82, -2.53)		

Source: EMPA-KIDNEY Trial data on file – Clinical trial documentation. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA: not available; SoC, standard of care

B19. Appendix J Table 6 suggests that in the absence of the quality-of-life effects of complications those in G3aA1, G3bA3, G4A3 and G5A3 experience a QALY loss from empagliflozin. Please provide an account of each of these results with particular reference to those of G3bA3 and G4A3 in the light of Document B Table 29. Please state which costs are included in Appendix J Table 7. Please also provide the equivalent of Appendix J Table 6 and Table 7 but reporting each subgroup individually without weighting the individual subgroup outcomes by the subgroup percentage, together with the assumed distribution between the subgroups. Please similarly provide the equivalent of Appendix J Table 6 and Table 7 including the QoL and cost effects of the complications, again without weighting by the subgroup percentage. Please ensure that the deterministic model estimates of net costs and net QALYs have converged when reporting these.

Patients in the empagliflozin arm in the health states the EAG has referred to in this question do experience a QALY loss. Appendix J, Table 6 only accounts for the utilities associated to health states and does not include disutilities associated with complications. Table 33 below shows the time patients are on each health state. CKD progression is faster in the SoC arm, meaning these patients reach advanced disease health states sooner and progress beyond them faster i.e., G3bA3, G4A3, G5A3.

The QALY loss in G3aA1 represents the higher number of patients in the SoC arm getting a renal transplant, thus moving to this health state sooner than patients in the empagliflozin arm.

Table 33: Time spent by patients in KDIGO health states (LYs)

KDIGO classification	Empagliflozin + SoC	SoC	Incremental
G1 * A1	-	-	0.00
G2 * A1	-	-	0.00
G3a * A1	0.57	0.58	-0.01
G3b * A1	0.14	0.03	0.11
G4 * A1	0.01	0.01	0.00
G5 * A1	-	-	0.00
G1 * A2	-	-	0.00
G2 * A2	0.07	0.06	0.01
G3a * A2	0.66	0.50	0.16
G3b * A2	2.65	1.40	1.25
G4 * A2	2.50	0.51	1.99
G5 * A2	0.15	0.03	0.12
G1 * A3	-	-	0.00
G2 * A3	0.06	0.05	0.01
G3a * A3	0.39	0.34	0.05
G3b * A3	1.46	1.55	-0.09
G4 * A3	2.81	3.26	-0.45
G5 * A3	1.62	2.02	-0.40

Abbreviations: SoC, standard of care; LYs, life years.

Table 7 of appendix J includes health state cost only. Depending on the option selected in the executive summary, in G5, health state costs can include conservative therapy or both conservative therapy cost and G5 costs. By default, for this submission only conservative

therapy costs are included. RRT costs are described in the Total RRT costs- row 26 of results page.

The purpose of table 6 and 7 of appendix J is to show how the delay of the progression of the disease in the two arms is impacting the costs and QALYs over time, and show the differences observed in the two arms under comparison. As empagliflozin delays the progression of the disease, by having smaller declines in eGFR compared to SoC, and in parallel also have slower progression of albuminuria compared to SoC.

At this stage is not possible to provide this detail for complication groups, the model does not include specific traces to collect this info per KDIGO class. Additional changes to the engine require time for implementation.

This CKD-PM is a microsimulation model, to account for a high heterogeneity of patients and observe their evolution over time. Thus, trackers check when the patient has an event or not, and separately costs and utility are recorded for all patients in additional trackers. Not weighting these patients is not possible in a microsimulation model, as the result shown are for the full cohort of patients. If we limit the model to an average patient, we are not tracking the typical patient heterogeneity in the CKD population, we will have a single patient starting in the model in a single health state, which progresses over time in CKD, but this patient is not representative of CKD population itself.

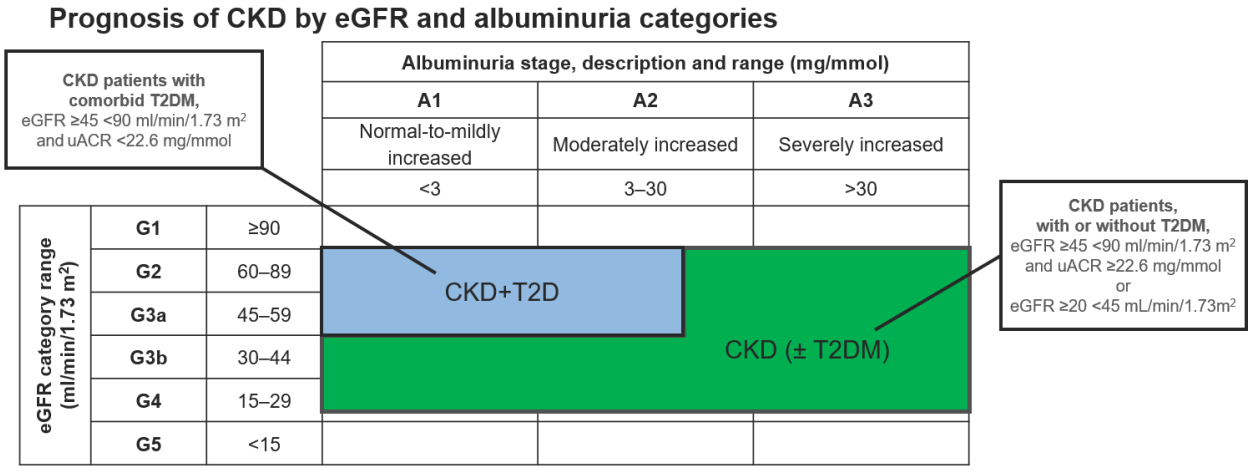
Additional

B20. Please clarify quite what population the economic modelling is intended to cover in terms of sampling and clinical effectiveness estimates, with particular reference to the groups of Document B Figure 1. Please also clarify what population the economic modelling actually samples and models, in terms of both patient baseline characteristics, with particular reference to the groups of Document B Figure 1, and clinical effectiveness estimates.

Company response: The target population for this submission is, as shown in Document B Figure 1 (Figure 15 below), adults with CKD having individually optimised standard of care, and having:

- eGFR ≥20 <45 mL/min/1.73m2 or
- eGFR ≥45 <90 mL/min/1.73m2 and either:
    - uACR ≥22.6 mg/mmol (200 mg/g) or
    - T2DM

Figure 15. Patient population addressed in the submission, according to KIDGO categories



- *Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus*

The population sampled in the model has baseline characteristics in line with the EMPA KIDNEY trial ITT population (mean, standard deviation, and distributions information from the trial baseline). Baseline characteristics of modelled patients were sampled from these distributions. This represents the patient population in the green area of Document B Figure 1, specifically patients with or without T2DM, with either eGFR ≥45 <90 ml/min/1.73m2 and uACR ≥22.6 mg/mmol, or with eGFR ≥20 <45 ml/min/1.73m2. Clinical effectiveness estimates are derived from the EMPA KIDNEY ITT population.

As discussed during the clarification questions call, it is not possible to model the full target population for this submission (i.e., the green and blue areas of Document B Figure 1) together using one set of baseline characteristics and treatment effects. EMPA-REG OUTCOME and EMPA-KIDNEY provide the characteristics and treatment effects for the blue and green areas, respectively. But neither trial includes CKD patients across the full spectrum of KDIGO categories included in the target population. Due to differences in the trial populations and study designs, the characteristics and treatment effects are different. Thus, there would be clinically implausible changes as patients progressed through the model if a blend of EMPA-REG OUTCOME and EMPA-KIDNEY treatment effects were used.

Although not requested, a scenario analysis was conducted, sampling the M2.2 population of EMPA-REG OUTCOME (specifically CKD patients with eGFR ≥45 <90 ml/min/1.73m2 and without albuminuria [uACR < 200 mg/g [22.6mg/mmol]) at baseline; the blue area of the target population). Treatment effects as detailed in the responses to questions A3 and A4 were used. In this scenario, empagliflozin is dominant (less cost, more QALYs) vs SoC alone, with a net monetary benefit of £8,234. The full results are presented in “B20 model scenario results”. It should be noted this scenario does not model the full CKD+T2D target population, just those with eGFR ≥45 <90 ml/min/1.73m2 and without albuminuria.

B21. Please clarify if the coefficients in Document B Table 34 are five yearly or annual.

Company response: The coefficients in Document B Table 34 are for annual progression of HbA1c.

B22. Please clarify if the rates for Document B Table 35 relate to those remaining on study treatment, OC-OT, or remaining on study, OC-AD. What has been assumed for those discontinuing treatment?

Company response: The event rates for lower limb amputations (LLA) in Document B Table 35 relate to patients on treatment and up to 7 days after treatment discontinuation. Specifically, these are events that resulted in or prolonged hospitalisation. On-treatment analyses of the effects of allocation to empagliflozin versus placebo were conducted as LLA (overall and by level) were prespecified AEs of special interest.

Event rates for LLA (and so costs and utilities) are not applied for LLA following treatment discontinuation as this information wasn't identified in the literature. In patients with CKD, LLA are typically an outcome of PAD (1,2), which is tracked separately in the model and implicitly includes the impact of LLA.

References:

1. Garimella PS, et al. Peripheral Artery Disease and CKD: A Focus on Peripheral Artery Disease as a Critical Component of CKD Care, American Journal of Kidney Diseases. 2012;60(4):641-654.
2. NICE Clinical guideline [CG147], Peripheral arterial disease: diagnosis and management. 2020. Available online: https://www.nice.org.uk/guidance/cg147/resources/nice-guidance-points-the-way-to-better-diagnosis-and-management-of-common-cardiovascular-condition.

B23. Within the model please clarify which events are solely a function of eGFR, uACR and the other risk factors such as HbA1c, SBP, smoking etc and which are functions of these and other modelled events. Similarly, is there any feedback from the modelled events to the evolution of the risk factors, such as the development of T2DM.

Company response: Table 34 and Table 35 below show relationships between model parameters concerning the evolution of risk factors, and the occurrence of complications. Risk factors and events impacted by treatment effect are also indicated.

Table 34: Risk factors evolution in CKD-PM

Risk factor	**Update of risk factor value at current cycle based on:**	
	Risk factor (Time-dependent in bold font)	**Previous modelled events (status checked in previous cycle)**
Age	**Current cycle number**	
eGFR	**Previous KDIGO class**	Diabetes status RRT status Treatment status
uACR	**Previous uACR class**	RRT status Treatment status
HbA1c	With T2DM: **age**, race, **baseline and previous HbA1c, time since T2DM diagnosis** (UKPDS)	Diabetes status Treatment status

	No T2DM: **age, previous HbA1c**	
BMI	With T2DM: **age**, race, **baseline and previous BMI, time since T2DM diagnosis** (UKPDS) No T2DM: **age, previous BMI**	Diabetes status Treatment status
SBP	**Age**, sex, **baseline and previous SBP**, (Framingham)	Treatment status **SBP controlled status**
TC	**Age**, sex, **baseline and previous TC** (Framingham)	
HDL	**Age**, sex, **baseline and previous HDL-C** (Framingham)	
Diabetes status	T2DM risk as per QDiabetes (cf next table)	T2DM history (baseline or from previous cycles)
CVD history	CVD risk as per CKD Patch (cf. next table)	CVD history (baseline or from previous cycles)

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CKD-PM, chronic kidney disease progression model; CVD, cardiovascular disease; eGFR, estimated glomerular function rate; HbA1c, glycolated haemoglobin; HDL, high-density lipoprotein; KDIGO, kidney disease improving global outcomes; RRT, renal replacement therapy; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; uACR, urinary albumin:creatinine ratio

Table 35: Event evolution in CKD-PM

Event in the model	**Risk in current cycle predicted based on:**	
	Risk factor **(Time-dependent in bold font)**	**Previous modelled events (status checked in previous cycle)**
Non-specific death	**Age**, sex	
Cardiovascular death	**Age**, sex, smoking status, **eGFR, uACR, TC, SBP**	
RRT death	**Age**, **eGFR** (death if < 3 mL/min/1.73m²)	
RRT initiation	**Age**, sex, **eGFR, uACR** (Tangri 2016) Split PD, HD, RT: statistics per **age**	Diabetes status Hypertension status (baseline or from previous cycles)
RRT > Peritonitis	Fixed probability per cycle	RRT/PD status
RRT > AV access	Fixed probability per cycle	RRT/HD status
RRT > BSI	Fixed probability per cycle	RRT/HD status
ASCVD	Sex, Ethnicity, HTN treatment, smoking status, **Age, TC, HDL-C, SBP, eGFR, uACR (CKD Patch model)**	Diabetes status
HHF	**eGFR, uACR (class)**	Diabetes status Treatment status
PAD	**eGFR, uACR (class)**	Treatment status
Recurrent CHD	**Age**, sex, smoking status, **TC, HDL-C, SBP**	Diabetes status
Recurrent Stroke		Years since first stroke
T2DM development	**Age**, sex, ethnicity, smoking status, **BMI**, **HbA1c**, receiving atypical antipsychotics, receiving corticosteroids, learning disabilities, schizophrenia or bipolar affective disorder, receiving statins, receiving treatment for hypertension, family history of diabetes, gestational diabetes, polycystic ovary syndrome (QDiabetes model)	CVD history
Hypertension - Uncontrolled	**SBP, eGFR (class)** - **eGFR (class)**	HTN history

- Resistant	- **eGFR (class)**	
AKI	**eGFR, uACR (classes)**	Diabetes status
Infections	**eGFR (class)**	RRT/RT status
Bone/mineral disorders	**eGFR (class)**	
Cancer	**eGFR (class)**	
Adverse events	**Fixed probability per cycle**	Treatment status
All-cause hospitalisation	**eGFR, uACR (classes)**	Treatment status (optional)
Treatment discontinuation	Fixed probability per cycle	RRT status (stopping rule)

Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; AV, arteriovenous; BMI, body mass index; BSI, bloodstream infection; CHD, coronary heart disease; CKD, chronic kidney disease; CKD-PM, chronic kidney disease progression model; CVD, cardiovascular disease; eGFR, estimated glomerular function rate; HD, haemodialysis; HbA1c, glycolated haemoglobin; HDL, high-density lipoprotein; HTN, hypertension; KDIGO, kidney disease improving global outcomes; PD, peritoneal dialysis; RRT, renal replacement therapy; RT, renal transplant; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; uACR, urinary albumin:creatinine ratio.

B24. If it was recorded during the trial what number of those without T2DM at baseline developed T2DM during the course of EMPA-KIDNEY?

Company response: Of the 1,790 patients in the empagliflozin arm and 1,779 patients in the placebo arm who did not have diabetes at trial baseline, 51 (2.9%) and 61 (3.4%) of patients in each arm developed diabetes, respectively. The number of patients developing diabetes during the course of EMPA-KIDNEY is summarised in Table 36, including among those with pre-diabetes and normoglycaemia at baseline.

Table 36: Number of patients who developed diabetes during EMPA-KIDNEY

	Empagliflozin 10mg	**Placebo**
Patients without diabetes at baseline, n	1779	1790
Of those, patients who developed diabetes during the study – n (%)	51 (2.9)	61 (3.4)
Patients without diabetes and with pre-diabetes (HbA1c >=39 to <48 mmol/mol) at baseline, n	561	536
Of those. patients who developed diabetes during the study – n (%)	45 (8.0)	47 (8.8)
Patients without diabetes and with normoglycaemia at baseline, n	1218	1254
Of those. patients who developed diabetes during the study – n (%)	6 (0.5)	14 (1.1)

Abbreviations: HbA1c, glycated haemoglobin

B25. Please clarify if the units of Document B section B.3.3.2.2 and the units of Patient_Inputs cells K52:K54 are both in mg/g with neither being in mg/mmol. The economic model appears in places to define the boundaries between A1 and A2 as 30 mg/g and A2 and A3 as 300 mg/g; e.g. Cost_Inputs cells D11:D28. The ERG was under the impression that these boundaries were 3mg/mmol and 30 mg/mmol, or 26.6 mg/g and 266mg/g. Please clarify the uACR A1, A2 and A3 boundaries that were used to generate Document B Tables 29 and 31. Please clarify whether the uACR boundaries

for model inputs and model health states are all consistent and if so what these are, or outline where there are any disparities.

Company response: Document B Table 31 presents ratios of changes since previous period (no unit). In cells K52:K54, as well as throughout the model, the unit used for uACR is mg/g.

uACR boundaries are as follows in Document B Tables 29 and 31: A1 1-29 mg/g; A2 30-300 mg/g, A3: > 300 mg/g. This is aligned with model inputs and assumptions, and reflects the boundaries used in clinical guidelines by KDIGO, NICE, UKKA etc.

B26. Please clarify if the annual discontinuation rate of 12.56 per 100 patient-years for empagliflozin implies that within a cohort of 100 patients at the end of the 1st year of EMPA-KIDNEY (not within the model):

1. **among those remaining alive 87.44% of patients would remain on treatment and 12.56% patients would have discontinued**

2. **87.44 of patients would remain on treatment and 12.56 patients would either remain alive but off treatment or would have died; or**

3. **something else – please specify.**

Company response: Interpretation 2 is correct. The discontinuation rate of 12.56 per 100 patient-years for patients treated with empagliflozin implies that within a cohort of 100 patients at the end of the 1st year of the EMPA-KIDNEY trial, 87.44 patients would remain on treatment and 12.56 would discontinue. Discontinuation considered both patients that stayed alive but stopped treatment with empagliflozin and patients who had died.

As a follow up to this question, the company has produced an additional alternative endpoint: time to treatment discontinuation, with exclusion of treatment discontinuations that occurred on the same day as ACM (as it can't be determined if these occurred before death). According to above definition, the discontinuation rate was 10.57 (9.76-11.40) pts with event per 100 pts years at risk in the empagliflozin arm and 12.01 (11.15 – 12.90) in the placebo arm. A scenario analysis was conducted using these discontinuation rates. In this scenario, empagliflozin is dominant (less cost, more QALYs) vs SoC alone, with a net monetary benefit of £24,625. The full results are presented in "B26 model scenario results".

B27. Please outline what possible sources were identified from the literature for the following and why the chosen source was selected:

Company response: (*Mortality)* As per Table 37 and Table 38, twelve articles were found with potential clinical evidence and algorithms that could support the CKD model predictions of all-cause mortality and CV mortality. Preference was given to equations/ prediction data that depend on eGFR and uACR as continuous variables, or secondly on KDIGO class. Risk predictions based on eGFR decline, older data sources, smaller registries, more complex risk factors were not considered. As a result, Matsushita et al 2020 and 2010 from the CKD-PC registry were preferred, the first integrated uACR and eGFR variables with the CKD patch version of the SCORE equation and the second the detail per eGFR and uACR classes.

Table 37: (1) Mortality_inputs cells I24:I54

All-cause mortality		
Source	Research Group	Final selection
Coresh et al. 2014 (1)	CKD-PC	N/A – Matsushita et al. 2010 selected as per below.
Naimark et al. 2016 (2)	CKD-PC	
Wang et al. 2020 (3)	CRIC dataset	
Grams et al. 2020 (4)	CRIC participants	
CV and/or all-cause mortality		
Source	Research Group	Final selection
Coresh et al. 2019 (5)	CKD-PC	Matsushita et al. 2010
Matsushita et al. 2010 (6)	CKD-PC	

Sources: **[1]** Coresh, J., et al., Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA, 2014. 311(24): p. 2518-2531. **[2]** Naimark, D.M., et al., Past Decline Versus Current eGFR and Subsequent Mortality Risk. J Am Soc Nephrol, 2016. 27(8): p. 2456-66. **[3]** Wang, K., et al., Cardiac Biomarkers and Risk of Mortality in CKD (the CRIC Study). Kidney International Reports, 2020. 5(11): p. 2002-2012. **[4]** Grams et al., Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association, 2021. 36(9): p. 1685-1693. **[5]** Coresh, J., et al., Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. The Lancet. Diabetes & Endocrinology, 2019. 7(2): p. 115-127. **[6]** Matsushita, K., et al., Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet, 2010. 375(9731): p. 2073-81. Abbreviations: CKD-PC, Chronic kidney disease prognosis consortium; CRIC, Chronic Renal Insufficiency Cohort

Table 38: (2) Mortality_inputs cells I62:I92

CV mortality		
Heerspink et al. 2011 (1)	-	Matsushita et al. 2020
Orlandi et al. 2020 (2)	CRIC participants	
Grams et al. 2017 (3)	CKD-PC	
Matsushita et al. 2020 (4)	CKD patch	
Carrero 2017 (5)	SCREAM project	
Bansal et al. 2014 (6)	Kaiser dataset	

References: **[1]** Heerspink, H.J., et al., Monitoring kidney function and albuminuria in patients with diabetes. Diabetes Care, 2011. 34 Suppl 2(Suppl 2): p. S325-9. **[2]** Orlandi, P.F., et al., Slope of Kidney Function and Its Association with Longitudinal Mortality and Cardiovascular Disease among Individuals with CKD. Journal of the American Society of Nephrology: JASN, 2020. 31(12): p. 2912-2923.**[3]** Grams, M.E., et al., Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int, 2018. 93(6): p. 1442-1451. **[4]** Matsushita, K., et al., Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EClinicalMedicine, 2020. 27: p. 100552. **[5]** Carrero, J.J., et al., Albuminuria changes and subsequent risk of end-stage renal disease and mortality. Kidney international, 2017. 91(1): p. 244-251. **[6]** Bansal, N., et al., Incident Atrial Fibrillation and Risk of Death in Adults With Chronic Kidney Disease. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 2014. 3(5). Abbreviations: CKD-PC, Chronic kidney disease prognosis consortium; CRIC, Chronic Renal Insufficiency Cohort

(CVD events) Similar to the selection of the mortality approach, for the CVD predictions preference was given to algorithms that used eGFR and uACR as continuous variables or clinical data from large CKD registries describing evidence per KDIGO class. As per Table 39, Matsushita et al 2020 CKD patched risk equation, clinical data from Grams et al 2020 and Matsushita et al. 2017 were considered, to predict the risk of ASCVD, HF and PAD events, respectively. No alternative references were identified for recurrent CHD and Stroke events.

Table 39: (3) Appendix P Table 1 and Table 29

CVD clinical outcomes/events		
Source	Research Group	Final selection
Grams et al. 2020 (1)	CRIC participants	Matsushita et al. 2020, Grams et al. 2020, Matsushita et al. 2017
Orlandi et al. 2020 (2)	CRIC participants	
Grams et al. 2017 (3)	CKD-PC	
Matsushita et al. 2020 (4)	CKD patch	
Schlackow et al. 2016 (5)	SHARP population	
Grunwald et al. 2020 (6)	CRIC	
Bansal et al. 2018 (7)	CRIC	

Bansal et al. 2019 (8)	CRIC dataset	
Stein et al. 2020 (9)	CRIC dataset	
Matsushita et al. 2017 (10)	CKD-PC dataset	
Beck et al. 2015 [132] (11)	GCKD study	
Marwick 2019 [133] (12)	KDIGO review	

References: **[1]** Grams et al., Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association – European Renal Association, 2021. 36(9): p. 1685-1693. **[2]** Orlandi, P.F., et al., Slope of Kidney Function and Its Association with Longitudinal Mortality and Cardiovascular Disease among Individuals with CKD. Journal of the American Society of Nephrology: JASN, 2020. 31(12): p. 2912-2923. **[3]** Grams, M.E., et al., Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int, 2018. 93(6): p. 1442-1451 **[4]** Matsushita, K., et al., Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EclinicalMedicine, 2020. 27: p. 100552. **[5]** Schlackow, I., et al., A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease. Heart, 2017. 103(23): p. 1880-1890. **[6]** Grunwald, J.E., et al., Progression of retinopathy and incidence of cardiovascular disease: findings from the Chronic Renal Insufficiency Cohort Study. Br J Ophthalmol, 2021. 105(2): p. 246-252. **[7]** Bansal, N., et al., Cardiovascular events after new-onset atrial fibrillation in adults with CKD: Results from the Chronic Renal Insufficiency Cohort (CRIC) study. Journal of the American Society of Nephrology, 2018. 29(12): p. 2859-2869. **[8]** Bansal, N., et al., Burden and Outcomes of Heart Failure Hospitalizations in Adults With Chronic Kidney Disease. Journal of the American College of Cardiology, 2019. 73(21): p. 2691-2700. **[9]** Stein, N.R., L.R. Zelnick, A.H. Anderson, R.H. Christenson, C.R. deFilippi, et al., Associations Between Cardiac Biomarkers and Cardiac Structure and Function in CKD. Kidney International Reports, 2020. 5(7): p. 1052-1060. **[10]** Matsushita, K., et al., Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. The lancet. Diabetes & endocrinology, 2017. 5(9): p. 718-728. **[11]** Beck, H., et al., Heart Failure in a Cohort of Patients with Chronic Kidney Disease: The GCKD Study. PLoS ONE, 2015. 10(4). **[12]** Marwick, T.H., et al., Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International, 2019. 96(4): p. 836-849. Abbreviations: CKD-PC, Chronic kidney disease prognosis consortium; CRIC, Chronic Renal Insufficiency Cohort; GCKD, German Chronic Kidney Disease; KDIGO, Kidney Disease Improving Global Outcomes; SHARP, Study of Heart and Renal Protection

(Bone and mineral disorder events; Appendix P Table 10) BMD are commonly reported together in many papers. Some studies reported evidence only for a single complication, other studies focused on the progression of the biomarker that causes the complication. These studies were excluded. For the model exercise, the goal was to collect risk data for the different complications per eGFR or uACR class, or both. As per Table 40, Moranne et al. 2009, using NephroTest study data, provided this detail for the majority of BMD complications except hypocalcaemia which was obtained from Levin et al. 2007. For fractures, Runesson et al. 2020 provided evidence on the risk of events per eGFR class.

Table 40: Appendix P, section P.2 Bone and Mineral disorders

Bone and mineral disorder		
Source	Research Group	Final selection
Pimentel et al. 2017 (1)	Systematic literature review	Runesson et al. 2020 Levin et al. 200 Moranne 2009
Runesson et al. 2020 (2)	SCREAM project	
Muhammad 2020 (3)	Systematic review	
Miller 2010 (4)	National database	
Levin et al. 2007 (5)	Cross-sectional study	
Milica Bozic *et al.* 2021 (6)	NEFRONA cohort	
Moranne 2009 (7)	NephroTest cohort	
Vikrant 2016 (8)	Tertiary care hospital study	

References: **[1]** Pimentel, A., et al., Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation. Kidney International, 2017. 92(6): p. 1343-1355. **[2]** Runesson, B., et al., Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine Measurement project. Nephrology Dialysis Transplantation, 2020. 35(11): p. 1908-1915. **[3]** Tariq, M.H. and S.A.S. Sulaiman, Prevalence of Osteopenia and Osteoporosis among Chronic Kidney Disease Patients: A Systematic Review. The Open Urology & Nephrology Journal, 2020. 13(1). **[4]** Miller, J.E., et al., Association of Cumulatively Low or High Serum Calcium Levels with Mortality in Long-Term Hemodialysis Patients. American Journal of Nephrology, 2010. 32(5): p. 403-413. **[5]** Levin, A., et al., Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney International, 2007. 71(1): p. 31-38. **[6]** Bozic, M., et al., Independent effects of secondary hyperparathyroidism and hyperphosphatemia on chronic kidney disease progression and cardiovascular events: an analysis from the NEFRONA cohort. Nephrology, Dialysis, Transplantation: Official

Publication of the European Dialysis and Transplant Association - European Renal Association, 2021: p. gfab184. **[7]** Moranne, O., et al., Timing of Onset of CKD-Related Metabolic Complications. Journal of the American Society of Nephrology, 2009. 20(1): p. 164-171. **[8]** Vikrant, S. and A. Parashar, Prevalence, and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India. Indian Journal of Endocrinology and Metabolism, 2016. 20(4): p. 460-467. Abbreviations: NEFRONA, National Observatory of Atherosclerosis in Nephrology ; SCREAM, Stockholm Creatinine Measurement

(Hypertension) Hypertension is a highly prevalent comorbidity in CKD population. Publications provided detail data about the prevalence of hypertension in CKD and/or the distribution of SBP in CKD patients. As per Table 41, Vidal-Petiot 2018 displays the most recent data on the prevalence of hypertension for different eGFR classes, but also described those that would be control and not controlled when under hypertensive treatment.

Table 41: Appendix P Table 14

Hypertension		
Source	Research Group	Final selection
Vidal-Petiot 2018 (1)	A NephroTest Cohort Study (France)	Vidal-Petiot 2018
Schneider et al. 2018 (2)	GCKD	
Muntner et al. 2010 [142] (3)	CRIC	
Peralta et al. 2005 [143] (4)	NHANES	
Zhang 2019 [144] (5)	Cross-sectional study	

References: **[1]** Vidal-Petiot, E., et al., Extracellular Fluid Volume Is an Independent Determinant of Uncontrolled and Resistant Hypertension in Chronic Kidney Disease: A NephroTest Cohort Study. Journal of the American Heart Association, 2018. 7(19): p. e010278. **[2]** Schneider, M.P., et al., Left Ventricular Structure in Patients With Mild-to-Moderate CKD—a Magnetic Resonance Imaging Study. Kidney International Reports, 2018. 4(2): p. 267-274. **[3]** Muntner, P., et al., Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis, 2010. 55(3): p. 441-51. **[4]** Peralta, C.A., et al., Control of hypertension in adults with chronic kidney disease in the United States. Hypertension (Dallas, Tex.: 1979), 2005. 45(6): p. 1119-1124. **[5]** Zhang, J., et al., Blood pressure management in hypertensive people with non-dialysis chronic kidney disease in Queensland, Australia. BMC Nephrol, 2019. 20(1): p. 348. Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; GCKD, German Chronic Kidney Disease; NHANES, National Health and Nutrition Examination Survey

(Infections) As per Table 42, Hong Xu et al. 2017 was preferred as it provided risk data of different types of infections and degree of severity by eGFR class. Further, the registry it was based on included CKD populations, whereas the Ishigami et al. 2017 patient population had diabetes only and, therefore, was not considered as the best source.

Table 42: Appendix P Table 18 and 19

Infections		
Source	Research Group	Final selection
Ishigami 2017 [45] (1)	ARIC study	Hong Xu 2017
Hong Xu 2017 [170] (2)	SCREAM	

References: **[1]** Ishigami, J., et al., CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis, 2017. 69(6): p. 752-761. **[2]** Xu, H., et al., eGFR and the Risk of Community-Acquired Infections. Clinical journal of the American Society of Nephrology: CJASN, 2017. 12(9): p. 1399-1408. Abbreviations: ARIC, Atherosclerosis Risk In Communities ; SCREAM, Stockholm CREAtinine Measurements Project

(Appendix P Table 4, Table 5) Recurrent CVD events are predicted using Framingham recurrent event data as per Eriksson et al. (2001).

B28. The ERG is unclear how Appendix P Tables 11 and 12 are used to calculate a hazard ratio, what the hazard ratio is and how this hazard ratio is applied. Please provide an account of this.

Company response: The 1-year risk of anaemia in stage 4 (74.7%) and stage 5 (95.3%) from Appendix P, Table 12 were used to estimate the risk of anaemia in eGFR class “less 20”,

which was missing from the main source study (Moranne et al. 2009). The estimated risk for patients with eGFR < 20 mL/min/1.73m² (88.43%) was obtained via a linear trendline based on 2 dots, assuming eGFR=30 in stage 4 (risk=74.7%), and eGFR=15 in stage 5 (risk=95.3%).

In the model, the risk of anaemia at each cycle was specific to current eGFR class, as per Table 11. No hazard ratios were used.

B29. Why was the Model C of QDiabetes-2018 chosen over the alternatives? How were the 10-year risks converted to annual risks?

Company response: QDiabetes 2018 is a prediction algorithm model that predicts the 10-year risk of T2DM, using data from more than 1,000 general practitioner (GP) practices in England, involving more than 11 million individuals in the UK. Other risk engines are available in the literature for the development of diabetes, but they are not derived from UK patients. For example, data as published by Wilson et al 2007[4] or the Wilkinson et al 2020. Conversion from 10-year to 1-year annual risk was performed using the Miller and Homan formula (cf. question B11.4).

B30. Appendix P Table 15 and 16 provide HRs for AKI relative to eGFR 45-59 and uACR 0-29. The ERG is unclear about the use of the 150/10,000 from Sawhey and the incidences of Table 17 from Hatakeyama. How was the rate of AKI events for T2DM patients with eGFR 45-59 and uACR 0-29 estimated and what sources were used? How was the rate of AKI events for non-T2DM patients with eGFR 45-59 and uACR 0-29 estimated and what sources were used? Is it possible to estimate these rates from EMPA-KIDNEY and if so, what were they? Please clarify if the model only models 1st incidence of AKI, or reapplies the probabilities implied by Appendix P Table 15, 16 and 17 and the HR of 0.78, to estimate recurrent annual AKI.

In the model, the background rate of AKI was estimated from Sawhey et al. (2017) study, which reported 150 AKIs per 10,000 person-years. This rate was assumed to be the event rate in the reference category (eGFR 45-59 and ACR 0-29) from James et al. (2015) study, regardless of the diabetes status. Hazard ratios were then applied to the background AKI rate, according to current eGFR and uACR levels of patients without diabetes (HR from Table 15) and with diabetes (HR from Table 16). The hazard rate was converted into a “per cycle” probability to determine the incidence of AKI at each cycle.

AKI rates cannot be estimated from EMPA KIDNEY as this population was excluded from the scope of the trial. First and recurrent AKIs were modelled (using the same rate). From Table 17, only the proportion of patients treated in hospital was used in the model (regardless of T2DM status), to estimate the cost per AKI event.

[4] Wilson et al. (2007) Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Archives of Internal Medicine. 167(10):pp1068-74. https://pubmed.ncbi.nlm.nih.gov/17533210/

B31. Are the PD and HD infection rates of Appendix P applied every year for those on PD and HD?

Company response: Correct; a fixed risk of infection is applied during each cycle spent in PD (risk of peritonitis) or in HD (risk of AV access, bloodstream infection [BSI]).

B32. Please outline which of the model inputs differ, with full cell referencing, when modelling a cohort of 1,000 T2DM patients compared to when modelling a cohort of 1,000 non-T2DM patients. Ignoring the baseline characteristics, when modelling a cohort of 1,000 all patient please outline which of the model inputs differ when a T2DM patient is being simulated within this cohort compared to when a non-T2DM patient is being simulated within this cohort.

To generate a cohort of 1000 patients with T2DM, the user should select “Option 2 - EMPA KIDNEY With diabetes” on Executive Summary cell D25. With this selection, the model will automatically run on the following “T2DM-specific” inputs:

- Baseline characteristics: tab Other default data, column F8:J104.
- Progression of risk factors (tab Risk factors inputs): eGFR natural progression (G51:I54), HbA1c (G153:G159), BMI (G198:G204)
- Risk specific to T2DM (Risk equations): the same equations are used, but the factor for “T2D” is set to 1
- Risk of complications (Risk data inputs): risk of heart failure (E13:E26), risk of AKI (E460:E485).

All other inputs are independent of the T2DM status, as well as treatment effect.

When a T2DM patient is being simulated, the impact on input is the same as described above, except that baseline characteristics are from the “all patients cohort”.

B33. Appendix N Table 3 outlines very good EQ-5D-5L completion rates among those attending at each follow-up time point, but very different numbers attending at each time point. Please clarify how the follow-up attendance of Appendix N Table 3 corresponds with that for the assessment of eGFR in Document B Figure 18 and any reasons for differences between these. Please also tabulate the numbers followed up for eGFR at the Appendix N Table 3 timepoints separately by arm.

Company response: The varying numbers attending at each time point are the result of EuroQol-5 Dimensions-five Levels (EQ-5D-5L) being a prespecified assessment at baseline, month 18 and final visit only (that could have happened at any time point as EMPA KIDNEY is an event driven trial). The numbers of EQ-5D-5L assessments at prespecified visits for EQ-5D data collection are broadly aligned with eGFR assessments at those visits.

Compliance rates shown in Appendix N Table 4 represent the % completion of questionnaire out of all available response (after excluding data for patients who did not have a baseline measurement or did not have measurement following baseline), while Appendix N **Error! Reference source not found.** provides estimates for records that ultimately were used in the MMRM.

For example:

The non-matching number for empagliflozin at 18 months reflects that 5 patients had complete questionnaires at 18 months but followed an uncomplete questionnaire at baseline and thus could not be included in the MMRM models.

The non-matching number for placebo at baseline reflects the fact that 5 placebo patients had a complete baseline EQ-5D assessment but then later on only had partial measurements for later visits and thus could not be included in the MMRM analyses.

The % number reflects the Number of complete records out of all records available e.g., at baseline for empagliflozin 3146 questionnaires were available, with 3140 being complete. (This is a correction to the definition of compliance given under the original Appendix N Table 4 [*Compliance is defined as the number of EQ-5D-5L forms completed divided by the number of forms expected. The number of forms expected is the number of patients who came to the visit at each time point].)

eGFR was assessed at each visit, as per protocol. The numbers followed up for eGFR at each visit at the Appendix N Table 3 timepoints are provided in Table 43.

As EMPA-KIDNEY was conducted during the COVID-19 pandemic and associated restrictions, follow up visits were permitted to be carried out outside of the normal window of ±30 days, and eGFR measurements used included central or local measurements.

Table 43: Frequency of eGFR measurements by follow-up visit

Visit	Empa (n)	Placebo (n)	Total (N)
Baseline	3,304	3,305	6,609
12 months	3,123	3,122	6,245
18 months	2,867	2,861	5,728
24 months	1,841	1,822	3,663
30 months	1,289	1,269	2,558
36 months	313	309	622

Abbreviations: eGFR, estimated glomerular filtration rate

B34. Priority: Please provide the equivalent of Appendix N Table 4 to three decimal places for the baseline visit and if possible, Appendix N Table 4 to three decimal places as well. Appendix N Table 4 is not necessarily consistent with the health state utilities reported on pages 77 and 78 of the IQVIA pdf in embedded Appendix O. Please provide an account of this.

Company response: In the model base-case the health state utility values from Jesky 2016 were used. The PDF embedded in Appendix O shows the Jesky 2016 values, which are presented to clinicians. Table 44 and Table 45 below, which are equivalent to Table 4 and Table 5 in Appendix N to three decimal places, show EMPA-KIDNEY trial derived health state utilities. These values were used as a scenario in the model (see B.3.11.3) and resulted in less than a 10% change from the base-case.

Table 44: Descriptive Summary of UK EQ-5D-3L Utility Scores at Scheduled Visits

Visit	Empagliflozin			Placebo			Total		
	Compliance (%)*	Mean utility (SD)	Mean EQ-VAS (SD)	Compliance (%)*	Mean utility (SD)	Mean EQ-VAS (SD)	Compliance (%)*	Mean utility (SD)	Mean EQ-VAS (SD)
Baseline	3140 (99.809)	0.853 (0.175)	77.208 (16.415)	3122 (99.744)	0.859 (0.164)	78.424 (15.694)	6262 (99.777)	0.856 (0.170)	77.813 (16.070)
12 months	212 (100.000)	0.857 (0.190)	76.302 (18.744)	203 (100.000)	0.851 (0.181)	77.079 (18.258)	415 (100.000)	0.854 (0.185)	76.681 (18.490)
18 months	2876 (99.861)	0.849 (0.195)	76.989 (16.727)	2866 (99.791)	0.848 (0.194)	76.833 (17.318)	5742 (99.826)	0.849 (0.194)	76.911 (17.023)
24 months	561 (99.645)	0.848 (0.208)	76.418 (17.415)	549 (99.637)	0.849 (0.192)	77.058 (16.762)	1110 (99.641)	0.848 (0.200)	76.735 (17.090)
30 months	981 (100.000)	0.829 (0.204)	75.376 (17.439)	960 (99.585)	0.827 (0.209)	74.701 (18.810)	1941 (99.794)	0.828 (0.207)	75.042 (18.129)
36 months	317 (100.000)	0.817 (0.239)	75.297 (16.967)	308 (99.676)	0.818 (0.224)	74.461 (17.558)	625 (99.840)	0.817 (0.231)	74.885 (17.252)

*Compliance is defined as the number of EQ-5D-5L forms with a corresponding eGFR value, whether from the same visit or from a previously recorded eGFR if it occurred no longer than 6 months before. Abbreviations: EQ-5D-3L, EuroQol five-dimension three-level; EQ-VAS, EuroQol visual analogue scale; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; UK, United Kingdom

Table 45: Descriptive summary of UK EQ-5D-3L utility scores by eight KDIGO states excluding the baseline visit

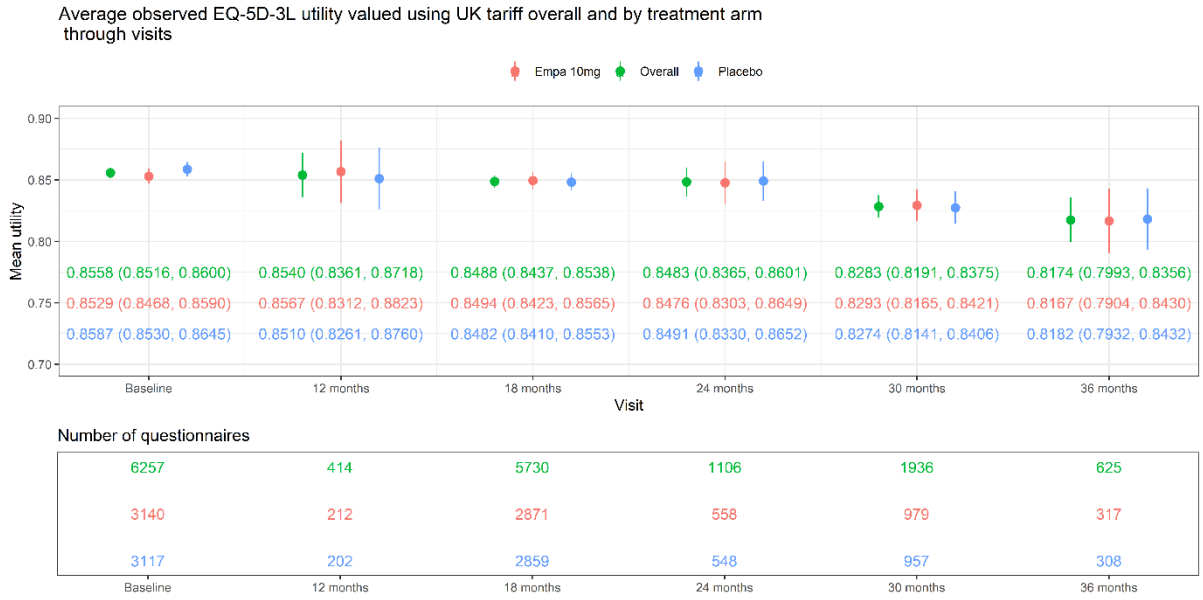
	Empagliflozin				Placebo				Total			
KDIGO State	N visits	Mean (SD)	Median (Q1-Q3)	Min-Max	N visits	Mean (SD)	Median (Q1-Q3)	Min-Max	N visits	Mean (SD)	Median (Q1-Q3)	Min-Max
G2A2	86	0.921 (0.097)	0.987 (0.860, 0.987)	0.565, 0.989	57	0.912 (0.109)	0.986 (0.860, 0.987)	0.564, 0.989	143	0.917 (0.101)	0.986 (0.860, 0.987)	0.564, 0.989
G2A3	172	0.917 (0.147)	0.987 (0.891, 0.987)	0.215, 0.989	180	0.934 (0.096)	0.987 (0.891, 0.987)	0.547, 0.989	352	0.926 (0.124)	0.987 (0.891 ,0.987)	0.215, 0.989
G3A1	521	0.814 (0.204)	0.868 (0.723, 0.987)	-0.113, 0.989	505	0.817 (0.209)	0.868 (0.704, 0.988)	-0.024, 0.989	1026	0.816 (0.206)	0.868 (0.715, 0.988)	-0.113, 0.989
G3A2	753	0.862 (0.178)	0.934 (0.788, 0.987)	-0.135, 0.989	712	0.849 (0.190)	0.893 (0.781, 0.987)	-0.205, 0.989	1465	0.855 (0.184)	0.909 (0.786, 0.987)	-0.205, 0.989
G3A3	797	0.880 (0.176)	0.985 (0.825, 0.987)	-0.187, 0.989	853	0.881 (0.159)	0.985 (0.804, 0.987)	-0.135, 0.989	1650	0.880 (0.167)	0.985 (0.810, 0.987)	-0.187, 0.989
G4A1	354	0.767 (0.243)	0.823 (0.676, 0.987)	-0.104, 0.989	270	0.773 (0.231)	0.828 (0.675, 0.987)	-0.131, 0.989	624	0.769 (0.238)	0.825 (0.675, 0.987)	-0.131, 0.989
G4A2	633	0.820 (0.203)	0.868 (0.719, 0.987)	-0.228, 0.989	513	0.812 (0.203)	0.868 (0.697, 0.987)	-0.096, 0.989	1146	0.816 (0.203)	0.868 (0.708, 0.987)	-0.228, 0.989
G4A3	883	0.869 (0.184)	0.985 (0.797, 0.987)	-0.262, 0.989	989	0.868 (0.173)	0.985 (0.793, 0.987)	-0.409, 0.989	1872	0.869 (0.178)	0.985 (0.797, 0.987)	-0.409, 0.989

Missing stage	424	0.774 (0.272)	0.868 (0.657, 0.987)	-0.386, 0.989	437	0.758 (0.272)	0.826 (0.666, 0.987)	-0.386, 0.989	861	0.766 (0.272)	0.847 (0.662, 0.987)	-0.386, 0.989
Other stages	314	0.850 (0.170)	0.891 (0.749, 0.987)	0.033, 0.989	358	0.844 (0.201)	0.908 (0.781, 0.987)	-0.295, 0.989	672	0.847 (0.187)	0.902 (0.776, 0.987)	-0.295, 0.989

Abbreviations: EQ-5D-3L, EuroQol five-dimension three-level; KDIGO, Kidney Disease: Improving Global Outcomes; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; UK, United Kingdom

B35. Please tabulate the data of Appendix N Figure 2: mean, s.e. and N.

Company response: Appendix N Figure 2 has been updated to also show the mean utility values, to 3 decimal places for completeness. The data shown in Appendix N Figure 2 are tabulated in Table 46 below.



Abbreviations: EQ-5D-3L, EuroQol five-dimension three-level; UK, United Kingdom

Table 46: Appendix N Figure 2 tabulated

	TRTP	Estimand	Baseline	12 months	18 months	24 months	30 months	36 months
1	Overall	Mean utility	0.8558 (0.8516, 0.8600)	0.8540 (0.8361, 0.8718)	0.8488 (0.8437, 0.8538)	0.8483 (0.8365, 0.8601)	0.8283 (0.8191, 0.8375)	0.8174 (0.7993, 0.8356)
2	Overall	Number of questionnaires	6257	414	5730	1106	1936	625
3	Empa 10mg	Mean utility	0.8529 (0.8468, 0.8590)	0.8567 (0.8312, 0.8823)	0.8494 (0.8423, 0.8565)	0.8476 (0.8303, 0.8649)	0.8293 (0.8165, 0.8421)	0.8167 (0.7904, 0.8430)
4	Empa 10mg	Number of questionnaires	3140	212	2871	558	979	317
5	Placebo	Mean utility	0.8587 (0.8530, 0.8645)	0.8510 (0.8261, 0.8760)	0.8482 (0.8410, 0.8553)	0.8491 (0.8330, 0.8652)	0.8274 (0.8141, 0.8406)	0.8182 (0.7932, 0.8432)
6	Placebo	Number of questionnaires	3117	202	2859	548	957	308

B36. In the Patient_Inputs worksheet P8 states that the distribution is truncated between 20 and 94, but the values in S8 and T8 are 20 and 80. What was the minimum age and maximum age in the trial, and which is correct for modelling? There is no need to submit an updated set of analyses.

Company response: The baseline age was initially truncated at 94 years (in view of maximum age + 2*Standard Deviations in the 35 cohorts used to derive key risk equations in the model) (Matsushita 2020). This is indicated in cell P8. With age truncation at 94 years, there were still 5.0% of patients aged 85+ at baseline in the model, whereas EMPA-KIDNEY age distribution indicates 2.0% of patients aged 85 or above at baseline. These patients have particularly high mortality rates in the first years, which may yield results not representative of the EMPA-KIDNEY population. For this reason, baseline age was further truncated to a lower value (80 years, as shown in cell T8).

B37. Other_Default_Data F120 has value -1.90 but L120 is left empty. Are there any concerns around this when modelling a T2DM subset?

Company response: Other_Default_Data Cell F120 (and the entirety of row 120) is not used in the CKD-PM and was added only to account for potential non-SoC comparators which are not presented in this submission. The EAG does not need to consider this row in the model for the purposes of this submission.

B38. In the model, the proportion who are hypertensive is 86.1%: Patient_Inputs F62. the proportion of those receiving hypertensive medication conditional upon them being hypertensive is also 86.1%: Patient_Inputs F87. Does this imply 100% of those with HT receive HT treatment or 86.1% of patients with HT receive HT treatment?

Company response: The hypertension status (yes/no) at baseline is sampled from a binomial distribution (86% diagnosed with hypertension, cell F62). The “treated HTN” status at baseline is also sampled from a binomial distribution; however, only patients with hypertension at baseline can have “treated hypertension” (so the correct interpretation is “86.1% of patients with HT receive HT treatment”). It was assumed that the proportion of patients treated for hypertension was equal to the proportion of patients diagnosed with hypertension (86.1%).

B39. What values are permissible for the user defined random seed on the Executive Summary worksheet? The ERG has not yet fully parsed the VBA. Random numbers within Microsimulation_Click appear to be sampled as below:

```
If Sheets("CONTROL").Range("Seed_option").Value = 1 And arm = 1 Then

   Randomize (Rnd)

   Sheets("Executive_Summary").Range("Seed").Value = Rnd

End If

Rnd (-2)

Randomize (Sheets("Executive_Summary").Range("Seed").Value)
```

The ERG would be grateful if the logic for the inclusion of Randomize (Rnd) within the If statement could be given, and also the logic of the inclusion of Rnd (-2) within the code.

Company response: The user defined seed on the Executive Summary can take any numeric value (any real number between negative and positive infinity).

The “Randomize(Rnd)” is used to generate a random seed for the vba random number generator (“Rnd” function). The subsequent “Rnd” in the next line of code, uses this number as a seed to generate a random number which is then saved as the model seed for that run. This extra step of randomising the “Rnd” seed is necessary to ensure that a random seed is used for the “random seed” option on the Executive Summary, as the model randomisation within this option should not be influenced by a previous run or user defined seed.

“Rnd” while using a negative argument before “Randomize” allows the “Randomize” function to generate a repeatable sequence of random numbers. The model logic runs 1 treatment arm at a time; these lines of code are necessary, so the same random numbers are applied for both treatment arms. Therefore, the set of patients, and random chance of an event, is the same across arms.

B40. Setting HHF and AKI HRs to 1.00 in Other_Default_Data cells F171 and F172 appears to only affect total costs and not total QALYs. Is this the correct implementation of no clinical effect for empagliflozin for these variables, particularly in the light of the disutility for AKI in Document B Table 36?

Company response: Changing the hazard ratios (HRs) of HHF and AKI to 1 in the empagliflozin arm has a minor impact on the QALYs for the empagliflozin arm, from 7.091 to 7.086 (discounted) and from 9.274 to 9.268 (undiscounted) with 1000 patients. The incremental QALY is slightly decreased from 0.849 to 0.844 (discounted, difference -0.005) and from 1.289 to 1.283 (undiscounted, difference -0.006). A simple calculation to demonstrate the magnitude of the impact on QALYs when removing treatment effect on HHF and AKI has been performed:

The differences in incidence between the 2 scenarios, multiplied by the respective disutility of each event, yields a QALY loss in line with the finding: (2.4% x -0.11) + (3.4% x -0.04) = -0.004 QALYs.

In the scenario where HRs of 1 are used for both HHF and AKI, empagliflozin is dominant (less cost, more QALYs) vs SoC alone, with a net monetary benefit of £21,942. The full results are presented in "B40 model scenario results".

B41. Please clarify if in either arm of EMPA-KIDNEY if any patients recorded an annual improvement in their eGFR health state; e.g. between baseline and 12 months improved from G3b to G3a or between 12 months and 24 months improved from G4 to G3b.

Company response: It is not possible to determine changes in KDIGO risk category over time (decline or improvement) for individual patients as change in eGFR category didn't trigger collection of confirmatory values 90 days apart. As detailed in the response to question B2, the average annual rate of change in eGFR (ml/min/1.73m^2) for patients in each KDIGO risk category at baseline were used.

B42. Please clarify if in the Results worksheet hypothetically reported ESKD as per eGFR under 15 ml/min/ 1.73m^2 as 59% for empagliflozin and 69% for SoC means the of the 1,000 cohort under empagliflozin 590 were modelled as at some stage having eGFR < 15 and 690 under SoC.

Company response: The EAG's interpretation above is correct.

B43. When the population is restricted to those without diabetes the trial mean HbA1c appears to be 5.5%. But in the sampling if the patient is pre-diabetes based upon the Patient Inputs worksheet it appears that the truncated normal distribution applies a lower limit of 5.7%. Is this the case and is it intended?

Company response: The HbA1c threshold for pre-diabetes was not obtained from the EMPA-KIDNEY trial but instead set in line with the prediction model of HbA1c progression for patient without diabetes (as used in the model, Risk factors inputs, cell C209 and below). Patients with HbA1c below 5.7% who are not treated with glucose lowering drugs will be considered as patients with normoglycemia, thus 5.7% HbA1c threshold was applied to identify these patients with impaired glucose tolerance.

Reference: Pani LN, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care. 2008 Oct;31(10):1991-6.)

[B44] No question B44 was received.

B45. The deterministic model appears to use random numbers to model the eGFR decline, Patient_Engine cells E152:E133 for cells E46:E127, and to model the uACR change-fold, cells F152:F133 for cells I46:I127, the reasons for which are not obvious. Even if this is only within the PSA modelling the requirement for these random numbers is still not obvious, each PSA iteration being a single deterministic model run. An account of this would be much appreciated. An account of (A) the conceptual difference

between eGFR treatment effect, G46:G127, and eGFR decline, E46:E127, and (B) the conceptual difference between uACR Tx Effect K46:K127 and uACR change-fold l46:l127 would also be much appreciated.

Company response: eGFR decline in cells E46:E127 described the eGFR decline/decrements/increments in each cycle. The model includes two options to model annual eGFR progression/changes: The first option uses Grams et al. 2020 (*Table 29*) – this paper provides eGFR decrements in line with each KDIGO category and is used in the CKD-PM CEA. The second option uses the Coresh 2014 and Naimark et al. 2016 data, which is based on a distribution of eGFR changes observed in the CKD-PC registry. The random numbers are only used in the second option, as a different eGFR change from the distribution is used, and this option was not used in CKD-PM CEA presented in this submission. Both options were considered as the CKD population is highly heterogenous, thus these options are incorporated to model two different natures of eGFR decline. The Grams et al. 2020 option links the evolution of eGFR with progression through KDIGO stages. The Naimark et al. (2016) option allows to mimic both fast and slow progression of eGFR, both of which commonly occur in CKD patients. When selected, both of these options are used in the deterministic and probabilistic analyses as they relate to the nature of the microsimulation, where we want to study the impact of the drug across different types of patients with CKD.

For uACR change fold, the only source of information available was taken from CKD-PC registry, where a distribution of these changes was available for a CKD population. Here the random numbers are used to generate a different uACR change-fold in each cycle and per patient to reflect the heterogeneous nature of CKD patients.

Cells G46:G127 are the tracker for treatments effects in eGFR in the patient engine. In case there are different from zero and patients are on treatment, it overwrites/replaces the natural progression of the disease changes data by the treatment effect data. In eGFR, treatment effect replaces the Grams et al 2020 data. In the uACR columns, the same logic is followed, if patients are on treatment, the treatment effect uACR fold changes (on cells K46:K127) replaces the Coresh and Naimark changes data, that represent the natural progression of the disease.

B46. Is there any mortality associated with renal cancer or urothelial cancer?

Company response: No, the model does not separately model fatal cancer events. Mortality is a composite endpoint, in which non-specific mortality, CV death and renal death account for all causes of death. The first element (non-specific mortality) implicitly incorporates cases of cancer mortality, and no further separate modelling of cancer deaths is performed.

B47. Does the model include any treatment stopping rules for either empagliflozin or SoC; e.g. entry to G5?

Company response: The EMPA-KIDNEY did not report any treatment effects in patients in G5 health states, for both eGFR and uACR; thus, for these patients, the natural progression of the disease is employed, no additional treatment effect was assumed. While no treatment effect was assumed in G5, treatment costs were accrued until treatment termination, that was assumed at the time of initiation of RRT according to the EMPA KIDNEY trial protocol.

B48. It would be much appreciated if a table of each event modelled as described within Appendix P, disaggregating events e.g., from BMD to hyperphosphataemia, hypocalcaemia, secondary hyperthyroidism, hip fracture, other fracture, no fracture, could be supplied stating the assumed duration that the event has upon quality of life and the assumed duration that the event has upon cost.

Company response: The current structure of the model does not permit to split the QALYs per event. For the complication events the EAG has outlined in question B48 above, only hip fractures and other fractures are associated with a disutility. For the remaining listed events, it is assumed that the utility resulting from those events is already accounted in the health state utilities. In the event the EAG deems this table is necessary, more time will be needed to provide this detail.

B49. What eGFR changes have been assumed for those remaining on empagliflozin and in G5, A1, in G5, A2 and in G5, A3? Similarly, what eGFR changes have been assumed for those remaining on SoC and in G5, A1, in G5, A2 and in G5, A3? Please also provide the corresponding changes for uACR

Company response: The EMPA-KIDNEY trial did not report any treatment effects in patients in G5 classes, for both eGFR and uACR; thus, for these patients, the natural progression of the disease is employed as per Grams et al. 2020 (Table 29, detailed in question B7).

Section C: Textual clarification and additional points

\Additional documents

C1**.** Please provide the following "data on file" documents which are referenced in Document B and/or Appendices, but not supplied in the reference pack:

1. **Priority: Boehringer Ingelheim. Clinical Trial Report. A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease [data on file]. 2022. (Appendix D Reference 25) (note the reference pack document named 'EMPA-KIDNEY CTR 2022.pdf' is 'Design, recruitment and baseline characteristics of the EMPA-KIDNEY trial' - the same as ''EMPA-KIDNEY Design, Recruitment 2022.pdf')**
2. DOF EMP 23-04
3. DOF EMP 23-05
4. DOF EMP 23-06
5. DOF EMP 23-07
6. DOF EMP 23-08
7. **Priority: DOF EMP 23-09**
8. DOF EMP 23-10
9. DOF EMP 23-11
10. DOF EMP 23-12

Company response: The requested references are now supplied. Please note, all are confidential.

C2. Please also provide the EMPA-KIDNEY protocol and statistical analysis plan

Company response: These are now supplied in the following two confidential documents:

- C2.1_EMPA-KIDNEY Protocol
- C2.2_EMPA-KIDNEY Final SAP.

Also enclosed is the response to the EMA request for supplementary information, in confidence:

- C2.3_ID6131_EMA-CKD-response 1-final RSI-content-final

Please note EU Commission Decision for the new indication of Jardiance (empagliflozin) for the treatment of chronic kidney disease was received on 24 July 2023.

C3. Appendix D.1.1.6.1: The embedded Excel files 'List of included publications.xlsx' and 'List of excluded publications.xlsx' cannot be opened – please send as separate files.

Company response: These are now supplied in the following two documents:

- C3.1_List of included publications
- C3.2_List of excluded publications.

Section S: Supplementary questions after clarification call

S1 Please provide the estimates of the annual eGFR change, mean (95% C.I.), that are applied for eGFR health state G5. Please also provide the equivalent of this for uACR. To the extent that any of this data is taken from EMPA-KIDNEY, if time permits please also provide it separately for those with T2DM at baseline and those without T2DM at baseline. Please provide any additional references as necessary.

Company response: The EMPA-KIDNEY trial did not report any treatment effects in patients in G5 classes, for both eGFR and uACR; thus, for these patients, the natural progression of the disease is employed as per Grams et al. 2020 (Table 29, detailed in question B7).

S2. The EAG has not been able to source the Framingham risk factor progression functions from Wilson 1993, Doc B Table 32, and would be grateful if more explicit referencing (e.g. Table or Page and paragraph) could be provided for these values and the associated functional form. Given the description of Alfa in Risk_Equations B114 the EAG would also be grateful if it could be confirmed that this aspect in the Patient_engine risk factor evolutions should reference the baseline value and baseline age rather than the previous year value and previous year age. If this is correct should the baseline age element also be subject to the maximum Framingham age constraint? If this is not correct please do not supply a corrected model version or updated analyses. The Patient_engine DBP evolution also references Framingham but there is nothing in Doc B Table 32 about this. Clarification of whether Framingham provides a DBP evolution equation would be appreciated.

Company response: The Framingham progression equations for total cholesterol, HDL, and SBP were developed by the IQVIA Core Diabetes Model team internally, there was no separate publication for these equations.

This was done by fitting polynomial functions to the data in the Framingham study (Table 2 of *Wilson and Evans 1993*). The polynomials are of the form:$\alpha + \beta_1 x + \beta_2 x^2 + \beta_3 x^3$, in which$\alpha$ is the risk factor value when the patient is born and$x$ is the current age. α is calculated as: $\alpha = Risk\ factor\ value\ at\ baseline - (\beta_1 y + \beta_2 y^2 + \beta_3 y^3)$, y is age value at baseline. The calculation ofα is subjected to the maximum

Framingham age constraint (70 years of age). Thus, age is fixed in the equation once this age threshold is reached. Framingham progression equation for DBP was not used in the CKD-PM model, because DBP is not a risk factor impacting risk predictions. So the data currently shown is just a placeholder for future developments.

The cell G140 of Risk_factor input tab displays the following legend: Alfa= TC (previous year)-(CAge^3*Age^3)+(CAge2*Age^2)+Age*Cage, however the correct legend should be : Alfa= =TC (baseline year)-(CAge^3*Agebaseline^3)+(CAge2*Agebaseline^2)+Agebaseline*CAge

Source:Wilson and Evans, Coronary Artery Disease Prediction, Am J Hypertens, 1993 Nov;6(11 Pt 2):309S-313S

S3. Minor updates to the model.

A version of the cost-effectiveness model (01Aug2023) is enclosed that includes the following minor updates:

- mortality rate during KRT (HD, PD) in patients aged above 80 was rescaled to account for absence of RT in this population (this is related to question B17)
- HbA1c projection, coefficient for baseline HbA1c value was corrected (link was incorrect)
- ratio to extrapolate from nonfatal ASCVD to nonfatal CVD including UA and TIA was corrected accounting for stroke fatality rate

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

Company response to further clarification questions received 10th August 2023

17th August 2023

File name	Version	Contains confidential information	Date
ID6131_Empagliflozin_Further-Qs-response_[Redacted]	1	No, redacted	25th Oct 2023 (redacted version of 17th August 2023 responses)

The EAG is grateful to the company for supplying responses to the extensive set of EAG clarification questions in a timely manner. Time pressures may have contributed to some confusion. The EAG would be grateful of some of this confusion could be addressed, with a view to avoiding Technical Engagement prior to the 1st ACM.

Clarification 1: Please clarify that the units for HbA1c of Table 4 are correct, and also provide the units for Tables 25 and 27. Tables 25 and 27 when combined weighted 46:54 appear to suggest somewhat different values than those of Table 4. The EAG would be grateful if these values could be checked for consistency and an account given for any apparent inconsistencies.

Tables 25 and 27 combined	EMPA	PLAC
HbA1c	0.02	-0.15
Weight	-2.56	-1.69
Hb	0.63	-0.14
SBP	-3.84	-2.22
DBP	-2.57	-1.66

Company response:

The units for HbA1c in Table 4 (from original clarification questions response) are confirmed to be mmol/mol. HbA1c, weight, SBP, and DBP in Table 4 are based on results from mixed-model repeated measures (MMRM) averaged over time. The result for each visit where the respective measurement was taken is weighted by the duration of the visit window when calculating this estimated average over time. It excludes data from Month 36 from this average due to the low number of patients for which measurements were taken at this visit. These are treatment effects as used in the cost-effectiveness model. Please note they were inaccurately labelled as 'incremental' treatment effects. Table 1 below includes the same results as original Table 4 but with an updated title and footnotes for added clarity.

Tables 25 and 27 (from original clarification questions response) have been checked for consistency vs original Table 4. The changes in HbA1c, weight, SBP, and DBP presented in Tables 25 and 27 were based on results from mixed-model repeated measures for the change from baseline to the month 36 visit for patients with and without diabetes at baseline.

Table 2 and Table 3 below are replacements for original Tables 25 and 27. These provide the equivalent of Table 1 (original Table 4; MMRM averaged over time), for patients with and without diabetes. It should be noted that as the values reported in current Table 1, 2, and 3 are based on models that include patient-level covariate-adjustments, the average of estimation results from Table 2 and Table 3 weighted by the proportion of patients with and without diabetes is not expected to result in the values averaged over all visits reported in Table 1.

The units for all values have now been added to Table 2 and Table 3 below (as per the request to confirm units in original Tables 25 and 27). To confirm, the unit for HbA1c is also mmol/mol, consistent with Table 1.

Please note that haemoglobin (Hb; g/dL) results (in Tables 1, 2 and 3) are based on an ANCOVA analysis for change from baseline to Month 18 in patients from the UK only, as Hb measurements were taken at baseline and Month 18 in this subpopulation only. Again, weighting by the proportions of patients in subgroups featuring patient-level covariate adjustment is not expected to result in the values presented in Table 1 (the respective adjusted values for the overall population).

Table 1 (with reference to Table 4 from original clarification questions response): Treatment effect per risk factor in EMPA-KIDNEY for the full cohort (average change from baseline MMRM results over time (centrally assessed) - RS (OC−AD))

Risk factor	Empagliflozin 10mg				Placebo			
	Mean	SE	Lower min	Upper max	Mean	SE	Lower min	Upper max
HbA1c (mmol/mol)*	-0.56	0.14	-0.83	-0.29	-0.15	0.14	-0.41	0.12
Weight (kg)*	-1.55	0.09	-1.74	-1.37	-0.68	0.09	-0.86	-0.49
BMI (calculated)*	-0.55	-	-	-	-0.24	-	-	-
Hb (g/dL)†	0.60	0.06	0.49	0.71	-0.14	0.06	-0.26	-0.02
SBP (mmHg)*	-3.92	0.21	-4.32	-3.51	-1.29	0.21	-1.70	-0.88
DBP (mmHg)*	-1.64	0.12	-1.88	-1.40	-1.22	0.12	-1.47	-0.98

Abbreviations: BMI, body-mass index; DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, glycated haemoglobin; max, maximum; min, minimum; SBP, systolic blood pressure; SE, standard error
Source: EMPA-KIDNEY trial output. Data on File.

Table 2 (with reference to Table 25 from original clarification questions response): Treatment effect per risk factor in EMPA-KIDNEY for patients with DM (average change from baseline MMRM results over time (centrally assessed) - RS (OC−AD))

Treatment effects for the full cohort	Empagliflozin 10mg	Placebo
HbA1c (mmol/mol)*	-1.5	-0.5
Weight (kg)*	-2.14	-1.06
Hb (g/dL)†	0.75	-0.14
SBP (mmHg)*	-5.3	-1.7
DBP (mmHg)*	-1.2	-0.7

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; Hb, haemoglobin; HbA1c, glycated haemoglobin; SBP, systolic blood pressure
Source: EMPA-KIDNEY trial output. Data on File.

Table 3 (with reference to Table 27 from original clarification questions response): Treatment effect per risk factor in EMPA-KIDNEY for patients without DM (average change from baseline MMRM results over time (centrally assessed) - RS (OC−AD)

Treatment effects for the full cohort	Empagliflozin 10mg	Placebo
HbA1c (mmol/mol)*	0.3	0.2
Weight (kg)*	-1.05	-0.35
Hb (g/dL)†	0.52	-0.14
SBP (mmHg)*	-2.7	-0.9
DBP (mmHg)*	-2.0	-1.6

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; Hb, haemoglobin; HbA1c, glycated haemoglobin; SBP, systolic blood pressure
Source: EMPA-KIDNEY trial output. Data on File.

* Model includes age (5 cat.), sex, local screening eGFR (CKD−EPI) (5 cat.), local screening UACR (5 cat.), region, visit by treatment by baseline diabetes status interaction, baseline value by visit interaction as fixed effect(s). The following covariance structure has been used to fit the mixed model: Unstructured. Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

† Haemoglobin (g/dL) change from baseline ANCOVA results at 18 months (only measured in UK patients at baseline and 18 months). Model for 18 months includes baseline value as linear covariate(s) and treatment, baseline diabetes status, Treatment by baseline diabetes status interaction as fixed effect(s). Note: all covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

Clarification 2: Tables 20 and 21 are not fully populated so are not aligned with the B4 request and Table 19. Tables 26 and 28 appear to permit Tables 20 and 21 to be fully populated. Given that this is possible for the OC-AD analysis the EAG would be grateful if either Tables 23 and 24 could be fully populated as requested in B4, or the equivalent of Tables 26 and 28 could be presented for the OC-OT analysis.

Company response:

Table 4 and Table 5 below represent fully populated updates to Tables 20 and 21 from the original clarification questions response, in line with the original B4 request. As noted in the original response, further split of patients with and without diabetes per KDIGO category analyses have inherent limitations. When this subgroup analysis was originally attempted using the shared parameter model, convergence was not achieved. The results presented therefore use random slope and intercept model; further details on this model and assumptions are detailed in the response to Clarification 3 below. The analyses are not adjusted for multiple testing, and outputs reported in small subgroups are prone to random variation and might not be representative of the true treatment effect. [redacted].

For the CEA, treatment effect in the overall population was applied in all scenarios for patients while on treatment rather than subgroup specific treatment effects (for subgroups with or without diabetes); this assumption was driven by the limitation of the size of the dataset and supported by evidence of T2DM not being a treatment effect modifier (1). Upon treatment discontinuation, differential annual eGFR decline rates are used for patients with and without T2DM (based on published literature supporting faster CKD progression among patients with T2DM).

Scenario analyses show that empagliflozin remains highly cost-effective (dominant) if the treatment effects presented in Table 4 and 5 are applied.

Table 4 (with reference to Table 20 from original clarification questions response): Annual eGFR change in patients receiving empagliflozin and SoC – RS (OC-AD) patients with diabetes

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3a	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]			[redacted]		

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA: not available; OC-AD, Observed Case-All Data; RS, randomised set; SoC, standard of care

Table 5 (with reference to Table 21 from original clarification questions response): Annual eGFR change in patients receiving empagliflozin and SoC – RS (OC-AD) patients without diabetes

	Mean annual eGFR change – mL/min/1.73m^2 (95% CI)					
	Empagliflozin 10 mg on top of SoC			Placebo on top of SoC		
	A1	A2	A3	A1	A2	A3
G2	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3a	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
G3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]			[redacted]		

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NA: not available; OC-AD, Observed Case-All Data; RS, randomised set; SoC, standard of care

Reference:
1. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400(10365):1788-801

Clarification 3: The response to B2 states "*The subgroup analysis displayed in Document B Table 29 is based on KDIGO categories at baseline only, no transitions between KDIGO categories during the trial are considered in the random slope and intercept model*." Given the importance of Table 29 to the economic modelling, to avoid any misunderstanding by the EAG does this mean that patients who were at baseline in, say, (G3a, A2) only contribute eGFR change to the (G3a, A2) cell of Table 29? Supposing that a subset of these baseline (G3a, A2) patients worsened to (G3b, A2), would the eGFR change data subsequent to this change contribute to the Table 29 (G3a, A2) change or to the Table 29 (G3b, A2) change? Document B did not document that Table 29 was based upon a random slope and intercept model and as a consequence the EAG could not ask about this analysis. If there is an internal BI report that sets out the process by which the random slope and intercept model was determined as being the most appropriate and finalised, it would be much appreciated if this could be supplied.

Company response:

Document B Table 29 estimates the annual rate of change in eGFR by baseline KDIGO risk category to account for different disease severity at baseline and to provide an evaluation of variability potentially applicable to different states of disease progression that patients are in at the beginning of their follow-up in EMPA-KIDNEY. The underlying assumption is that the average annual rate of change in eGFR might differ between patients starting with different disease severities, i.e., the linear decline estimated by means of the random slope and intercept model may differ between patients with different KDIGO risks at baseline. In the subgroup analysis reported in Document B Table 29, a patient who is in KDIGO risk category (G3a, A2) at baseline contributes to the estimation of the respective baseline category-specific average annual rate of change in eGFR, i.e., to cell (G3a, A2) in the example above. In short, yes, a patient who was (G3a, A2) at baseline only contributes to the (G3a, A2) cell of Table 29; and patients worsening from a baseline of (G3a, A2) to (G3b, A2) would also only contribute to the (G3a, A2) cell of Table 29.

The EMPA-KIDNEY TSAP pre-specifies the shared parameter model to be the main model for the annual rate of change in eGFR in EMPA-KIDNEY. The shared parameter model jointly models:

- The annual rate of change in eGFR using a random slope and intercept model (a linear mixed model with random effects for each patient's slope and intercept); and
- The time to event for ESKD or death using a Weibull survival model in which the scale parameter is assumed to be linearly related to the random effects from the random slope and intercept model. This allows for the dependence between the annual rate of change in eGFR and time to ESKD or death in the model (i.e., those with faster rates of change in eGFR will generally have a shorter time to ESKD or death).

An analysis using the random slope and intercept model, i.e., not accounting for the potential informative censoring of ESKD or death was pre-specified in the EMPA-KIDNEY TSAP as a sensitivity analysis to the shared parameter model. The random slope and intercept model was chosen for the subgroup analysis by KDIGO risk at baseline (as per Table 29), as no convergence could be achieved applying the shared parameter model in this subgroup (due to small subgroups). The results estimated by the shared parameter model and the random slope and intercept model were very similar in the overall population (reported in Section 11.1.3.1.3 of the CTR, on the annual rate of change in eGFR), and therefore considered appropriate in this situation.

Clarification 4: The response to B3 has not addressed "*Please clarify to what extent the same calculations for uACR annual changes matched the calculations for eGFR, as queried in the question B2 above".* The EAG would be grateful for clarification on this along similar lines to whether for patients who were at baseline in (G3a, A2) only contribute uACR change to the (G3a, A2) cell of Table 31? And supposing that a subset of these baseline (G3a, A2) patients worsened to (G3b, A2), would the uACR change data subsequent to this change contribute to the Table 31 (G3a, A2) change or to the Table 31 (G3b, A2) change? The response to B3 has also not addressed *"Please clarify why the uACR data was arbitrarily cut-off at 18 months and the effect of extending this analysis to an OC-AD of all trial data, i.e., to 36 months*." The EAG would be grateful for clarification of this.

Company response:

Document B Table 31 estimates the uACR relative change from baseline to month 18 by baseline KDIGO risk category based on a mixed-model repeated measure. The mixed-model repeated measure was pre-specified as analysis method for uACR in the TSAP. It is very different from the random-slope and intercept model that was pre-specified in the TSAP for eGFR. The MMRM compares values at specific visits to baseline values and does not provide annual / annualized rates of change. In the subgroup analysis reported in Document B Table 31, a patient who is in KDIGO risk category (G3a, A2) at baseline contributes to the estimation of the respective baseline category-specific change from baseline to month 18 in uACR, i.e., to cell (G3a, A2) in the example above. Therefore, patients worsening from a baseline of (G3a, A2) to (G3b, A2) would also only contribute to the (G3a, A2) cell of Table 31.

In EMPA-KIDNEY, uACR measurements were taken at Month 2, 18 and the final follow-up visit. There was no uACR measurement planned at the month 12 visit as per protocol. Final follow-up visits for patients occurred at different time-points during the study (depending on when a patient was randomised); this data was slotted to the 6-monthly scheduled visits (as pre-defined in the EMPA-KIDNEY TSAP). As the study was stopped early (due to benefit), at Month 36 only 570 patients (280 placebo and 290 empagliflozin) had a measurement, compared to 4966 measurements at Month 18 (2483 in placebo and 2483 in empagliflozin). In addition, the uACR relative change from baseline to Month 18 was similar to the weighted average over Month 2, 18, 24 and 30 in the overall population (Tables 15.2.4.10.1:1 and 15.2.4.10.1:3 in the CTR). Therefore, in the absence of Month 12 measurements, the similarity between the Month 18 and the averaged results over the trial period

and substantially fewer measurements post 18 months, the Month 18 values were considered most representative and the closest proxy to Month 12, considering the nature of uACR this assumption was deemed plausible.

The implications of assumptions on treatment benefit on uACR have been explored in scenario analyses, including a scenario that assumes no additional treatment effect on uACR after first 12 months for the remaining time on treatment. These outputs were provided in the original clarification questions response.

Clarification 5: There appears to have been some crossed wires over B9.2 and B9.3. This is not asking for disaggregate model outputs after having run the model. This is simply asking for answers along the lines of e.g. B.2.1 The mortality risk for a 60 year old man in (G3a,A2) with no CVD or all cause hospitalisation is calculated as 3% * 5% as sourced from cells X4 of worksheet ZZZ and Y3 of worksheet YYY. If all cause hospitalisation is irrelevant this aspect will obviously not appear in the worked example. For parsing the model structure it would be hugely helpful if the requested worked examples could be supplied as requested under B9.2 and B9.3, much as per the answer to B17, with full cell referencing to the model inputs required for these calculations.

Company response:

Thank you for clarifying the request. The enclosed file 'ID6131_Empagliflozin_Mortality risk worked examples' includes worked examples of the mortality risk for each of the patient profiles requested in original clarification question B9 (B9.2 and B9.3), with cell referencing.

The first table includes the annual risk of death for each patient profile. Below that, the calculation steps are detailed, as performed in the model '***Patient engine***', with references to the column of ***Patient engine*** + any 'precedent cells' used in the calculation. The tested patient profile is also shown, with a description of active risk factors and where they are found in the model.

The worked examples provided use the base case setting, i.e., the risk of death is a composite of unspecific death + CV death (from CKD patch methodology for low-risk country) + KRT death.

The impact of all-cause hospitalisations on the risk of death is not considered in the base case settings, and so all-cause hospitalisations do not affect the mortality risks in B9.2.

Clarification 6: The response to B15 does not address why the chosen function was selected. Please clarify this.

Company response:

The risk equation used to predict renal replacement therapy (RRT) initiation in the base case is the pooled, 6 variable (6v) equation by Tangri *et al*. 2016. This version is based on the most recent data and the largest number of cohorts (pooled North America and non-North America). The 6 variable option was selected over the 4 variable option as it includes the risk factors diabetes and hypertension, and so predictions could be sensitive to these comorbidities. An alternative source, Major *et al*. 2019, is specific to the UK population but based on four variables only, thus it was not retained in the base case. Scenario analysis using the UK-specific Major *et al*. 2019 risk equation results in similar results to the base case scenario with Tangri et al. 2016 pooled 6v.

Cost-effectiveness results						
	Tangri et al 2016			Major el al 2019		
	Empagliflozin + SoC	SoC	Incrementals	Empagliflozin + SoC	SoC	Incrementals
Total discounted costs (£)	87,946	93,407	-5,460	87,589	92,100	-4,511
Total undiscounted costs (£)	123,784	127,873	-4,089	123,448	126,140	-2,691
Total discounted LYs	9.54	8.48	1.055	9.58	8.48	1.098
Total undiscounted LYs	12.52	10.87	1.646	12.59	10.87	1.726
Total discounted QALYs	7.09	6.24	0.849	7.13	6.25	0.880
Total undiscounted QALYs	9.27	7.99	1.289	9.34	7.99	1.348
Incremental cost (£) per LYs	ICER < 0	Dominant (less cost, more LY)		ICER < 0	Dominant (less cost, more LY)	
Incremental cost (£) per QALYs	ICER < 0	Dominant (less cost, more QALY)		ICER < 0	Dominant (less cost, more QALY)	
Net monetary benefit (NMB) (£)	22,449.97	Cost-effective at 20000£/QALY		22,116.99	Cost-effective at 20000£/QALY	
Net health benefit (NHB) at £20,000 per QALY	1.12			1.11		
Net health benefit (NHB) at £30,000 per QALY	1.03			1.03		
	Incidence			Incidence		
ESKD as per KDIGO classification and KRT pathw	Empagliflozin + SoC	SoC	Incrementals	Empagliflozin + SoC	SoC	Incrementals
ESKD as per eGFR under 15 ml/min per 1.73 m2	60.30%	70.80%	-10.50%	60.30%	70.80%	-10.50%
ESKD patients treated with conservative therap	36.00%	38.80%	-2.80%	39.80%	43.90%	-4.10%
ESKD defined as per initiating KRT	52.60%	63.00%	-10.40%	51.20%	61.50%	-10.30%

Clarification 7: The response to S2 outlines that the Framingham equations are not taken from Wilson et al but are derived through an internal BI statistical analysis. This was not stated in Document B so the EAG could not ask about it. The EAG would be grateful for any internal BI report that outlines this statistical analysis and how and why the final functional form was determined.

Company response:

The Framingham equations used in the current model (CKD-PM) were originally developed by IQVIA for the Core Diabetes Model; these have been applied without changes to the current company model (CKD-PM). They were not developed specifically for the current company model and nor by internal BI statistical analysis. It has not been possible for us to source the original statistical analysis; however, it should be noted that the use of these Framingham equations in the Core Diabetes Model has been previously accepted by NICE in Technology Appraisals (e.g., TA336).

Please find attached a confidential document (Excel file 'ID6131_Empagliflozin_CDM Framingham progressions') which details the calculations and presents risk factor progression results for a given patient (please use editable cells *Calculations A4:C8*).

Clarification 8: In the light of clarification response S3 please outline the changes that need to be made to the original model to arrive at the 01Aug2023 model with full cell referencing.

Company response:

The 01Aug2023 version of the model includes the following updates vs the original model:

Correction 1 (Rescaling of mortality rate during KRT (HD, PD) in patients aged above 80 to account for absence of RT in this population), involves the following changes in the **Risk data inputs** tab:

- Cell M385: add % failure among patients on PD, = 1 - p_pt_d_RRT_PD_sucess
- Cell J387, correct formula as follows: =p_pt_d_RRT_PD_move_HD/(p_pt_d_RRT_PD_move_HD+p_pt_d_RRT_PD_fail_die)***M385** (=29%)
- Cell J391, correct formulas as follows: =p_pt_d_RRT_PD_fail_die/(p_pt_d_RRT_PD_move_HD+p_pt_d_RRT_PD_fail_die)***M385** (=13%)

- Cell M394: add % failure among patients on HD, =1 - J364
- Cell J398, correct formula = p_pt_d_RRT_HD_move_PD/(p_pt_d_RRT_HD_move_PD+p_pt_d_RRT_HD_fail_die**)*M394** (4%)
- Cell J400, correct formula = p_pt_d_RRT_HD_fail_die/(p_pt_d_RRT_HD_fail_die+p_pt_d_RRT_HD_move_PD**)*M394** (=22%)

Correction 2 (HbA1c projection, coefficient for baseline HbA1c value was corrected (link was incorrect), involves the following changes in the **Patient engine** tab:

- Cell L46 and below: use correct coefficient for baseline HbA1c, "RE_UKPDS90_A1cPer_A1c_baseline" from Risk_factor_input sheet Cell G159, instead of "RE_UKPDS90_BMI_A1c_baseline"
- Drag and drop for all cycles.

Correction 3 (correction of ratio to extrapolate from nonfatal ASCVD to nonfatal CVD including UA and TIA, accounting for stroke fatality rate) involves the following changes in the **Risk equations** tab:

- Cell I50 (Nonfatal stroke excl TIA): formula = I49*(1-E42)
- Cell I56 (Nonfatal CVD): formula = I48+I50+I51-I54
- Cell I57 (Nonfatal ASCVD): formula = I52 - I54 + CHOOSE(P40;I49;I49*(1-E42))
- Replicate the 3 above steps for women, in column K
- Cell M46 and further down: create All column, sum of men (column I) and women (column K) data
- Cell E49 (ratio to extrapolate from nf ASCVD to nf ASCVD including TIA and UA): formula =(M48+M57+M53)/M57 (**value= 1.557**)

Company additional comment:

Original clarification question C1 requested the EMPA-KIDNEY clinical trial report. It has now been noted that the file was not uploaded in the response. Please find enclosed the confidential file 'C1.1_1245-0137--1-15--study-report-body-a_2'.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Empagliflozin for treating chronic kidney disease [ID6131]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is the country's leading diabetes charity representing the 4.9 million people living with diabetes in the UK. We help people manage their diabetes effectively by providing information, advice and support. We campaign with people with diabetes and healthcare professionals to improve the quality of diabetes care across the UK's health services. We fund pioneering research into care, cure and prevention for all types of diabetes. The majority of Diabetes UK's income is from legacies and donations. We also earn income from activities which support our charitable mission, such as our Diabetes UK Professional Conference. A small percentage of our income is from support for specific programmes of work from or sponsorship of events by the pharmaceutical industry. We are a growing community with more than 300,000 supporters nationwide – including people with diabetes, their friends and families – and more than 100,000 lay and healthcare professional members.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Diabetes UK receives some funding from the pharmaceutical industry to support specific programmes of work and conference sponsorship: Boehringer Ingelheim: £19,200
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**-**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	-

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**-**
8. Is there an unmet need for patients with this condition?	-

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**-**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	-

Patient population.

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Diabetes is the leading cause of end stage kidney disease in the UK which is treated with dialysis or transplantation. People with diabetes and kidney disease are living with two chronic conditions and the affect on physical and emotional wellbeing should not be underestimated. People with diabetes and chronic kidney disease are also at greater risk of worse cardiovascular outcomes than those with CKD without diabetes. Empagliflozin is currently used to treat type 2 diabetes and research has proven it can reduce death from cardiovascular disease and it has been shown to reduce onset and progression of chronic kidney disease in people with type 2 diabetes. A greater choice of medications that can be used to treat diabetes and chronic kidney disease would benefit people with type 2 diabetes offering more treatment options and better outcomes. Most people with diabetic kidney disease are treated in primary care and not seen in secondary care therefore access to different medications would benefit people that are seen in this setting.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Chronic Kidney disease and diabetes is more prevalent in people from lower social economic groups and those of black and Asian ethnicity. As stated in NICE guidance Type 2 Diabetes in adults management, some ethnic groups have a higher risk of micro and macrovascular complications and so may benefit more from SGLT2 inhibitors, this has been recommended as an area of further research: Recommendations | Type 2 diabetes in adults: management | Guidance | NICE

Other issues

13. Are there any other issues that you would like the committee to consider?	More research into the safety of SGLT2 inhibitors in those with established chronic kidney disease and diabetes would be welcomed.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• People with kidney disease are often living with diabetes alongside this putting them at greater risk of worse cardiovascular disease • Greater choice of medications for people with type 2 and kidney disease will improve outcomes • Certain ethnic groups are at greater risk of micro and macrovascular complication so will likely see greater benefit from SGLT2 inhibitors • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Empagliflozin for treating chronic kidney disease [ID6131]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Care UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (eg advocacy, counselling, Facebook support group, patient grants), social media channels, telephone helpline and website.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Astrazeneca:** £350 – July 2022 – honorarium for meeting attendance £45,000 – August 2022 - to support development of Kidney Kitchen £380 January 2023 - honorarium for meeting attendance £450 – May 2023– honorarium for meeting attendance £300 – May 2023– honorarium for meeting attendance £700 – May 2023– honorarium for meeting attendance

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This is a joint submission from Kidney Care UK and Kidney Research UK. The information and views represented in this submission has been gathered through a range of sources: - Kidney Research UK spoke to a range of people living with chronic kidney disease, both in a focus group, and in one-on-one interviews. We identified participants through our 'Kidney Voices' patient network. - Kidney Care UK carried out a survey of our patient advisory group. Information was also gained from Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients. We have also run regular surveys to explore the current challenges kidney patients are facing as well as the annual Patient Reported Experience Measures survey which reports on how kidney patients feel about their experience of care.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	For people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. When kidneys fail, patients need either dialysis or a transplant to survive. Both options, if available, are gruelling and expensive, requiring regular, extensive medical treatment with associated mental health challenges. A transplant is not a cure, lasting on average twenty years, and the fear of infection or rejection of the transplant has a significant impact upon patients' mental health. A diagnosis of CKD has huge implications for a person's quality of life. Challenges include the stress of coming to terms with a diagnosis of an incurable, progressive condition, as well as difficult decisions about treatment options and the strain of adjusting to new treatments. Many people with kidney disease must also adhere to strict medication regimes and dietary restrictions. Symptoms include debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised. There are almost 30,000 people receiving dialysis in the UK,[i] many of whom spend four hours a day, three days a week, every week, at hospital. A person with kidney disease explains "(in centre) dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many other things are banned or restricted. And you must spend 4 or 5 hours in a hospital 3 days a week, with 2 big needles plunged into your arm, connected to a machine. And all this gives you just 10% of your normal kidney function, and you probably feel even sicker after treatment than you did before, your blood pressure has dropped way down and you may be bleeding from where those great big needles were for a long time. You may be too weak to walk and you are likely to be depressed and out of work. You have a day off, and then it all starts again…and again….and again." The *Kidney disease – a public health emergency* report published in June 2023 estimates that the number of people received dialysis could rise to 143,000 in the next 10 years without interventions that will reduce the number of people progressing to renal failure. NHS capacity would need to increase by nearly 400% to meet the additional demand[ii]. Kidney transplant, while not a cure, is currently the treatment associated with the best health outcomes for people with kidney disease. However, there are more people waiting for a transplant than there are available organs and people from ethnic minority communities have to wait considerably longer than people from White backgrounds. Kidney transplants from deceased donors last on average 15-20 years and 20-25 years from a living donor, although some longer and some less. Kidney patients may therefore face returning to dialysis if their kidney fails.

	Unsurprisingly, CKD can take a huge toll on the mental health and emotional wellbeing of individuals. Nearly half of in-centre haemodialysis patients experience some form of distress[iii] and up to 1 in 3 kidney patients will experience deression at some point. This in turn exacerbates physical ill health and a person's ability to manage their condition. Symptoms of depression in people with early stage kidney disease increases their risk of progressing to end-stage renal disease (requiring dialysis or a transplant) and death.[iv,v] In people with transplants, depressive symptoms have been shown to increase the risk of death by 65%.[vi] A carer's role will depend partly on the individual's stage of kidney disease, their symptoms (eg fatigue), comorbidities and the treatment they receive. Roles can include helping with activities of daily living and mobility, transportation, personal care, and support with treatment, for example adhering to the medication regime and also with dialysis (for example if the person has dialysis at home). As well as the physical demands of caring, it can be emotionally challenging as the carer and the person with kidney disease come to terms with the change in role and the impact of a life changing diagnosis. Caregiving demands in managing dialysis has proved to be taxing on the physical, social and emotional health of informal caregivers.[vii,viii]

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	People who progress to kidney failure often find the burden of treatment is very significant. As described above, many people on dialysis can find living with four-hour dialysis sessions, three times a week every week, as well as the stringent fluid and dietary restrictions, very challenging. Receiving a kidney transplant, although not a cure, can make a huge different to the health and quality of life of a person with kidney disease. People fortunate enough to receive a kidney transplant will also need to follow certain restrictions on their diet and lifestyle, as well as being on medication for the rest of their lives. In the case of deceased donations, transplant comes with the emotional burden of knowing the donor has lost their life. Decisions regarding accepting a living donation can also be challenging. The introduction of NICE approved SGLT2 inhibitors for people with CKD is considered a huge step forward, but there is work to be done to increase the numbers of eligible patients accessing the treatments. At present, without these interventions, it can feel like there is "nothing between general diet and lifestyle advice, straight to dialysis" when you are at the earlier stages of chronic kidney disease. This "cliff edge" is viewed as being unlike other diseases. The uncertainty of knowing when this progression may occur also has a significant mental health burden. A person with kidney disease told us: "my progression has been steady, but I did have an episode several years ago where my function dropped by 5%. It is very worrying not knowing when that next drop will be".
8. Is there an unmet need for patients with this condition?	There is no cure for chronic kidney disease and limited options for medications that can slow or prevent decline in kidney function, although lifestyle, diet and treatments for problems linked with kidney disease such as high blood pressure are important. Progress in developing new pharmaceutical treatments has been extremely slow. In the UK, there are approximately 3.25 million people living with chronic kidney disease (CKD) stages 3-5. A further 3.9 million people are estimated to have CKD stages 1-2. Together reaching a total of 7.2 million – more than 10% of the entire population[ix]. The number of people affected by chronic kidney disease is growing due to an ageing population and the increasing prevalence of the risk factors associated with CKD, mainly diabetes, hypertension and obesity. Recently the NHS CVDPREVENT primary care audit confirmed CKD as a high-risk condition for cardiovascular disease. Increasing evidence from studies indicate that the benefits shown by SGLT2 inhibitors, including empagliflozin, do not appear to be modified by the level of eGFR, by primary kidney diagnosis, or whether the patient also has diabetes. Despite this, access to other SGLT2 inhibitors remain restricted – canagliflozin only for those with CKD and diabetes, and dapagliflozin based on its trial population.

Advantages of the technology **9. What do patients or carers think are the advantages of the technology?**	The EMPA-KIDNEY trial evaluated the effects of empagliflozin on kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD), as well as type 2 diabetes. The results showed that empagliflozin significantly reduced the risk of kidney disease progression and cardiovascular events in patients with CKD and type 2 diabetes. It showed that empagliflozin safely reduced the primary outcome of kidney disease progression or cardiovascular death by 28%. Relative benefits were consistent in patients both with or without diabetes, and across the range of eGFR studied (to at least 20mL/min/1.73m squared). Importantly, empagliflozin slowed chronic eGFR decline in all albuminuria subgroups. This supports other studies that have shown SGLT2 inhibitors to safely reduce the risk of kidney disease progression as well as acute kidney injury irrespective of diabetes status. We believe that the evidence indicates that empagliflozin (or other SGLT2i) should be used in patients with CKD at risk of progression, regardless of any response to treatment with standard care. Its benefits appear to be proportionally larger than those of Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II type 1 receptor blockers (ARB). Among such patients receiving standard care, risks of further progression and premature cardiovascular morbidity and mortality remain, so SGLT2i should be used to reduce these risks. They will likely be most effective early in the treatment of CKD, with the potential for delivery in primary care according to certain criteria. The benefits identified in the clinical trials of this technology, of lowering risk of CKD progression and cardiovascular events, would clearly be significantly advantageous for people with kidney disease in the context of a progressive and currently incurable condition such as CKD. While very few people will have direct experience of this technology, the evidence that it can delay the progression of CKD, so that people can live in better health for longer, is strongly welcomed by patients. **One person with kidney disease told us "I**f this drug slows progression down people will be able to live their lives without the need for dialysis for many years. This will make a major difference in quality of life for many people." Scenarios described to us included people who were struggling to manage childcare with dialysis sessions, which was making it very difficult for the person's carer to stay in employment. A treatment that can delay the need for dialysis clearly has very far reaching benefits. Another person at stage 3 of chronic kidney disease told us: "my general quality of life is still good at the moment, if there is something that can help me stay at this sort of level… that would be absolutely delightful, and end up costing the NHS a whole lot less in the process." The existence of treatment options for people with chronic kidney disease should also encourage the early identification of kidney damage, which clinical audits show is hampered by a failure to carry out NICE recommended annual checks. As well as pharmaceutical options such as empagliflozin, early identification should also enable patients to take action on diet and lifestyle to reduce their risk of further kidney damage

	People with CKD are at very high risk of death from cardiovascular causes and therefore the evidence that the technology lowers the risk of death from cardiovascular causes is an important advantage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantages of the treatment were considered to be some of the potential side effects, although the overall response from people with kidney disease was that the potential side effects did not outweigh the potential benefits. It is important that people are made aware of these potential side effects and encouraged to report them, to support ongoing monitoring of these drugs over the long term so that patients can make informed decisions about their use. A kidney patient told us that "if the treatment is safe, that is reassuring, as is that it has been used for some time and is an established drug".

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	EMPA-KIDNEY showed that SGLT2i inhibitors can preserve kidney function in people who don't have protein in their urine — a common marker of kidney damage. clinical studies indicate that the benefits shown by SGLT2 inhibitors, including empagliflozin, do not appear to be modified by the level of eGFR or by primary kidney diagnosis.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups. They are more likely to develop kidney disease, progress faster to renal failure and therefore require dialysis or a transplant. People from ethnic minority groups wait on average longer for a kidney transplant due to a shortage of kidneys with a suitable tissue and blood match. People from deprived communities are also more likely to be diagnosed at a later stage of disease progression and die earlier than other socio-economic groups[x]. "Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Also, clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression." (Mathur R, Dreyer G, Yaqoob MM, et al Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study BMJOpen 2018;8:e020145. doi: 10.1136/bmjopen-2017-020145)

13. Are there any other issues that you would like the committee to consider?	Kidney Care UK believes it's vital that people are provided with lifestyle and diet advice so they can take action to reduce their risk of further kidney damage, and it is important that any NICE guidance resulting from this review recommends the provision of suitable advice. Delaying progression is very valuable to patients and the NHS and this must be considered when assessing SGLT2i in people with more slowly-progressive CKD. SGLT2i also reduces risk of hospitalisation (of any cause). We believe that a discounting rate of 1.5% should be presented, per NICE's view that there is an evidence-based case for change from 3.5%, to adequately consider the long term value of the treatment. Cost effectiveness analyses need to consider not just quality of life, but also savings from a reduction in hospitalisation and lower risk of the need for dialysis or transplantation. Key findings from the *Kidney disease – a public health emergency* report showed that the current economic burden of kidney disease in the UK is £7 billion per year, with £6.4 billion being direct costs to the NHS. By 2033, if projected figures for the number of dialysis patients are realised, those figures could rise to as much as £13.9 billion and £10.9 billion respectively. Greater use of new medications such as SGLT-2 inhibitors is one of the interventions modelled that showed economic savings, as well as saving 10,000 lives in that time. It will be vitally important for NICE and the NHS to consider how to identify patients who might be eligible for the treatment. At the moment, they are not routinely identified in primary care.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chronic kidney disease can have a hugely negative impact on quality of life, with a range of debilitating symptoms that can impact on many aspects of life and wellbeing. CKD is currently incurable with limited pharmacological options for delaying progression. Treatments for kidney failure are very burdensome with limited access to transplantation. • The findings that this drug can delay progression of CKD in patients offer real hope and could lead to a real step change in treatment of kidney patients. • Evidence from the trials of the technology suggest it is just as effective regardless of proteinuria or diabetes status. It is important to consider this and avoid an unnecessary restriction of the patient population. • Drug treatments such as empagliflozin must be accompanied by information and support about dietary, exercise and lifestyle interventions that can help to delay the progression of kidney disease, and supported to report side effects as the ongoing monitoring and evaluation of adverse events is important. • Treatments that can slow or prevent the progression of kidney disease to end stage renal failure is highly likely to prove cost effective in the long-term to the health system, reducing the increase in the number of people on dialysis.

[i] UK Renal Registry, 2020, UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from: renal.org/audit-research/annual-report

[ii] [ii] https://www.kidneyresearchuk.org/2023/06/05/kidney-disease-is-a-public-health-emergency-that-threatens-to-overwhelm-the-nhs-major-new-report-reveals/

[iii] Seekles, M., Ormandy, P., & Kamerāde, D. (2020). Examining patient distress and unmet need for support across UK renal units with varying models of psychosocial care delivery: a cross-sectional survey study. BMJ open, 10(9), e036931. Available at: https://doi.org/10.1136/bmjopen-2020-036931

[iv] Tsai YC, Chiu YW, Hung CC, Hwang SJ, Tsai JC, Wang SL, et al. Association of symptoms of depression with progression of CKD. Am J Kidney Dis. 2012;60(1):54–61. Available at: https://www.ajkd.org/article/S0272-6386(12)00533-1/fulltext

[v] Palmer SC, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. Am J Kidney Dis. 2013;62(3):493–505. Available at: https://www.ajkd.org/article/S0272-6386(13)00589-1/fulltext

[vi] Dew, M. A., Rosenberger, E. M., Myaskovsky, L., DiMartini, A. F., DeVito Dabbs, A. J., Posluszny, D. M., … Greenhouse, J. B. (2015). Depression and Anxiety as Risk Factors for Morbidity and Mortality after Organ Transplantation: A Systematic Review and Meta-Analysis. Transplantation, 100(5), 988– 1003. Available at: http://doi.org/10.1097/TP.0000000000000901

[vii] Belasco AG, Sesso R. Burden and quality of life of caregivers for hemodialysis patients. Am J Kidney Dis. 2002;39(4):805–12.

[viii] Tong A, Sainsbury P, Craig JC. Support interventions for caregivers of people with chronic kidney disease: a systematic review. Nephrol Dial Transplant. 2008;23(12):3960–5

[ix] https://www.kidneyresearchuk.org/2023/06/05/kidney-disease-is-a-public-health-emergency-that-threatens-to-overwhelm-the-nhs-major-new-report-reveals/

[x] https://www.kidneyresearchuk.org/wp-content/uploads/2019/09/Health_Inequalities_lay_report_FINAL_WEB_20190311.pdf

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Empagliflozin for treating chronic kidney disease [ID6131]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved health outcomes for patients. Our latest annual report 2021/22 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Yes, we received £30,000 in the past 12 months from Boehringer Ingelheim. This was for sponsorship of the Industry Partnership Programme, and the planning of a future policy report on chronic kidney disease in England. For comparator companies: AstraZeneca: £53,760

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**This is a joint submission from Kidney Care UK and Kidney Research UK.** The information and views represented in this submission has been gathered through a range of sources: A survey of our patient advisory group. Information gained from Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients. We have also run regular surveys to explore the current challenges kidney patients are facing as well as the annual Patient Reported Experience Measures survey which reports on how kidney patients feel about their experience of care. Kidney Research UK spoke to a range of people living with chronic kidney disease, both in a focus group, and in one-on-one interviews. We identified participants through our 'Kidney Voices' patient network.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	For people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. When kidneys fail, patients need either dialysis or a transplant to survive. Both options, if available, are gruelling and expensive, requiring regular, extensive medical treatment with associated mental health challenges. A transplant is not a cure, lasting on average twenty years, and the fear of infection or rejection of the transplant has a significant impact upon patients' mental health. A diagnosis of CKD has huge implications for a person's quality of life. Challenges include the stress of coming to terms with a diagnosis of an incurable, progressive condition, as well as difficult decisions about treatment options and the strain of adjusting to new treatments. Many people with kidney disease must also adhere to strict medication regimes and dietary restrictions. Symptoms include debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised. There are almost 30,000 people receiving dialysis in the UK,[i] many of whom spend four hours a day, three days a week, every week, at hospital. A person with kidney disease explains *"(in centre) dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many other things are banned or restricted. And you must spend 4 or 5 hours in a hospital 3 days a week, with 2 big needles plunged into your arm, connected to a machine. And all this gives you just 10% of your normal kidney function, and you probably feel even sicker after treatment than you did before, your blood pressure has dropped way down and you may be bleeding from where those great big needles were for a long time. You may be too weak to walk and you are likely to be depressed and out of work. You have a day off, and then it all starts again…and again….and again."* The *Kidney disease – a public health emergency* report published in June 2023 estimates that the number of people received dialysis could rise to 143,000 in the next 10 years without interventions that will reduce the number of people progressing to renal failure. NHS capacity would need to increase by nearly 400% to meet the additional demand[ii].

	Kidney transplant, while not a cure, is currently the treatment associated with the best health outcomes for people with kidney disease. However, there are more people waiting for a transplant than there are available organs and people from ethnic minority communities have to wait considerably longer than people from White backgrounds. Kidney transplants from deceased donors last on average 15-20 years and 20-25 years from a living donor, although some longer and some less. Kidney patients may therefore face returning to dialysis if their kidney fails. Unsurprisingly, CKD can take a huge toll on the mental health and emotional wellbeing of individuals. Nearly half of in-centre haemodialysis patients experience some form of distress[iii] and up to 1 in 3 kidney patients will experience depression at some point. This in turn exacerbates physical ill health and a person's ability to manage their condition. Symptoms of depression in people with early stage kidney disease increases their risk of progressing to end-stage renal disease (requiring dialysis or a transplant) and death.[iv,v] In people with transplants, depressive symptoms have been shown to increase the risk of death by 65%.[vi] A carer's role will depend partly on the individual's stage of kidney disease, their symptoms (eg fatigue), comorbidities and the treatment they receive. Roles can include helping with activities of daily living and mobility, transportation, personal care, and support with treatment, for example adhering to the medication regime and also with dialysis (for example if the person has dialysis at home). As well as the physical demands of caring, it can be emotionally challenging as the carer and the person with kidney disease come to terms with the change in role and the impact of a life changing diagnosis. Caregiving demands in managing dialysis has proved to be taxing on the physical, social and emotional health of informal caregivers.[vii,viii]

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People who progress to kidney failure often find the burden of treatment is very significant. As described above, many people on dialysis can find living with four-hour dialysis sessions, three times a week every week, as well as the stringent fluid and dietary restrictions, very challenging. Receiving a kidney transplant, although not a cure, can make a huge different to the health and quality of life of a person with kidney disease. People fortunate enough to receive a kidney transplant will also need to follow certain restrictions on their diet and lifestyle, as well as being on medication for the rest of their lives. In the case of deceased donations, transplant comes with the emotional burden of knowing the donor has lost their life. Decisions regarding accepting a living donation can also be challenging. The introduction of NICE approved SGLT2 inhibitors for people with CKD is considered a huge step forward, but there is work to be done to increase the numbers of eligible patients accessing the treatments. At present, without these interventions, it can feel like there is *"nothing between general diet and lifestyle advice, straight to dialysis"* when you are at the earlier stages of chronic kidney disease. This "cliff edge" is viewed as being unlike other diseases. The uncertainty of knowing when this progression may occur also has a significant mental health burden. A person with kidney disease told us: *"my progression has been steady, but I did have an episode several years ago where my function dropped by 5%. It is very worrying not knowing when that next drop will be".*

8. Is there an unmet need for patients with this condition?	There is no cure for chronic kidney disease and limited options for medications that can slow or prevent decline in kidney function, although lifestyle, diet and treatments for problems linked with kidney disease such as high blood pressure are important. Progress in developing new pharmaceutical treatments has been extremely slow. In the UK, there are approximately 3.25 million people living with chronic kidney disease (CKD) stages 3-5. A further 3.9 million people are estimated to have CKD stages 1-2. Together reaching a total of 7.2 million – more than 10% of the entire population[ix]. The number of people affected by chronic kidney disease is growing due to an ageing population and the increasing prevalence of the risk factors associated with CKD, mainly diabetes, hypertension and obesity. Recently the NHS CVDPREVENT primary care audit confirmed CKD as a high-risk condition for cardiovascular disease. Increasing evidence from studies indicate that the benefits shown by SGLT2 inhibitors, including empagliflozin, do not appear to be modified by the level of eGFR, by primary kidney diagnosis, or whether the patient also has diabetes. Despite this, access to other SGLT2 inhibitors remain restricted – canagliflozin only for those with CKD and diabetes, and dapagliflozin based on its trial population.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The EMPA-KIDNEY trial evaluated the effects of empagliflozin on kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD), as well as type 2 diabetes. The results showed that empagliflozin significantly reduced the risk of kidney disease progression and cardiovascular events in patients with CKD and type 2 diabetes. It showed that empagliflozin safely reduced the primary outcome of kidney disease progression or cardiovascular death by 28%. Relative benefits were consistent in patients both with or without diabetes, and across the range of eGFR studied (to at least 20mL/min/1.73m squared). Importantly, empagliflozin slowed chronic eGFR decline in all albuminuria subgroups. This supports other studies that have shown SGLT2 inhibitors to safely reduce the risk of kidney disease progression as well as acute kidney injury irrespective of diabetes status. We believe that the evidence indicates that empagliflozin (or other SGLT2i) should be used in patients with CKD at risk of progression, regardless of any response to treatment with standard care. Its benefits appear to be proportionally larger than those of Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II type 1 receptor blockers (ARB). Among such patients receiving standard care, risks of further progression and premature cardiovascular morbidity and mortality remain, so SGLT2i should be used to reduce these risks. They will likely be most effective early in the treatment of CKD, with the potential for delivery in primary care according to certain criteria. The benefits identified in the clinical trials of this technology, of lowering risk of CKD progression and cardiovascular events, would clearly be significantly advantageous for people with kidney disease in the context of a progressive and currently incurable condition such as CKD. While very few people will have direct experience of this technology, the evidence that it can delay the progression of CKD, so that people can live in better health for longer, is strongly welcomed by patients. One person with kidney disease told us *“If this drug slows progression down people will be able to live their lives without the need for dialysis for many years. This will make a major difference in quality of life for many people.”* Scenarios described to us included people who were struggling to manage childcare with dialysis sessions, which was making it very difficult for the person’s carer to stay in employment. A treatment that can delay the need for dialysis clearly has very far reaching benefits. Another person at stage 3 of chronic kidney disease told us: *“my general quality of life is still good at the moment, if there is something that can help me stay at this sort of level… that would be absolutely delightful, and end up costing the NHS a whole lot less in the process.”*

	The existence of treatment options for people with chronic kidney disease should also encourage the early identification of kidney damage, which clinical audits show is hampered by a failure to carry out NICE recommended annual checks. As well as pharmaceutical options such as empagliflozin, early identification should also enable patients to take action on diet and lifestyle to reduce their risk of further kidney damage People with CKD are at very high risk of death from cardiovascular causes and therefore the evidence that the technology lowers the risk of death from cardiovascular causes is an important advantage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantages of the treatment were considered to be some of the potential side effects, although the overall response from people with kidney disease was that the potential side effects did not outweigh the potential benefits. It is important that people are made aware of these potential side effects and encouraged to report them, to support ongoing monitoring of these drugs over the long term so that patients can make informed decisions about their use. A kidney patient told us that *"if the treatment is safe, that is reassuring, as is that it has been used for some time and is an established drug".*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	EMPA-KIDNEY showed that SGLT2i inhibitors can preserve kidney function in people who don't have protein in their urine — a common marker of kidney damage. Clinical studies indicate that the benefits shown by SGLT2 inhibitors, including empagliflozin, do not appear to be modified by the level of eGFR or by primary kidney diagnosis.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups. They are more likely to develop kidney disease, progress faster to renal failure and therefore require dialysis or a transplant. People from ethnic minority groups wait on average longer for a kidney transplant due to a shortage of kidneys with a suitable tissue and blood match. People from deprived communities are also more likely to be diagnosed at a later stage of disease progression and die earlier than other socio-economic groups[x]. "Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Also, clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression." (Mathur R, Dreyer G, Yaqoob MM, et al Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study BMJOpen 2018;8:e020145. doi: 10.1136/bmjopen-2017-020145)

Other issues

13. Are there any other issues that you would like the committee to consider?	Kidney Care UK believes it's vital that people are provided with lifestyle and diet advice so they can take action to reduce their risk of further kidney damage, and it is important that any NICE guidance resulting from this review recommends the provision of suitable advice. Delaying progression is very valuable to patients and the NHS and this must be considered when assessing SGLT2i in people with more slowly-progressive CKD. SGLT2i also reduces risk of hospitalisation (of any cause). We believe that a discounting rate of 1.5% should be presented, per NICE's view that there is an evidence-based case for change from 3.5%, to adequately consider the long term value of the treatment. Cost effectiveness analyses need to consider not just quality of life, but also savings from a reduction in hospitalisation and lower risk of the need for dialysis or transplantation. Key findings from the *Kidney disease – a public health emergency* report showed that the current economic burden of kidney disease in the UK is £7 billion per year, with £6.4 billion being direct costs to the NHS. By 2033, if projected figures for the number of dialysis patients are realised, those figures could rise to as much as £13.9 billion and £10.9 billion respectively. Greater use of new medications such as SGLT-2 inhibitors is one of the interventions modelled that showed economic savings, as well as saving 10,000 lives in that time. It will be vitally important for NICE and the NHS to consider how to identify patients who might be eligible for the treatment. At the moment, they are not routinely identified in primary care.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chronic kidney disease can have a hugely negative impact on quality of life, with a range of debilitating symptoms that can impact on many aspects of life and wellbeing. CKD is currently incurable with limited pharmacological options for delaying progression. Treatments for kidney failure are very burdensome with limited access to transplantation • The findings that this drug can delay progression of CKD in patients offer real hope and could lead to a real step change in treatment of kidney patients. • Evidence from the trials of the technology suggest it is just as effective regardless of proteinuria or diabetes status. It is important to consider this and avoid an unnecessary restriction of the patient population. • Drug treatments such as empagliflozin must be accompanied by information and support about dietary, exercise and lifestyle interventions that can help to delay the progression of kidney disease, and supported to report side effects as the ongoing monitoring and evaluation of adverse events is important. • Treatments that can slow or prevent the progression of kidney disease to end stage renal failure are very likely to prove cost effective in the long-term to the health system, reducing the increase in the number of people on dialysis

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

Your privacy The information that you provide on this form will be used to contact you about the topic above.

For more information about how we process your personal data please see our privacy notice.

[i] UK Renal Registry, 2020, UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from: renal.org/audit-research/annual-report

[ii] https://www.kidneyresearchuk.org/2023/06/05/kidney-disease-is-a-public-health-emergency-that-threatens-to-overwhelm-the-nhs-major-new-report-reveals/

[iii] Seekles, M., Ormandy, P., & Kamerāde, D. (2020). Examining patient distress and unmet need for support across UK renal units with varying models of psychosocial care delivery: a cross-sectional survey study. BMJ open, 10(9), e036931. Available at: https://doi.org/10.1136/bmjopen-2020-036931

[iv] Tsai YC, Chiu YW, Hung CC, Hwang SJ, Tsai JC, Wang SL, et al. Association of symptoms of depression with progression of CKD. Am J Kidney Dis. 2012;60(1):54–61. Available at: https://www.ajkd.org/article/S0272-6386(12)00533-1/fulltext

[v] Palmer SC, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. Am J Kidney Dis. 2013;62(3):493–505. Available at: https://www.ajkd.org/article/S0272-6386(13)00589-1/fulltext

[vi] Dew, M. A., Rosenberger, E. M., Myaskovsky, L., DiMartini, A. F., DeVito Dabbs, A. J., Posluszny, D. M., … Greenhouse, J. B. (2015). Depression and Anxiety as Risk Factors for Morbidity and Mortality after Organ Transplantation: A Systematic Review and Meta-Analysis. Transplantation, 100(5), 988– 1003. Available at: http://doi.org/10.1097/TP.0000000000000901

[vii] Belasco AG, Sesso R. Burden and quality of life of caregivers for hemodialysis patients. Am J Kidney Dis. 2002;39(4):805–12.

[viii] Tong A, Sainsbury P, Craig JC. Support interventions for caregivers of people with chronic kidney disease: a systematic review. Nephrol Dial Transplant. 2008;23(12):3960–5

[ix] https://www.kidneyresearchuk.org/2023/06/05/kidney-disease-is-a-public-health-emergency-that-threatens-to-overwhelm-the-nhs-major-new-report-reveals/

[x] https://www.kidneyresearchuk.org/wp-content/uploads/2019/09/Health_Inequalities_lay_report_FINAL_WEB_20190311.pdf

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Empagliflozin for treating chronic kidney disease [ID6131]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Kidney Association (UKKA)
3. Job title or position	Consultant Nephrologists Dr Riding is a member of the UKKA Working Group for SGLT-2 inhibition in Adult Kidney Disease
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	UKKA was created through merger of the Renal Association, British Renal Society and its affiliates to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants and capitation and works in partnership with Kidney Care UK and Fresenius.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Dr Caplin was local Principal Investigator for the EMPA-KIDNEY trial. He has also received research funding from AstraZeneca (Dapagliflozin).
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow progression of chronic kidney disease and modify associated cardiovascular risk The largest multi-centre, randomised, placebo-controlled trial using empagliflozin in renal patients to date, EMPA-KIDNEY [EMPA-Kidney Collaborative Group, 2022], used a composite end point of progression of kidney disease (sustained decrease in ≥40% eGFR from baseline, end stage renal failure or death from renal causes) and death from cardiovascular causes. EMPA-KIDNEY demonstrated a 28% risk reduction in this composite outcome (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Clinical significance of empagliflozin can therefore be measure using any of these parameters and empagliflozin confers significant health benefits and cost-savings in both renal and cardiovascular healthcare domains. Considering renal progression in isolation, EMPA-KIDNEY demonstrated a 1.37 ml/min/1.73m^2 (95%CI 1.16-1.59) improvement in eGFR over two years compared to placebo, which will delay progression to end stage renal failure and its associated morbidity and cost.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In chronic kidney disease (CKD), clinical significance is best measured using both renal and cardiovascular outcomes, owing to the strong association between kidney function decline and cardiovascular events. Substantial mortality and morbidity occur from the increased risk of cardiovascular disease in kidney patients. Treatments that reduce the risk of cardiovascular or renal events by more than 10% are considered clinically significant. A meta-analysis of the four major SGLT-2 inhibitor trials in CKD, including EMPA-KIDNEY, showed a reduction in kidney progression equivalent to 11 events/1000 patient years in those with type 2 diabetes mellitus and 15 events/1000 patient years in those without diabetes mellitus [The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists Consortium, Lancet, 2022]. The same analysis reported a reduction in acute kidney injury and cardiovascular death or hospitalisation for heart failure for those with CKD. The protective effects of SGLT-2 inhibition for those with CKD should not be understated and these agents are a critical strategy in the management of CKD.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently, the management of CKD relies on lifestyle modification, blood pressure management, reduction of proteinuria and management of the underlying renal disease. Generic strategies for disease modification in CKD was a previously unmet need, but the use of SGLT-2 inhibitors has been demonstrated to be effective. Empagliflozin has extended the scope of use to those with more advanced CKD, regardless of proteinuria as demonstrated in EMPA-KIDNEY in the following aspects of renal care: • Decelerating the progression of renal failure, which has implications for delaying renal replacement therapy and increased risks of cardiovascular disease, CKD-bone and mineral disease (CKD-MBD) and cognitive decline. • preventing death from cardiorenal causes in CKD • preventing hospitalisation, particularly with heart failure reducing proteinuria • therapeutic management of type 2 diabetes mellitus Consequently, UKKA recommends the use of SGLT-2 inhibition is extended to include those with eGFR ≤20 ml/min/1.73m^{2,} as safe and efficacious, as demonstrated by the use of Empagliflozin in EMPA-KIDNEY. This represents a change to incorporate a group of patients with advanced CKD that had previously been excluded.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current guidance for the management of CKD relies on blood pressure control, reduction in proteinuria (using renin-angiotensin-aldosterone (RAAS) inhibition) and control of the underlying condition (eg diabetic control for diabetic nephropathy). Dapagliflozin was also approved for use in CKD by NICE in March 2022 (TA775) using data from DAPA-CKD [Wheeler et al., 2021], DECLARE-TIMI58 [Wiviott et al, 2019] and DAPA-HF [McMurray et al, 2019] and the committee acknowledged the use of canagliflozin as preferred by some clinicians/local practice. UKKA guidance recommends that the effect of SGLT-2 inhibition on cardiorenal outcomes is likely to be a class-effect and recommends the use of SGLT-2 inhibition and RAAS blockade for most patients with CKD. The sequelae of advanced CKD (typically stage 3B and beyond) are managed in secondary care for control of renal anaemia, CKD-MBD and renal replacement therapy (dialysis or transplantation) and are costly. The CKD in England: The Human and Financial Cost of resources (NHS Kidney Care) report estimated that the direct and indirect costs of dialysis totalled £580 million in 2009-2010. Delaying progression of CKD will have significant cost-savings in terms of managing the complications of advanced CKD.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	UKKA Working Group for SGLT-2 inhibition in Adults with Kidney Disease: https://guidelines.ukkidney.org/, April 2023. KDIGO Guidance: Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, 2022 NICE Guidance: • Chronic Kidney Disease Assessment and Management [NG203], Nov 2021 • Dapagliflozin for treating chronic kidney disease [TA775], March 2022 Association of British Clinical Diabetologists and Renal Association Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease (DKD), 2021
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Owing to the limited strategies available in managing CKD, consensus on the use of SGLT-2 inhibitors has been reached in the recent UKKA guidance (https://guidelines.ukkidney.org/), creating clear guidance for initiation of SGLT-2 inhibition Referral criteria and shared-care agreements between primary and secondary care may vary by region, but the principles of CKD management will be broadly similar and should align with UKKA guidance. The UKKA working group committee for the use of SGLT-2 inhibitors in adult kidney disease ensured that guidance aligned with that produced by the Association of British Clinical Diabetologists (ABCD and Renal Association Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease (DKD), 2021). Data on the use of SGLT-2 inhibition is lacking in certain patient groups, such as transplant recipients, patients on immunosuppression and those with autosomal dominant polycystic kidney disease, owing to their exclusion from the large SGLT-2 inhibition in CKD trials. The use of SGLT-2 inhibition may therefore be variable in these patient groups.
9c. What impact would the technology have on the current pathway of care?	EMPA-KIDNEY and the use of empagliflozin has been demonstrated to be safe and effective in advanced CKD (to eGFR 20ml/min/1/73m^2), thus expanding the number of patients who could benefit beyond the DAPA-CKD trial (use of dapagliflozin in CKD).Inclusion of some participants with eGFR <20 ml/min/1.73m^2 in EMPA-KIDNEY has led to a UKKA grade 2B recommendation to consider the use of SGLT-2 inhibition for those within that category of more advanced CKD. EMPA-KIDNEY confirmed the results of DAPA-CKD, recruiting greater numbers of patients without diabetes demonstrating empagliflozin's efficacy regardless of the presence of type 2 diabetes mellitus and efficacy in slowing eGFR decline regardless of the level of proteinuria.

	UKKA guidance has issued grade 1 recommendations for the use of SGLT-2 inhibitors in patients with CKD, proteinuria and/or heart failure. The impact associated with the use of empagliflozin for patients with eGFR ≥20 ml/min/1.73m^2 will improve current cardiorenal outcomes and slow referral rates to secondary care for advanced kidney care and renal replacement therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Empagliflozin can be used in the same was as other SGLT-2 inhibitors in routine care, with demonstrated efficacy for stage 2-4 CKD.
10a. How does healthcare resource use differ between the technology and current care?	N/A
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	UKKA recommends that SGLT-2 inhibition is included in routine CKD care for eligible patients, which can be initiated in primary or secondary care. Ineligible patients, eg renal transplant patients or those on systemic immunosuppression, may be prescribed SGLT-2 inhibitors on the advice of Renal Clinicians in secondary care. UKKA does not recommend the use of SGLT-2 inhibition in children or during pregnancy and breastfeeding.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The use of empagliflozin in groups for whom there has not been evidence supporting use of SGLT2i, specifically those with advanced kidney disease is expected to slow renal progression and has implications for delaying renal replacement therapy. This has significant benefits in terms of improving cardiorenal outcomes for patients and reducing the costs of advanced kidney care and renal replacement therapy.
11a. Do you expect the technology to increase length of life more than current care?	The EMPA-KIDNEY composite outcome included death from renal and cardiovascular causes and demonstrated a significant benefit with the use of empagliflozin (see point 6). We would therefore expect to see an increased life expectancy for those that are given SGLT-2 inhibitors for any of the described indications within the UKKA recommendations.

11b. Do you expect the technology to increase health-related quality of life more than current care?	CKD confers significant morbidity, both in terms of associated cardiovascular disease, renal anaemia, CKD-MBD and dialysis care. EMPA-KIDNEY demonstrated clear trends in improvements in hospitalisation for heart failure and cardiovascular causes and progression of kidney disease in favour of empagliflozin. Minimising the burden of symptoms from cardiorenal disease and dialysis has clear benefits in improving health-related quality of life, though it is acknowledged that this is likely to be a class effect of SGLT-2 inhibition.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The effect of empagliflozin on progression of kidney disease and death from cardiovascular causes in those with proteinuric kidney disease is more pronounced. As has been demonstrated by EMPA-KIDNEY and meta-analysis of other large SGLT-2 inhibitor trials, the improvement in cardiorenal outcomes for patients with CKD is preserved regardless of the presence of diabetes The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, 2022.]. Despite a reduction in the glycosuric effect of SGLT-2 with progression of CKD, the benefits for cardiorenal outcomes are preserved.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is not anticipated that increased monitoring will be required and UKKA guidance recommends that renal function does not need to be checked on initiating SGLT-2 inhibitors. A reduction in CKD progression may lead to a reduction in frequency of CKD monitoring in both primary and secondary care as per current NICE guidance (NG203). A small number of patients who are at increased risk of ketoacidosis may require ketone monitoring (eg type 1 diabetes), but this would be managed in collaboration with Diabetic services in secondary care. The incidence of ketoacidosis in EMPA-KIDNEY was low at 0.09/100 patient-years in the empagliflozin group and 0.02/100 patient-years in the placebo group.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Standard 'sick day rules' are advised when using any SGLT-2 inhibitor and these are already in using RAAS inhibition. Additional testing is not required and patients resume their medication when they feel well. Monitoring

include any additional testing?	of renal function is not advised on starting SGLT-2 inhibitors, as there is an expected fall in eGFR within the first 1-2 months that recovers over time in comparison to placebo.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	SGLT-2 inhibitors have been demonstrated to promote weight loss, improve BP control and act as a adjunct diuretic therapy. This has implications for improved health and quality of life and may help to reduce the pill burden that patients face when managing CKD, cardiovascular disease and diabetes.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No.
16a. Is the technology a 'step-change' in the management of the condition?	The SGLT-2 inhibitor class of medication has produced a step-change in the management of CKD, with recent evidence supporting the use of empagliflozin in an expanded group of patients including those with eGFR as low as 20mL/min/1.73m^2.
16b. Does the use of the technology address any particular unmet need of the patient population?	No.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most noticeable side effect that SGLT-2 inhibitors confer is of mycotic genital infection, which can be managed through improved hygiene and application of topical or systemic anti-fungal agents. The benefits of SGLT-2 inhibition on optimising weight and fluid retention promote improved quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The current UK Kidney Association guidance was updated in April 2023 to include all available and relevant clinical trials for the use of SGLT-2 inhibition in CKD.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	1. Effect on primary composite outcomes of progression of renal failure, hospitalisation for heart failure, any hospitalisation and death from cardiorenal causes. CREDENCE [Perkovic et al, 2019], SCORED [Bhatt et al., 2021], DAPA-CKD and EMPA-KIDNEY recruited patients with CKD showing clear benefits for the use of SGLT-2 inhibition. 2. Safety data on the SGLT-2 inhibition in CKD, confirmed at meta-analysis of large RCTs indicating the safety of these agents and justifying the benefit over the more common risks of mycotic genital infections and ketosis. Reassuringly, the association of amputation and fracture risk identified in CANVAS [Neal et al., 2017] and CREDENCE have not been replicated in DAPA-CKD

	and EMPA-KIDNEY. The incidence of serious genital infections was not increased in the treatment groups of DAPA-CKD and EMPA-KIDNEY. 3. DAPA-CKD identified the benefits for cardiorenal disease for non-diabetic CKD, replicated by EMPA-KIDNEY. RCTs recruiting patients at high risk of atherosclerotic cardiovascular disease and heart failure have included patients with CKD stage ≥3 and demonstrated cardiorenal benefit in favour of SGLT-2 inhibition (DAPA-HF, EMPEROR-REDUCED [Packer et al., 2020], SOLOIST-WHF [Bhatt et al., 2021], EMPEROR-PRESERVED [Anker et al., 2021], DELIVER, EMPA-REG OUTCOME [Zinman, 2015], CANVAS, VERTIS-CV [Cannon et al., 2020]). See meta-analysis of RCT data by The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, 2022. 4. Empagliflozin has demonstrated efficacy at lower levels of renal function (EMPA-KIDNEY)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcomes were not required to show benefit in DAPA-CKD and EMPA-KIDNEY (median follow-up 2.4 and 2 years respectively), however eGFR slopes have been validated as marker for treatment effects for clinical benefit in diabetes, glomerular disease, CKD or cardiovascular disease [Inker et al., 2023]. Patients may develop CKD over a number of years, thus a 1.37 ml/min/1.73m^2 reduction in CKD progression demonstrated in EMPA-KIDNEY projected over 5-10 years represents a clinically significant preservation of renal function in delaying renal replacement therapy (dialysis or transplantation).

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA775]?	EMPA-KIDNEY compared empagliflozin to placebo. We are not aware of any trials comparing dapagliflozin and empagliflozin in CKD, however a meta-analysis of RCTs recruiting patients with CKD has demonstrated a class effect of SGLT-2 inhibition in modifying cardiorenal outcomes [The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, 2022.].
21. How do data on real-world experience compare with the trial data?	The use of SGLT-2 inhibitors for CKD within the UK is being established, as publication of guidance for the use of these agents was published by UKKA in October 2021, updated April 2023. As such, limited real-world experience is limited to anecdotal reports of benefit.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Chronic kidney disease is up to five times more common in people from BAME communities. Strategies to improve outcomes for those with CKD and limit progression to end stage renal failure will therefore benefit those from ethnic minority groups, who are disproportionality represented in cohorts with advanced renal failure and in whom barriers to accessing renal transplantation persist.
22b. Consider whether these issues are different from issues with current care and why.	Empagliflozin can be safely used at CKD stage 2-4 to modify cardiorenal outcomes and represents a therapy that can be initiated by a community healthcare practitioner. This overcomes barriers to accessing treatment in secondary care that persist for many people from BAME backgrounds, who have higher rates of renal, metabolic and cardiac disease and may have much to gain from SGLT-2 inhibition.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Empagliflozin has proven benefit in significantly improving cardiorenal outcomes in CKD. The importance of SGLT-2 inhibition in the management of CKD cannot be understated. • Few strategies exist to modify disease progression in CKD and empagliflozin has demonstrated clear benefits for those with and without proteinuria renal disease and with and without diabetes mellitus • Empagliflozin is safe and efficacious in patients with eGFR as low as 20mL/min and in those with non-proteinuric CKD. Extending the use of SGLT-2 inhibitors to those with advanced kidney disease is a priority in CKD management. • Empagliflozin can be used in primary and secondary care to slow renal disease progression in CKD and reduce health burdens for patients and the NHS. • UKKA guidance uses grade 1 recommendations for the use of SGLT-2 inhibition in the management of CKD for those with eGFR ≥20-45 ml/min/1.73m^{2}and with or without diabetes and regardless of the level of proteinuria, as per the evidence provided by EMPA-KIDNEY. UKKA therefore support this application for the use of empagliflozin in CKD.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

External Assessment Group's report

Title: *Empagliflozin for treating chronic kidney disease [ID136047]*

Produced by	*Warwick Evidence*
Authors	Mubarak Patel, Research Fellow, Statistics, Warwick Evidence Professor Norman Waugh, Professor of Public Health, Aberdeen Univesirty Anna Brown, Information Specialist, Warwick Evidence Dr. Ewen Cummins, McMDC Ltd. – contribution: Reviewed the economics of the company submission Dr. Rhona Johnston, McMDC Ltd. – contribution: Parsed the visual basic of the company model and rebuilt some model element Dr, Lena Al-Khudairy, Associate Professor, Warwick Evidence
Correspondence to	*Lena Al-Khudairy* *Lena.al-khudairy@warwick.ac.uk*
Date completed	*Date completed (04/08/2023)*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136047.

Declared competing interests of the authors
None.

Acknowledgements
Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services Research. University of Warwick.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Copyright statement:

This report should be referenced as follows:
Patel M, Waugh N, Brown A, Cummins E, Johnstons R, Al-Khudairy L. Empagliflozin for treating chronic kidney disease [ID136047]. EAG Report: A Single Technology Appraisal. Warwick Evidence, 2023.

Contributions of authors
Mubarak Patel critiqued statistical analysis in the company submission. Norman Waugh critiqued clinical effectiveness evidence and supported clinical advice. Anna Brown critiqued the company's searches and conducted additional EAG searches. Ewen Cummins *and* Rhona Johnston *critiqued the cost-effectiveness evidence and undertook EAG's modelling. Lena Al-Khudairy supported the critique of the clinical*

effectiveness evidence, coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are "[redacted] Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Issues

Table of Figures

Acronym	Definition
ACH	all-cause hospitalisations
ACE	angiotensin-converting enzyme
ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
APD	automated peritoneal dialysis
ARB	angiotensin II receptor blockers
BI	Boehringer Ingelheim
BMD	bone mineral disorders
BMI	body mass index
BNF	British National Formulary
CAD	coronary artery disease
CAPD	continuous ambulatory peritoneal dialysis
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CKD	chronic kidney disease
CKD-PC	chronic kidney disease prognosis consortium
CPRD	Clinical practice research datalink
CRIC	Chronic Renal Insufficiency Cohort
CTR	clinical trial report
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit
CV	Cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DKD	diabetic kidney disease
DOF	data on file
DM	diabetes mellitus
EAG	External assessment group
eGFR	estimated glomerular filtration rate
EKPF	European Kidney Patients Federation
ESKD	end-stage kidney disease
FE	fixed effects
HbA1c	glycated haemoglobin
HCHS	Hospital and Community Health Services
HCRU	healthcare resource utilisation
HD	haemodialysis
HDL	high-density lipoproteins
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalisation for heart failure
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
JAGS	Just Another Gibbs Sampler
KCUK	Kidney Care UK
KDIGO	Kidney Disease Improving Global Outcomes
KRUK	Kidney Research UK
LVEF	left ventricular ejection fraction
LY	life year
MAIC	matching adjusted indirect comparison

Acronym	Definition
MI	myocardial infraction
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
OD	once daily
OC-AD	observed case including data after treatment discontinuation (for the duration of follow-up)
OC-OT	observed case on treatment (for the duration of treatment/study drug)
PD	peritoneal dialysis
PICOS	population, intervention, comparator, outcomes, and study
PID	patient identifiable data
PKD	polycystic kidney disease
PPPY	per patient per year
PVD	peripheral vascular disease
QoF	quality outcomes framework
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitor
RCT	randomised controlled trial
RRID	renal risk in Derby
RRT	renal replacement therapy
RS	randomised set
SAE	serious adverse event
SE	Standard error
SGLT1	sodium-glucose cotransporter 1
SGLT2	sodium-glucose cotransporter 2
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
T2DM	type 2 diabetes mellitus
TA	technology appraisal
TC	total cholesterol
TIA	transient ischaemic attack
TLR	targeted literature review
uACR	urine albumin-to-creatine ratio
UK	United Kingdom
UKKA	United Kingdom Kidney Association
UKRR	UK Renal Registry
US	United States of America
USRDS	United States Renal Data System
WTP	willingness-to-pay

Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) for empagliflozin for treating adults with chronic kidney disease (CKD) (patients with or without type 2 diabetes mellitus [T2DM], with a broad range of estimated glomerular filtration rate [eGFR] from 20 to 90 mL/min/1.73m^2, and varying levels of albuminuria.

All issues identified in **Error! Reference source not found.** represent the EAG's view, not the opinion of NICE.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

Table 1. Summary of key issues

ID3934	Summary of key issue	Report sections
Issue 1	Annualised changes in eGFR and uACR in the economic model	4.15.4
Issue 2	The company model when run using the baseline characteristics of a long term follow-up study in the literature predicts too much ESKD and too little survival. There are reasons to think that this may worsen beyond the 15 year duration of the long term follow-up study.	4.12.5
Issue 3	The modelling does not explore whether it is more cost effective to reserve empagliflozin treatment until patients progress to either (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state. This also relates to the possibility of there being fast progressors and slow progressors.	4.15.2
Issue 4	The company model does not converge when run over 1,000 patients. The EAG thinks it should be run over 20,000 patients. Company validation work suggests that occasional patients with extreme values may be simulated. If these persist running the model over 20,000 patients will not address this.	4.3
Issue 5	The position sought where placebo is the comparator and the key clinical effectiveness estimates seem likely to differ by diabetes status. The EAG thinks that this argues for modelling them separately.	4.15.3
Issue 6	Cost effectiveness may differ by KDIGO health state at baseline. The EAG thinks that this argues exploring the effects of KDIGO health state at baseline upon cost effectiveness.	4.12.4, **Error! Reference source not found.**
Issue 7	The main clinical effectiveness estimates for the model are specific to the KDIGO health state at baseline. The model structure applies these to patients who change KDIGO health state. The two may be incompatible.	4.15.4, 4.15.5
Issue 8	The evolution of patients' uACR is driven by the uACR fold/multipliers observed during EMPA-KIDNEY at 18 months.	

	36 month data suggests that the reapplication of these uACR fold multipliers may not be justified.	
Issue 9	There is a lack of information about the company estimate for the off treatment uACR fold/multiplier. It seems misaligned with other estimates.	4.15.7, 4.15.8, 4.15.9
Issue 10	The model includes treatment discontinuations. Those on treatment should be modelled using estimates from the on treatment OC-OT data of EMPA-KIDNEY.	**Error! Reference source not found.**
Issue 11	The original company submission did not present the effect estimates for HbA1c, BMI, weight and SBP or the assumed duration of these effects. Their modelled evolution on treatment and off treatment is questionable.	4.8.3, 4.15.14
Issue 12	The company uses an American risk function for the risk of renal replacement therapy. The EAG prefers the UK risk function. The company applies these risks as soon as the patient falls to an eGFR of 15 ml/min/1.73m^2. Given the UK renal registry report it may be more reasonable to apply a lower threshold.	**Error! Reference source not found.**, **Error! Reference source not found.**
Issue 13	The UK renal registry report suggests renal replacement therapy has different modalities by age and very different mortality by age. There is no easy means for the model to take this into account. This increases modelling uncertainty.	4.15.16, 4.15.17
Issue 14	The modelling does not explore limiting the assumed duration of clinical effects. This is not aligned with the NICE methods guide.	**Error! Reference source not found.**
Issue 15	Summation of all the complications' disutilities may overestimate their pooled effects.	4.16.4
Issue 16	The annualization of multi-year event probabilities may estimate them occurring too soon and also is likely to overestimate the number of events.	**Error! Reference source not found.**
Issue 17	The model structure is a bit of a mixed bag. It might be more coherent to use the KDIGO health state specific quality of life values and costs to account for the effects of the complications of CKD, retaining the separate modelling of renal replacement therapy and its costs and the other events that affect progression through KDIGO health states and mortality.	4.15.21

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) for empagliflozin in adults with chronic kidney disease (CKD) (patients with or without type 2 diabetes mellitus [T2DM], with a broad range of estimated glomerular filtration rate [eGFR] from 20 to 90 mL/min/1.73m^2, and varying levels of albuminuria.

This summary also provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 gives an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

The company's submission (CS) of the comparative clinical effectiveness and cost effectiveness of empagliflozin was mainly obtained from a multicentre trial that involved 241 centres (EMPA-KIDNEY). The primary outcome for the study was kidney disease progression or CV death. Secondary outcomes included time to occurrence of all-cause hospitalisation (ACH; first and recurrent combined), time to first occurrence of HHF or CV death, and time to adjudicated death from any cause. Tertiary outcomes included time to first occurrence of kidney disease progression, time to adjudicated CV death, time to first occurrence of adjudicated CV death or ESKD, and annual rate of change in eGFR (total and long-term; defined as from 2 months until final follow-up visit).

Therefore, this EAG report focuses on the cohort of patients in EMPA-KIDNEY (n=6609, 1,133 from the UK) with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio of at least 200.

We refer to participants and data related specifically to this cohort as EMPA-KIDNEY throughout this report.

The company provided an anchored network meta-analysis (NMA) to compare the efficacy of empagliflozin to canagliflozin, dapagliflozin, and finerenone. The treatments were anchored by placebo across all the studies included in the NMA.

1.1. Overview of the EAG's key issues

Table 2: Summary of key issues

ID3934	Summary of key issue	Report sections
Issue 1	Annualised changes in eGFR and uACR	4.15.4
Issue 2	The company model when run using the baseline characteristics of a long term follow-up study in the literature predicts too much ESKD and too little survival. There are reasons to think that this may worsen beyond the 15 year duration of the long term follow-up study.	4.12.5
Issue 3	The modelling does not explore whether it is more cost effective to reserve empagliflozin treatment until patients progress to either (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state. This also relates to the possibility of there being fast progressors and slow progressors.	4.15.2
Issue 4	The company model does not converge when run over 1,000 patients. The EAG thinks it should be run over 20,000 patients. Company validation work suggests that occasional patients with extreme values may be simulated. If these persist running the model over 20,000 patients will not address this.	4.3
Issue 5	The position sought where placebo is the comparator and the key clinical effectiveness estimates seem likely to differ by diabetes status. The EAG thinks that this argues for modelling them separately.	4.15.3
Issue 6	Cost effectiveness may differ by KDIGO health state at baseline. The EAG thinks that this argues exploring the effects of KDIGO health state at baseline upon cost effectiveness.	4.12.4, **Error! Reference source not found.**
Issue 7	The main clinical effectiveness estimates for the model are specific to the KDIGO health state at baseline. The model structure applies these to patients who change KDIGO health state. The two may be incompatible.	4.15.4, 4.15.5
Issue 8	The evolution of patients' uACR is driven by the uACR fold/multipliers observed during EMPA-KIDNEY at 18 months. 36 month data suggests that the reapplication of these uACR fold multipliers may not be justified.	
Issue 9	There is a lack of information about the company estimate for the off treatment uACR fold/multiplier. It seems misaligned with other estimates.	4.15.7, 4.15.8, 4.15.9
Issue 10	The model includes treatment discontinuations. Those on treatment should be modelled using estimates from the on treatment OC-OT data of EMPA-KIDNEY.	**Error! Reference source not found.**
Issue 11	The original company submission did not present the effect estimates for HbA1c, BMI, weight and SBP or the assumed duration of these effects. Their modelled evolution on treatment and off treatment is questionable.	4.8.3, 4.15.14

Issue 12	The company uses an American risk function for the risk of renal replacement therapy. The EAG prefers the UK risk function. The company applies these risks as soon as the patient falls to an eGFR of 15 ml/min/1.73m^2. Given the UK renal registry report it may be more reasonable to apply a lower threshold.	**Error! Reference source not found.**, **Error! Reference source not found.**
Issue 13	The UK renal registry report suggests renal replacement therapy has different modalities by age and very different mortality by age. There is no easy means for the model to take this into account. This increases modelling uncertainty.	4.15.16, 4.15.17
Issue 14	The modelling does not explore limiting the assumed duration of clinical effects. This is not aligned with the NICE methods guide.	**Error! Reference source not found.**
Issue 15	Summation of all the complications' disutilities may overestimate their pooled effects.	4.16.4
Issue 16	The annualization of multi-year event probabilities may estimate them occurring too soon and also is likely to overestimate the number of events.	**Error! Reference source not found.**
Issue 17	The model structure is a bit of a mixed bag. It might be more coherent to use the KDIGO health state specific quality of life values and costs to account for the effects of the complications of CKD, retaining the separate modelling of renal replacement therapy and its costs and the other events that affect progression through KDIGO health states and mortality.	4.15.21

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

The company base case results in the following deterministic cost effectiveness estimates when using the lightly revised model supplied at clarification and the company random number seed of 0.200 run over 1,000 patients.

Table 3: Company base case: model (RS 0.200)

	EMPA	PLAC	Net
Undiscounted LY	12.615	10.985	1.631
QALY	7.124	6.282	0.842
Cost	£89,907	£95,937	-£6,030
ICER			Dom*
NHB			1.143
*Dominant			

The probabilistic estimates are similar

EAG work using a model run over 20,000 patients suggests the following for the company base case.

Table 4: Company base case: model (multirun)

	EMPA	PLAC	Net
Undiscounted LY	12.847	11.091	1.756
QALY	7.234	6.325	0.910
Cost	£91,786	£94,737	-£2,951
ICER			Dom
NHB			1.057

Empagliflozin is estimated to be dominant: i.e. it provides patient gains while also saving the NHS money.

The company provides some scenario analyses all of which suggest empagliflozin dominates. The company also provides some outcomes disaggregate by baseline KDIGO health state but does not take this through to full clinical effect estimates. EAG work using a model run over 20,000 patients suggests the following for the company base case by KDIGO health state at baseline.

Table 5: Company base case by baseline KDIGO health state: net QALYs and Costs

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.071	0.096	0.885	£2,628	£3,055	-£3,295
G3a	0.363	0.846	1.411	£1,233	-£776	-£5,680
G3b	0.718	1.187	1.129	£727	-£2,642	-£6,226
G4	0.963	1.246	0.347	£2,310	-£3,485	-£4,778

Table 6: Company base case by baseline KDIGO health state: ICERs and NHBs

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£37,110	£31,905	Dom	-0.061	-0.057	1.050
G3a	£3,398	Dom	Dom	0.301	0.885	1.695
G3b	£1,012	Dom	Dom	0.682	1.320	1.440
G4	£2,399	Dom	Dom	0.847	1.421	0.586

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

1.3. The decision problem: summary of the EAG's key issues

The population reflect the entry criteria of the EMPA-KIDNEY trial with race-adjusted: [redacted]

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1: Annualised changes in eGFR and uACR

Report section	4.15.4
Description of issue and why the EAG has identified it as important	KDIGO assessment should be done at each timepoint where data was measured, but eGFR and uACR were not measured at the same timepoints consistently throughout EMPA-KIDNEY. The annual eGFR change by yearly-KDIGO health state should be calculated and used in the economic model.
What alternative approach has the EAG suggested?	Please see Issue 7
What is the expected effect on the cost-effectiveness estimates?	Cannot be stated.
What additional evidence or analyses might help to resolve this key issue?	Please refer to issue 7.

1.5. The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2: Model validation

Report section(s)	4.12.5
Issue and why important.	The company model when run using the baseline characteristics of a long term follow-up study in the literature predicts too much ESKD and too little survival. There are reasons to think that this may worsen beyond the 15 year duration of the long term follow-up study.
Alternative EAG approach.	None. This is intrinsic to the model implementation.
Likely effect upon cost effectiveness.	This seems likely to bias the model in favour of empagliflozin. Any bias cannot be quantified.
Additional evidence or analyses required.	None, given the model structure.

Issue 3: Decision problem not fully addressed

Report section(s)	4.15.2
Issue and why important.	The modelling does not explore whether it is more cost effective to reserve empagliflozin treatment until patients progress to either (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state. This also relates to the possibility of there being fast progressors and slow progressors.
Alternative EAG approach.	Whether this should be addressed is a matter for Committee. It would require extensive revisions to the model structure as outlined below.
Likely effect upon cost effectiveness.	It may improve the overall cost effectiveness of empagliflozin. The closest the current model comes to modelling fast progressors and slow progressors is the modelling of those with and those without diabetes at baseline. Those with diabetes at baseline typically have a faster eGFR progression, both in the placebo arm and when off treatment. The overall NHBs for those with diabetes are modelled to be around 6-7 times larger than for those without diabetes.
Additional evidence or analyses required.	Extensive model reworking with those in the empagliflozin arm not being treated with empagliflozin and experiencing the placebo arm eGFR changes until they progress to either (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state, at which point they would receive empagliflozin and experience the empagliflozin arm eGFR changes.

Issue 4: Model convergence and extreme patient values

Report section(s)	4.3
Issue and why important.	The company model is run over 1,000 patients. This is not sufficient for the net cost estimate of the model to converge. Other estimates are more stable. Validation work presented by the company at clarification shows that the model occasionally simulates a patient with extreme values. One patient was simulated as having a total cost of around £630k when treated with standard care compared to a total cost of around £120k when treated with empagliflozin and a net saving of over £500k. This is quite alarming and the EAG cannot think how this can sensibly come about within the model structure. It is sufficient to affect the average across the 1,000 patients simulated.
Alternative EAG approach.	Running 20,000 patients through the model. This addresses convergence issues but does not address the model occasionally simulating extreme patient values if this persists over the 20,000 patients.
Likely effect upon cost effectiveness.	For the company base case net savings change from -£6,030 to -£2,951. Net QALYs are less affected and the net health benefits change from 1.143 QALYs to 1.057 QALYs.
Additional evidence or analyses required.	Consistently running 20,000 patients through the model. Evidence on the frequency of extreme patient values.

Issue 5: Modelling of those with diabetes and those without diabetes separately

Report section(s)	4.15.3
Issue and why important.	The company presents cost effectiveness estimates for those with diabetes at baseline and those without diabetes at baseline in Appendix S. But this only varies baseline characteristics. Clinical effectiveness estimates are not subgroup specific. The key clinical effectiveness estimates for eGFR changes for those on treatment seem likely to differ between those with diabetes at baseline and those without diabetes at baseline. For those discontinuing treatment the model assumes the eGFR changes differ between those with diabetes and those without diabetes, based upon values taken from the literature.
Alternative EAG approach.	Modelling those with diabetes at baseline and those without diabetes at baseline separately, with subgroup specific clinical effectiveness estimates.
Likely effect upon cost effectiveness.	Based upon OC-AD eGFR and uACR subgroup specific data suggests that the net health benefits are as much as 6-7 times greater among those with diabetes at baseline compared to those without diabetes at baseline.
Additional evidence or analyses required.	OC-OT eGFR change and uACR change EMPA-KIDNEY data for those with diabetes at baseline and for those without diabetes at baseline. KDIGO health state specific discontinuation data for all patients, for those with diabetes at baseline and for those without diabetes at baseline.

Issue 6: Modelling disaggregated by KDIGO health state at baseline

Report section(s)	4.12.4, **Error! Reference source not found.**, 4.19.3, 4.19.4, 4.19.5
Issue and why important.	The company presents some modelling estimates disaggregated by KDIGO health state at baseline in Appendix J. This suggests quite large variation between patients with different KDIGO health state at baseline. The company does not take this through to cost effectiveness analyses. The modelling only compares empagliflozin with standard care without dapagliflozin. The position sought by the company outside that approved for dapagliflozin by TA775 where standard care without dapagliflozin is the appropriate comparator is KDIGO class specific, and actually subsections of KDIGO class specific. The modelling across all KDIGO health states is therefore of questionable relevance. Cost effectiveness may differ by KDIGO health state at baseline.
Alternative EAG approach.	Presenting modelling results across all-patients and disaggregated by KDIGO health state at baseline. This may be more indicative of the likely cost effectiveness of empagliflozin for the position(s) sought where dapagliflozin is not a comparator.
Likely effect upon cost effectiveness.	The estimated cost effectiveness of empagliflozin typically improves towards the higher risk KDIGO categories towards the bottom right of the KDIGO classification matrix.
Additional evidence or analyses required.	OC-OT eGFR change and uACR change EMPA-KIDNEY data for those with diabetes at baseline and for those without diabetes at baseline. KDIGO health state specific discontinuation data for all patients, for those with diabetes at baseline and for those without diabetes at baseline.

Issue 7: Model inputs compatibility with model structure

Report section(s)	4.15.4, 4.15.5
Issue and why important.	The main clinical effectiveness estimates for the model are specific to the KDIGO health state at baseline. They are based upon the change between baseline and end of follow-up, and presented as an annual slope estimate. The model structure applies these estimates within an annual model cycle. Patients who change KDIGO health state within the model therefore have the KDIGO baseline specific estimates from another patient group applied to them.
Alternative EAG approach.	Assessing the number of EMPA-KIDNEY patients who changed KDIGO health state during the course of the trial, with a focus on the OC-OT analysis. If this suggests that changing KDIGO health state was significant during EMPA-KIDNEY, re-analysing the EMPA-KIDNEY data based upon annual changes. The EAG cannot address this.
Likely effect upon cost effectiveness.	This cannot be stated. But it can be noted that this approach might be linked to an assessment of the importance of the 2 month “dippers” in the empagliflozin arm. Anything that moves towards using the post 2 months “chronic phase” data rather than the entire follow-up seems likely to improve the cost effectiveness of empagliflozin, though this will also depend upon where the “dippers” are located in the baseline KDIGO distribution.
Additional evidence or analyses required.	Assessing the number of EMPA-KIDNEY patients who changed KDIGO health state during the course of the trial, with a focus on the OC-OT analysis. If this suggests that changing KDIGO health state was significant during EMPA-KIDNEY, re-analysing the EMPA-KIDNEY data based upon annual changes.

Issue 8: Duration of on treatment uACR fold multiplier

Report section(s).	4.15.6
Issue and why important.	The evolution of patients' uACR is driven by the uACR fold/multipliers observed during EMPA-KIDNEY at 18 months. The model reapplies these for each annual model cycle that a patient remains on treatment. Information supplied at clarification suggests that based upon the 36 month data the reapplication of these uACR fold multipliers. There may be more grounds for their reapplication within the placebo arm but this is not clear.
Alternative EAG approach.	Only applying the uACR fold multipliers during the first year of the model.
Likely effect upon cost effectiveness.	The reapplication of the on treatment uACR fold multipliers within the EAG revised base case causes the all patient OC-OT ICER to change from £2,201 to £441 per QALY.
Additional evidence or analyses required.	OC-OT data for all patients, those with diabetes at baseline and those without diabetes at baseline as per Figure 22. Clarification about why 30 month rather than 18 month OC-AD data was supplied for those without diabetes at baseline.

Issue 9: Estimation of off treatment uACR fold multiplier

Report section(s).	4.15.7, 4.15.8, 4.15.9
Issue and why important.	The company estimates an off treatment annual uACR fold/multiplier with a central estimate of 1.460 from a paper within the literature. This value is considerably higher than the company uACR A1, A2 and A3 specific estimates of 1.046, 1.090 and 0.939 from the same source. It is also somewhat higher than the paper reported three year fold of 1.2 which implies an annual fold of 1.062, and the reported one year fold of 1.02. It is also typically higher than the EMPA-KIDNEY estimates for placebo.
Alternative EAG approach.	Given the previous issue the EAG revised base case does not apply the off treatment uACR multiplier. The EAG also provides a sensitivity analysis that applies the company uACR A1, A2 and A3 specific estimates while also reapplying the on treatment uACR multiplier.
Likely effect upon cost effectiveness.	The all patient OC-OT ICER changes from £441 to empagliflozin being dominant.
Additional evidence or analyses required.	The detail of the company statistical analysis and how the single pooled estimate is consistent with the three uACR A1, A2 and A3 specific estimates.

Issue 10: Full follow-up OC-AD data or on treatment OC-OT data

Report section(s).	**Error! Reference source not found.**
Issue and why important.	The model assumes a proportion of patients come off treatment each year. These patients are modelled differently than those on treatment, applying eGFR and uACR change estimates derived from the literature. Consequently, the modelling of those on treatment should be based upon an analysis of the on treatment EMPA-KIDNEY data, an OC-OT analysis.
Alternative EAG approach.	Applying OC-OT estimates. The company has supplied these for the all patient analysis.
Likely effect upon cost effectiveness.	Within the EAG revised all patient analysis the OC-OT ICER of £2,201 per QALY improves to £88 per QALY of OC-AD data is used.
Additional evidence or analyses required.	OC-OT eGFR and uACR change data for those with diabetes at baseline and those without diabetes at baseline.

Issue 11: Undocumented treatment effects

Report section(s).	4.8.3, 4.15.14, **Error! Reference source not found.**
Issue and why important.	The original company submission did not present the effect estimates for HbA1c, BMI, weight and SBP or the assumed duration of these effects. The model appears to apply the estimates as annual changes for the duration of treatment. EAG recollection is that this is in contrast to previous empagliflozin submissions for T2DM which limited the effects on, say, HbA1c to the trial duration; e.g. an annual -0.5% change over a 2 year trial duration would be assumed to apply for 2 years hence a -1.0% change at 2 years but no further improvement thereafter. The current modelling repeatedly applies this to yield a -1.0% change at 2 years, a -2.0% change at 4 years, a -3.0% change at 6 years, etc… until the 3.0% HbA1c floor is achieved For those discontinuing treatment the model may also retain the full benefit at discontinuation for the remainder of the time horizon for those without diabetes. This may not be reasonable.
Alternative EAG approach.	Limiting the application of the annual effect to two years and providing a scenario analysis of not applying these effect estimates due to their questionable subsequent modelling.
Likely effect upon cost effectiveness.	For the company base case, restricting their duration to 2 years increases the net savings from -£2,951 to -£4,363 but causes the net QALYs to worsen from 0.910 to 0.775. The net health benefits worsen by around 6%. Not applying these effects in a model that applies the company base case assumptions worsens the net health benefits by around 9% for those with diabetes at baseline and by around 13% for those without diabetes at baseline.
Additional evidence or analyses required.	There is still a lack of clarity about the HbA1c, BMI, weight and SBP effect estimates and their evolution over the course of EMPA-KIDNEY. The EAG thinks this should be presented for all patients, for those with diabetes at baseline and for those without diabetes at baseline in a similar presentation as that for eGFR.

Issue 12: Renal replacement therapy probability function and eGFR cap

Report section(s).	**Error! Reference source not found.**, **Error! Reference source not found.**
Issue and why important.	The company chooses a function for the 5 year probability of renal replacement therapy estimated from American data. This suggests higher probabilities that the equivalent function estimated from UK data. These probabilities are applied when patients fall into G5 with an eGFR below 15 ml/min/1.73m$^{2.}$ The company annualization of the risk function suggests that between around 40% and 50% of patients with an eGFR of 15 ml/min/1.73m^2 will receive renal replacement therapy that year. The UK renal registry report suggests that very few with an eGFR of 15 ml/min/1.73m^2 receive renal replacement therapy and if patients are asymptomatic NICE guidance only recommends it for those with an eGFR of between 5 and 7 ml/min/1.73m^2. Renal replacement therapy is the main source of the model cost savings.
Alternative EAG approach.	Using the UK risk function. Providing sensitivity analyses that reduce the ceiling at which the risk function is applied to 10 and 7 ml/min/1.73m^2.
Likely effect upon cost effectiveness.	The UK risk function reduces the company base case net savings from -£2,951 to -£1,975 but slightly increases net QALYs from 0.910 to 0.918. The company base case net health benefits worsen by 4%. Within the EAG all patient OC-AD analysis applying renal replacement ceilings of 10 and 7 ml/min/1.73m^2. worsen the ICER from £2,201 per QALY and £3,508 and £3,919 per QALY respectively.
Additional evidence or analyses required.	None.

Issue 13: Renal replacement therapy modality and mortality by age

Report section(s).	4.15.16, 4.15.17
Issue and why important.	With the exception of those over 80 years the model assumes the same distribution between haemodialysis, peritoneal dialysis and kidney transplant and kidney transplant. The model also assumes a constant mortality for each type of renal replacement therapy. The UK renal registry report suggests that the type of renal replacement therapy differs by age. More alarmingly it also suggests that one year survival rates are hugely age dependent. Renal replacement therapy is the main source of the modelled cost savings.
Alternative EAG approach.	None. The EAG only highlights this as a major modelling uncertainty.
Likely effect upon cost effectiveness.	Unknown.
Additional evidence or analyses required.	Addressing this would require major model revision, and probably some quite heroic assumptions given the available data.

Issue 14: Extrapolation of clinical effects

Report section(s)	**Error! Reference source not found.**
Issue and why important.	The modelling does not explore limiting the assumed duration of clinical effects. This is not aligned with the NICE methods guide.
Alternative EAG approach.	The EAG provides scenarios that limit the effects upon eGFR to 2 years, 5 years and 10 years.
Likely effect upon cost effectiveness.	The ICERs for the all patient OC-OT pooled KDIGO analysis worsens from £2,201 per QALY to £7,450, £3,751 and £2,273 per QALY respectively
Additional evidence or analyses required.	None.

Issue 15: Quality of life of multiple complications

Report section(s)	4.16.4
Issue and why important.	Summation of all the complications' disutilities may overestimate their pooled effects.
Alternative EAG approach.	Applying only the maximum of the complications' disutilities.
Likely effect upon cost effectiveness.	Indeterminate. For empagliflozin the company base case suggests increased net costs from complications other than renal replacement therapy. Applying only the maximum of the complications' disutilities may improve the cost effectiveness of empagliflozin.
Additional evidence or analyses required.	A model option to apply only the maximum of the complications' disutilities.

Issue 16: Annualization and annual re-estimation of risk functions

Report section(s).	**Error! Reference source not found.**
Issue and why important.	The probabilities of the more important events in the model are based upon multi-year risk functions; e.g. the risk of diabetes is taken from the QDiabetes 10 year risk function. These are annualised assuming a constant annual risk. This may not be reasonable. The EAG thinks that the risk of some or all of these events may tend to increase over the period to which they relate. If so, assuming a constant annual risk unreasonably hastens the modelled events. The model also updates these multi-year risks each annual model cycle before annualising them. Due to the progression of the modelled risk factors this causes the modelled annual risk to increase. Compounding these annual risks results in a higher multi-year risk than the original multi-year risk estimate. The model probably estimates too many events, possibly by quite a large margin.
Alternative EAG approach.	None. This is integral to the structure of the model and cannot be addressed by the EAG.
Likely effect upon cost effectiveness.	If events are brought forward and too many events are modelled the EAG thinks that this is likely to bias the analysis in favour of empagliflozin. The amount of any bias cannot be quantified.
Additional evidence or analyses required.	None. Given the model structure and the data available there is no obvious means of addressing this.

Issue 17: Model indeterminacy

Report section(s).	4.15.21
Issue and why important.	The model structure is a bit of a mixed bag. For the complications that are modelled, some have their quality of life impacts accounted for by the KDIGO health state specific quality of life values while others have a disutility attached to them. It is a similar story for costing of the complications that are modelled. Some complications are a bit of both. It may be more coherent to retain the modelling of the complications in order to correctly model ESKD and mortality, but to account for their effects upon quality of life and cost solely through the KDIGO health state specific quality of life values and KDIGO health state specific costs. This would be with the exception of the costs of renal replacement therapy which are not within the KDIGO health state specific costs.
Alternative EAG approach.	Exploring using only the KDIGO health state specific quality of life values and KDIGO health state specific costs, with the retention of renal replacement therapy costs.
Likely effect upon cost effectiveness.	Scenario analyses suggest that net health benefits worsen by around 6% if only KDIGO health state specific quality of life values are applied and by around 40% if only KDIGO health state specific costs are applied, though retaining renal replacement therapy costs.
Additional evidence or analyses required.	None.

1.6. Other key issues: summary of the EAG's view

Issue 18: Generalisability to the UK context

Report section	3.2.6
Description of issue and why the EAG has identified it as important	The ERG noted that overall smoking prevalence in the diabetes group was 47%, which was likely to be higher than in the UK population, and that the mean HbA1c was 7.17%, which might be better than in the UK population. This might mean that outcomes in the UK might differ from those in the whole study.
What alternative approach has the EAG suggested?	None. EAG point of view.
What is the expected effect on the cost-effectiveness estimates?	Cannot be stated.
What additional evidence or analyses might help to resolve this key issue?	None.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG makes the following changes to the company base case.

- EAG01: Using OC-OT eGFR change estimates rather than OC-AD estimates.
- EAG02: Apply the uACR multipliers in the first year but not thereafter.
- EAG03: Use the probabilities of RRT estimated from UK patient data
- EAG04: Only apply the effects on HbA1c, BMI and SBP for two years

The EAG also makes what it thinks are minor changes to the model, grouped under EAG05 in

- A maximum baseline age of 94 years rather than 80 years.
- Sample baseline comorbidities by age group and diabetes status.
- Apply 2017-19 England and Wales life tables and 2019 complication specific mortality data..
- Correct the CKD patch equation logarithm base for uACR from 10 to 8
- Apply age weighting of utilities.

- Add diabetic treatment costs to the KDIGO health states when modelling those with diabetes.

For the subgroup modelling of those with diabetes and those without diabetes at baseline the EAG applies the subgroup specific eGFR

Table 7: EAG's preferred assumptions: Net QALYs and net costs

Preferred assumption	EAG report	ΔQALYs	ΔCosts
Company base-case (multirun)	4.3, **Error! Reference source not found.**	0.910	-£2,951
Submitted company model (RS 0.200)	4.3, **Error! Reference source not found.**	0.842	-£6,030
EAG01: OC-OT rather than OC-AD	**Error! Reference source not found.**	0.858	-£2,579
EAG02: uACR multiplier only year 1	4.15.6-4.15.10	0.373	£1,164
EAG03: UK RRT probabilities	**Error! Reference source not found.**	0.918	-£1,975
EAG04: 2 year effect HbA1c, BMI, SBP	4.15.14	0.775	-£4,363
EAG05: Minor changes	**Error! Reference source not found.**	0.971	-£2,201
Cumulative: EAG01 to EAG06	..	0.225	£495

Table 8: EAG's preferred assumptions: ICER and NHB

Preferred assumption	EAG report	ICER	NHB
Company base-case	4.3, **Error! Reference source not found.**	Dominant	1.057
Submitted company model (RS 0.200)	4.3, **Error! Reference source not found.**	Dominant	1.143
EAG01: OC-OT rather than OC-AD	**Error! Reference source not found.**	Dominant	0.987
EAG02: uACR multiplier only year 1	4.15.6-4.15.10	£3,119	0.315

Preferred assumption	EAG report	ICER	NHB
EAG03: UK RRT probabilities	**Error! Reference source not found.**	Dominant	1.017
EAG04: 2 year effect HbA1c, BMI, SBP	4.15.14	Dominant	0.993
EAG05: Minor changes	**Error! Reference source not found.**	Dominant	1.081
Cumulative: EAG01 to EAG06	..	£2,201	0.200

Analysis by diabetic subgroup using OC-AD data, due to OC-OT data having not been provided, suggest an ICER of £326 per QALY for those with diabetes at baseline and £10,254 per QALY for those without diabetes at baseline.

Exploratory analyses for the all patient OC-OT patient group by baseline KDIGO heath state suggests the following.

Table 9: EAG base case by baseline KDIGO: net QALYs and Costs: All patients

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.007	-0.024	0.436	£2,844	£768	-£795
G3a	0.007	0.202	0.339	£2,790	£1,485	-£2,370
G3b	0.108	0.305	0.324	£1,080	£2,802	-£2,397
G4	-0.014	0.307	0.235	£5,643	£5,479	-£1,061

Table 10: EAG base case by baseline KDIGO: ICERs and NHBs: All patients

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£407k	Dom'td	Dom	-0.135	-0.063	0.476
G3a	£424k	£7,367	Dom	-0.133	0.127	0.458
G3b	£10,021	£9,179	Dom	0.054	0.165	0.443
G4	Dom'td	£17,844	Dom	-0.296	0.033	0.288
*Dominated: Fewer benefits at higher cost						

Note that the above estimates do not address most of the issues identified by the EAG in section **Error! Reference source not found.** above. The EAG urges Committee to review the issues of section **Error! Reference source not found.** above together with the scenario analyses of section **Error! Reference source not found.** in order to decide whether the modelling:

- provides unbiased estimates,

- should be simplified in terms of QoL and cost to be more coherent,
- should analyse by diabetic and non-diabetic subgroup,
- should analyse by KDIGO baseline health state,
- applies the Committee preferred set assumptions, and,
- identifies the most cost-effective use of empagliflozin.

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1. Introduction

Remit of the appraisal

To appraise the clinical and cost effectiveness of empagliflozin for treating adults with chronic kidney disease (CKD) (patients with or without type 2 diabetes mellitus [T2DM], with a broad range of estimated glomerular filtration rate [eGFR] from 20 to 90 mL/min/1.73m^2, and varying levels of albuminuria.

2.2. Background

Renal function

The kidneys have several functions. Their main one is to filter the blood (plasma) to remove waste products of metabolism and control fluid balance, excreting excess fluid as urine. They can also excrete toxins and drugs. Filtration is done in the glomeruli which can filter the entire plasma volume in about 30 minutes. The kidneys also have roles in regulating body fluid volume and composition. They affect blood pressure through the renin-angiotensin system. That system can be restricted by two groups of drugs, the angiotensin-converting enzyme inhibitors (ACEis) and the angiotensin receptor blockers (ARBs), both used in hypertension.[1]

The filtration rate is reported as the glomerular filtration rate (GFR) and is usually 90-120ml/minute. The urine then passes into the tubules where some substances can be removed or conserved. For example, glucose is reabsorbed in the renal tubules by a transport system called the sodium-glucose co-transporter system (SGLT). There are two of these called SGLT1 and SGLT2. In uncontrolled diabetes, so much glucose is present in the urine that the SGLT systems cannot cope and glucose appears in the urine – known as glycosuria.

Most water and sodium are reabsorbed. The amount of water reabsorbed varies according to fluid and loss from other mechanisms such as perspiration, and is controlled by the hormones aldosterone and anti-diuretic hormone.[1]

A small amount of albumen is excreted in the urine – up to about 30g per day. This is also conserved, unless the amount in the tubules is too great in which case protein appears in the urine. In diabetes, this has traditionally been identified in two ways, depending on quantity. Amounts detectable by a dipstick test, the Albustix test, in the clinic are referred to as proteinuria or albuminuria - over 300mg/day. Smaller amounts not detectable by stick testing are called microalbuminuria – 30 to 300mg/day. It should be noted that microalbuminuria is associated with an increased risk of cardiovascular disease.

The kidneys are involved in controlling the acid-base balance in the bloodstream and hence the pH of blood. Too high an acid level is called acidosis/acidaemia.[1]
The kidney is also involved in maintaining the level of blood cells through a process called erythropoiesis involving the release of a compound called erythropoietin, 90 % of which is produced in the kidneys. The other 10% is produced In the liver. The production of erythropoietin is stimulated if tissue oxygen level falls. Most people with CKD do not have anaemia (only about 10% do) but erythropoietin can be given if need be. There are two NICE STAs underway on artificial erythropoiesis-stimulating drugs for roxadustat (TA 807) and daprodustat (ID3987 – guidance was due out June 2023). NG 203 recommends erythropoiesis-stimulating agents.

Chronic Kidney Disease

If the GFR falls due to disease, the ability to eliminate waste material and to regulate the composition and volume of body fluid may be impaired. The compounds excreted in the urine include creatinine and urea. If urea excretion is impaired, the levels in the blood rise and this is known as uraemia. Urea level depends on GFR and protein intake, and creatinine levels are a better guide to GFR. However, there is a considerable reserve capacity in the kidneys and plasma urea and creatinine levels do not rise until about half of the GFR capacity has been lost. Similarly, symptoms of CKD do not usually start till disease is advanced. This is one reason why CKD is often not diagnosed.[2]

GFR is usually measured by creatinine clearance

The stages of chronic kidney disease based on GFR are;[3]

- Normal - > 90 ml/minute
- Stage 2 -mild impairment – 60 to 89
- Stage 3 – mild to moderate – 45-59
- Stage 3b – moderate to severe – 30 to 45
- Stage 4 – severe – 15-29
- Stage 5 – renal failure - <15 ml/min.

Healthy kidneys conserve almost all protein. The appearance of protein in the urine – proteinuria – is another sign of renal disease. Because the level of protein in the urine is influenced by urine volume, the protein level is usually adjusted by the creatinine level – this is known as the urine albumin to creatine ratio or uACR. (Albumin is the main type of protein.)
Albuminuria = increased urinary albumin levels. The uACR is albumen concentration in mg divided by creatinine in g;

- Mild increase <30
- Moderate increase 30 to 300 (microalbuminuria)
- Severe - >300

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[3]
The KDIGO classification of CKD based on eGFR and uACR categories and the risks of progression are shown in Table 11.

Table 11. KDIGO categories and associated risks[3]

<table>
<tr><td></td><td colspan="3">uACR levels</td></tr>
<tr><td></td><td>A1 – normal to mild increase: <30 mg/g</td><td>A2 – moderately increased: 30 to 299</td><td>A3 – severely increased: >300mg/g</td></tr>
<tr><td colspan="4">GFR stages</td></tr>
<tr><td>G1 >90</td><td rowspan="2">Low risk of progression</td><td rowspan="2">Moderate risk of progression</td><td rowspan="6">Very high</td></tr>
<tr><td>G2 60-89</td></tr>
<tr><td>G3a 45-59</td><td>Moderate risk</td><td>High risk</td></tr>
<tr><td>G3b 30-44</td><td>High risk</td><td rowspan="3">Very high</td></tr>
<tr><td>G4 15-20</td><td rowspan="2">Very high</td></tr>
<tr><td>G5 <15</td></tr>
</table>

CKD causes and treatments

Leading causes of CKD include diabetes (NICE states 25% of cases, Australian health direct states 40%[4]) and hypertension. However, many in old age have no clear cause –the 15% uncertain aetiology in the company submission Table 5). NICE has defined optimised standard care as including the highest tolerated licensed dose of angiotensin-converting enzyme (ACEI) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, plus statins and anti-platelet drugs if indicated.

The NICE CKD guideline (NG203) recommends ACEI or ARB if uACR is 70mg/mmol or more in people without diabetes, and that they should be considered if uACR is 30 to 69. The main contra-indication is hyperkalaemia. The NICE guideline (NG203) states that 72% of CKD patients got RAAS. Only 52% got a statin. Care in both the empagliflozin and dapagliflozin trials appears to have been more optimised than UK practice as reported in the CKD guideline.

Not everyone with CKD is suitable for statins. Messow and Isles[5] conclude that statins are indicated in CKD stage 3, probably indicated in CKD4, not indicated in CKD stage 5, but that evidence for group 4 was limited.

Diabetic nephropathy goes through several stages. In the early stages reflected in microalbuminuria, good glycaemic control can slow progression, but once it reaches the stage of frank proteinuria (macroalbuminuria) the consensus is that in type 2 diabetes, improved control does not prevent progression.[6] However, there is good evidence that control of hypertension slows progression with ACE inhibitors and angiotensin receptor blockers being the drugs of choice.[7] Low protein diets may have a slight effect and delay progression by about 8 months but compliance can be a problem and the evidence is mostly from TIDM.[8, 9]

Dapagliflozin guidance

NICE guidance (TA775) issued the following in 2022:

Dapagliflozini is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if:

1. It is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and
2. People have an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 m 2 to 75 ml/min/1.73 m 2 at the start of treatment and: — have type 2 diabetes or — have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more.

The second point reflects the entry criteria to the Dapa Kidney trial which excluded people with uACR under 200mg/g (22.6g/mmol), and included people with GFR in the range 25-75ml/min.

NICE Clinical Guidance on Type 2 diabetes[10]

For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), offer an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:

- ACR is over 30 mg/mmol and
- they meet the criteria in the marketing authorisation (including relevant estimated glomerular filtration rate [eGFR] thresholds).

1.8.18 For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), consider an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:

- ACR is between 3 and 30 mg/mmol and
- They meet the criteria in the marketing authorisation (including relevant eGFR thresholds).

The NICE guidance on people with CKD with persistent proteinuria but without diabetes makes no recommendation on the flozins.

CPRD data

The CPRD provides data from a large group of UK general practices. The EAG thought the data would be useful partly as background information and partly to set the Empa-Kideny results in context.

Kanumilli et al[11] used CPRD data in the REVEAL-CKD study. They found that 56% of patients with two recorded GFRs in the Stage 3 (30-59ml/min) group did not have CKD recorded in their GP records. The proportions were 59% for stage 3a and 41% for stage 3b. Kanumilli et al concluded that there is considerable under-diagnosis of CKD. The abstract reports data only for people with two GRF estimations, so there could be more undiagnosed.

The NICE guidance on CKD recommends testing for CKD if the following conditions are present;

- diabetes
- hypertension
- previous episode of acute kidney injury
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement, for example, systemic lupus erythematosus
- gout
- family history of end-stage renal disease (GFR category G5) or hereditary kidney disease
- incidental detection of haematuria or proteinuria.

It therefore seems surprising that so many people with CKD are undiagnosed.

Progression rates vary. Several papers report data from the DISCOVERY CKD study[12] which uses data drawn from large databases in the UK (CPRD) the USA and Japan. Patients had GFRs of 15 to 75. Abdul Sultan et al (2021 abstract) defined rapid progressors as people having a decline of >4m/min/year. They made up about 11% of people with CKD and had a mean decline of 7.5ml/min/year. They had more

comorbidities, with progression rates higher in people with diabetes, hypertension and heart failure. Heersprink[13] reported 14% of CKD patients to be rapid progressors. Amongst the CPRD cohort, the mean decline was 0.5 ml/year which was lower than in the USA (1.3) and Japan (1.1).

One implication of these and other data from the CPRD, is that many people with CKD are currently not diagnosed and treated, and of those that are treated, many may not be receiving the standard of care as defined by NICE. This could have considerable cost implications if NICE guidance stimulates the use of the flozins in this situation.

The company submission envisages that empagliflozin will be used in patients on optimised standard of care such as treatment with ACE inhibitors or ARB, in accordance with the NICE scope and previous guidance on dapagliflozin for the same indication. The EMA has recently extended empagliflozin indication to include treatment of chronic kidney disease (CKD) in adults, based on final results from study EMPA-KIDNEY.

Conclusions of published evidence

- In type 2 diabetes, the SGLT2 inhibitors are used less frequently than the dipeptidyl peptidase-4 (DPP4) inhibitors, the gliptins. Idris and colleagues[14] used UK CPRD data in an observational study to compare renal outcomes amongst people with T2DM treated with flozins and gliptins. They identified 105,000 people on gliptins (mainly sitagliptin) and 27,000 on flozins and created two propensity matched cohorts of about 23,438 each. At baseline, 21% had recorded diagnosis of CKD. The groups were followed for 2 years for a composite outcome of 40% reduction in GFR, ESRF treatment, or GFR <15. Mean age was 56 years. At the start of flozin or gliptin treatment, mean HbA1c was 9.2% and mean GFR was 80. 71% were on an ACEI or ARB. Renal outcomes were commoner amongst people treated with gliptins, with a hazard ratio favouring the flozins of 0.64 for the composite CKD outcome. Renal outcomes were independent of HbA1c, but the difference in overall mortality (HR 0.74 (95% CI 0.64 to 0.86, event rates 6.30 and 8.50 per 1000 PYs) was seen mainly in people with better glycaemic control. There were differences in effects, with the flozins improving CKD outcomes in people with no previous MI (HR 0.56) but not in those who had had MI in the past (HR 0.93).

- Differing effects of flozins were also reported by Rhee et al[15] where flozins had advantages over gliptins in non-fatal MI and stroke in people with T2DM but no CKD (HR 0.77, 95& CI 0.70 to 0.85) but in CKD stages 1, 2 and 3a, the differences were not statistically significant.
- Idris and colleagues conclude that in combination treatment in type 2 diabetes, the flozins have advantages over the gliptins because of their effect of CKD onset and progression.
- The other group worth considering are the glucagon-like peptide-1 agonists (GLP-1As) which have been shown to improve renal outcomes in placebo-controlled trials. In the LEADER trial[16] comparing liraglutide versus placebo, 65% of patients had some degree of CKD at baseline, and the composite renal outcome was less frequent (HR 0.78, 95% Cis 0.67, 0.92) in the liraglutide arm.
- In the SUSTAIN 6 trial[17] of semaglutide versus placebo, 70% of patients had some degree of CKD and the HR for renal outcomes was 0.64 (0.46, 0.88); 3.8% versus 6.1%). In the SUSTAIN trial, the benefits of semaglutide were significant only in those with BMI <30. In the LEADER trial, differences by BMI were less.

Granata and colleagues[18] provide a narrative review of the renal effects of the GLP-1As based on 8 RCTs (liraglutide, semaglutide, exenatide, dulaglutide, lixisenatide, 7 versus placebo)) and noted that most reduced macroalbuminuria, and two (liraglutide, dulaglutide) slowed decline in GFR, but that evidence of benefit in more serious outcomes such as ESRF was lacking.

2.3. Critique of company's definition of decision problem

Table 12: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with CKD having individually optimised standard of care	Adults with CKD having individually optimised standard of care, and having: [redacted]	This population represents a subset of the original scope, following advice received during the Decision Problem Meeting. Available evidence does support the use of empagliflozin in the anticipated marketing authorisation for the full population (i.e., in adults with CKD). The company stated that, [redacted]	• The population reflect the entry criteria of the EMPA-KIDNEY trial with race-adjusted: • [redacted]
Intervention	Empagliflozin in combination with optimised standard of care	Empagliflozin in combination with individually optimised standard of care (treatment with or without ACE inhibitors or ARB).	Intervention is in alignment with NICE final scope.	As per NICE final scope
Comparator(s)	Established clinical management with or without dapagliflozin.	As per NICE final scope.	N/A	As per NICE final scope
Outcomes	The outcome measures to be considered include: • morbidity including CV outcomes, disease	As per NICE final scope.	N/A	As per NICE final scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	progression (such as kidney replacement, kidney failure), and markers of disease progression (such as eGFR, albuminuria) • mortality • hospitalisation • adverse effects of treatment health-related quality of life.			
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. • 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.	As per NICE final scope.	N/A	The economic analysis is broadly in line with the NICE reference case and the scope. PSS costs of complications do not appear to have been considered.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from an NHS and Personal Social Services perspective.			

Subgroups	If the evidence allows the following subgroups will be considered: • People with diabetes • People with CVD • People with other causes of CKD	• People with diabetes	In this submission, economic analyses are presented for the ITT population and the diabetes subgroups, which are relevant for decision making. Additional economic analyses in people with and without CVD are not considered necessary. The comparator treatment for these subgroups would not differ from the overall target population. Further, as cost-effectiveness analysis demonstrates that empagliflozin is cost-effective in the overall ITT population, an exploration of the cost-effectiveness of further subgroups is deemed inappropriate.	Subgroups presented
Special considerations including issues related to equity or equality	None.	Consideration should be given to equity and equality implications related to the availability of empagliflozin across primary and secondary care settings for patients with CKD.		

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

3.1.1 Searches

The Company Submission (CS) Appendix D reports a systematic literature review (SLR) to identify randomised controlled trials (RCTs) on the efficacy and safety of empagliflozin and potential comparator drugs of interest in CKD, as well as a targeted literature review (TLR) to identify any relevant observational studies. Only RCTs identified via the SLR were taken forward as included studies for the clinical effectiveness review [redacted]The TLR was used to obtain data on progression of GFR (15 studies) and progression of uACR (6 studies). The key studies such as Grams[19] are described later in this report 4.8.1. They are listed in Table 8 of the BI submission.

Inclusion criteria

Titles, abstracts, and full text studies were screened by two reviewers. Study assessment conflicts were resolved by a third independent reviewer. The SLR inclusion criteria was provided in Table 8, Appendix D of the CS. Briefly, it included RCTs that covered the following:

Population Adult patients with CKD or DKD, with or without comorbidities.

Intervention SGLT2 inhibitors (Empagliflozin, Dapagliflozin, Canagliflozin), Non-steroidal anti mineralocorticoid (Finerenone).

Comparator any other comparator that allows direct or indirect treatment comparison

Outcomes Composite renal outcome, ESKD/ESRD, eGFR change from baseline, eGFR slope, HHF, HHF or CV death, MACE, All-cause mortality, CV death, All-cause hospital admissions.

3.1.2. Critique of data extraction

Data extraction was carried out in a pre-defined data extraction sheet to capture key characteristics and data from included studies. Data extraction was carried out by one reviewer and checked by a second reviewer.

3.1.3. Quality assessment

Risk of bias was carried out using the Cochrane risk of bias tool.[20] Risk of bias was presented in Table 19, Appendix D of the CS.

3.1.4. Results of the SLR

The SLR included four trials investigating the efficacy of empagliflozin in CKD. The studies were EMPA-KIDNEY,[21] EMPA-REG OUTCOME[22] EMPEROR-Reduced,[23] and EMPEROR-Preserved.[24] The trial that was mainly discussed in the clinical effectiveness and cost-utility analysis was EMPA-KIDNEY.[21] The other three trials were excluded because of the population (not exclusively CKD patients) but are briefly reported below.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Evidence on the clinical efficacy and the cost-utility of Empagliflozin in patients with CKD was mainly obtained from EMPA-KIDNEY trial (NCT03594110).[21] EMPA-KIDNEY investigated the effect of empagliflozin in addition to SoC on the progression of kidney disease and CVD in a range of patients with CKD with or without DM. The trial was an international (included eight countries including the UK) multicentre study and involved 241 centres. EMPA-KIDNEY[21] was the main source of clinical efficacy evidence in the cost-utility model.

A detailed summary of EMPA-KIDNEY[21] is presented in CS section B.2.3.1. The EAG's critique of the key source of clinical evidence for this technology is presented in section 3.2.1.

Three other trials have reported the effect of empagliflozin on renal disease.

The main outcomes in the **Empa-Reg Outcome Trial** (NCT01131676)[22] in diabetes were cardiovascular death, and non-fatal MI and stroke. The secondary outcome was admission for unstable angina. GFR was reported only in an online appendix. The decline in GFR was 2ml/min on placebo, and 2.3ml/min on empagliflozin 10mg daily. Half of the recruits had had baseline GFR in the 60 to 89 ml/min range, with only 26% below 60.

Similarly, 60% were in ACR group 1 with only 11% in ACR3. Median follow-up was 3.1 years. Mean baseline HbA1c was 8.1% and mean BMI was 31 kg/m^2.

Empa-Reg Outcome was focused on cardiovascular outcomes but a post-hoc analysis by Wanner et al[25] provided more detail on the renal effects, Wanner et al divided the Empa Reg Outcomes recruits into three groups;

- Overt CKD with uACR >300mg/g, any GFR permitted, 11% of the total
- Non-overt CKD, GFR 30-50, uACR <300, 18% of total
- The others, GFR > 60, uACR <300.

It should be noted that this trial excluded people with GFR < 30 ml/min. Declines in GFR were seen in all groups but were less on empagliflozin than on placebo. In the empagliflozin groups, the declines were 1.6, 0.55 and 0.2 ml/min in the overt, non-overt and others groups respectively.

The EMPEROR-Reduced[23] was performed in 3730 patients with heart failure and a reduced ventricular rejection fraction of 40% or less. The primary outcome was a combination of cardiovascular death or admission to hospital with heart failure, but one secondary outcome was rate of decline in GFR, and another outcome was a composite renal outcome of need for haemodialysis or renal transplantation, a drop in GFR of 40% or GFR < 15 ml/min. Half of the recruits had diabetes, mean age was 67 years and mean baseline GFR was 62 ml/min. Mean BMI 28 kg/m^2. GFR declined by 0.55 ml/min on empagliflozin 10mg and by 2.23 on placebo. The composite renal outcome occurred in 1.6% on empagliflozin and in 3.1% on placebo. However overall mortality was similar – 13.4% and 14.2%. Median follow-up was 16 months.

The EMPEROR-Preserved[24] was similar except that it recruited 5068 people with LV ejection fraction > 40%. Mean BMI was 30 kg/m^2. The principal outcomes were similar as were the secondary renal outcomes. GFR fell by 1.75 ml/min on empagliflozin and by 2.62ml/min on placebo. The composite renal outcome was seen in 3.6% on empagliflozin and in 3.7% on placebo. Overall mortality was 14.1 %

on empagliflozin and 14.3% on placebo. Baseline GFR was 74 ml/min. Median follow-up was 26 months.

One issue with measurement of GFR in trials of the flozins is the initial dip phenomenon. This is a well-known occurrence with the flozins. After the immediate dip, the GFR stabilizes and thereafter declines at a slower rate than seen in the placebo groups.

The Empa Kidney trial paper (figure 3) shows an immediate drop in GFR after commecing empagliflozin of about 4-5 ml/min. After this, the GFR lines meet at about 18 months after which GFR was higher in the empagliflozin group. In the Dapa-Kidney trial[26] there was also an initial dip, with GFR lines meeting at 12 months after which GFR was higher in the dapagliflozin group.

Not all patients experience a dip in GFR. In the Empa Outcomes trial in type 2 diabetes, 28% of the empagliflozin group experienced a dip at 4 weeks. The proportion experiencing dips varies amongst trials, being 45% in the VERTiS-CV trial of ertugliflozin[27] and 45% in the CREDENCE trial of canagliflozin.[28] The size of the dip ranged from 3 to 6 ml/minute.[29] Dips were also seen in 13-21% of placebo patients. The dip effect is not regarded as clinically concerning and some authors have even suggested that it could be a sign of good response to flozins.[30] Dips are more likely to be seen in those on diuretics and in those in higher KDIGO subgroups.

One common feature of all four empagliflozin trials was that mean BMIs were just under or just over the BMI obesity threshold. Bolignano and Zoccali[31] carried out a systematic review of the effects of weight loss on renal function in obese CKD patients. They concluded that weight loss reduced albuminuria and improved or maintained GFR, but the most significant effects were observed after bariatric surgery and amongst people with diabetes. There were issues with the evidence base, with mainly observational studies, some too small for reductions in albuminuria to be statistically significant, and overall quality of most studies low or moderate. Most studies did not provide data by CKD stage. A trial of the DIRECT trial weight loss intervention in CKD would be useful. Mean weight loss at 24 months in DIRECT was 10kg with those with weight loss of over 10kg having a 64% remission of

diabetes rate. Weight loss was also associated with a reduction in blood pressure and reduced need for anti-hypertensive drugs.[32]

3.2.1. EMPA-KIDNEY

The EMPA-KIDNEY trial planned to recruit 6,000 patients in 200 to 250 sites and to continue the study until a minimum of 1,070 primary outcome events occurred. This would have provided 90% power at a two-sided p-value of 0.05 to detect an 18% relative reduction in the primary outcome (It is not clear to the EAG why the figure of 18% was chosen but this is statistically not important.) Formal interim analyses took place when 624/1,070 (58%) primary outcome events had taken place. The study was stopped as two conditions were met:

- Hazard ratio for the primary outcome of <0.778 with a two-sided p-value <0.0017, and
- Hazard ratio for the outcome of ESKD or CV death of <0.778 with a two-sided p-value <0.0017.

The company acknowledges that, as the study was stopped early, the trial may not be sufficiently powered for secondary/tertiary outcomes.

3.2.2. Characteristics of EMPAG-KIDNEY study participants

The trial included 6609 patients. Patients were recruited from 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the United Kingdom, and the United States of America). Baseline characteristics of these patients are described in the CS Table 15 (p. 48-49). The baseline characteristics varied due to inclusion criteria, especially regarding proteinuria. There was a high proportion of smokers in the trial. It seems high by UK standards even though smoking increases the risk of CKD.[33]

The EAG requested for UK participants' baseline characteristics. This was to evaluate if the UK participants would have similar characteristics to the rest of the EmpaKidney recruits and the company provided the UK data shown in Table 13.

Table 13. EMPAG-Kidney baseline characteristics

Parameter	Full-cohort	Empag-10	Placebo	UK Cohort	Western-Europe
Number of subjects, N	6609	3,304	3,305	[redacted]	[redacted]
Age (years), mean (SD)	63.30	63.9 (13.9)	63.8 (13.9)	[redacted]	[redacted]
Female sex, N (%)	2192 (33.2%)	1,097 (33.2)	1,095 (33.1)	[redacted]	[redacted]
History of DM, N (%)					
Yes	3,040 (46.0)	1,525 (46.2)	1,515 (45.8)	[redacted]	[redacted]
No	3,569 (54.0)	1,779 (53.8)	1,790 (54.2)	[redacted]	[redacted]
DM type, no./total no. (%)					
Type 1	68/3,040 (2.2)	34/1,525 (2.2)	34/1,515 (2.2)	[redacted]	[redacted]
Type 2	2,936/3,040 (96.6)	1,470/1,525 (96.4)	1,466/1,515 (96.8)	[redacted]	[redacted]
Other or unknown	36/3,040 (1.2)	21/1,525 (1.4)	15/1,515 (1.0)	[redacted]	[redacted]
HbA1c (%)	6.27%			[redacted]	[redacted]
Systolic blood pressure (SBP)	136.50	136.4 (18.1)	136.7 (18.4)	[redacted]	[redacted]
Diastolic blood pressure (DBP)	NA	78.1 (11.7)	78.1 (11.9)	[redacted]	[redacted]
Diabetes diagnosis (years)				[redacted]	[redacted]
Insulin use (%)				[redacted]	[redacted]
Proportion on lipid therapy (mainly statins) (%)	66.2%	66.3 %	66.2 %	[redacted]	[redacted]
Renin-angiotensin system (RAS) inhibitors (%)	5.2%	85.7%	84.6%	[redacted]	[redacted]
Diuretics therapy (%)	42.6%	41.2%	44.0%	[redacted]	[redacted]
Smokers (%)	44.60%			[redacted]	[redacted]

The UK cohort mean HbA1c was 58.6 mmol/mol, or about 7.5%. The National Diabetes Audit 2021 reported that about 63% of the England T2DM population achieved 58mmol/mol or less. The patients in the UK diabetes cohort had fairly similar glycaemic control to the general UK type 2 diabetes population, but slightly poorer glycaemic control than the whole Empa Kidney cohort. However, this was

unlikely to be sufficient to make a significant difference in outcomes, particularly as once CKD advances in people with diabetes, improving glycaemic control has little effect on progression,[6]

In the UK Empa Kidney cohort, 7% were active smokers, far fewer than the 45% overall in the trial, but another 42% were previous smokers. No data were available on duration since stopping. The much lower proportion could mean that the risk of cardiovascular outcomes is lower in UK.

Table 27 of the company submission states that 6.4% of the whole Empa Kidney cohort were on statins which seemed surprisingly low. In response to a clarification question A1, the company reported that 67% of the UK cohort were on statins, which is more what might be expected. There were some other unusual figures reported (table 27), such as the percentages with previous gestational diabetes which was similar in the group with diabetes and the group with no diabetes, whereas one would expect a higher proportion in the group with diabetes since gestational diabetes is often followed by T2DM. 83% of the UK patients were treated with ACEIs or ARBs, and 32% were on a diuretic.

It seems that the UK cohort were receiving standard of care as defined by NICE. Apart from the difference and uncertainties around smoking, statins and ethnicity, the characteristics of the UK cohort seem similar enough to the whole cohort for their outcomes to be also similar.

3.2.3. Statistical analysis of outcomes of EMPA-KIDNEY

The primary outcome of EMPA-KIDNEY (ITT population) was kidney disease progression or CV death. Secondary outcomes included time to occurrence of all-cause hospitalisation (ACH; first and recurrent combined), time to first occurrence of HHF or CV death, and time to adjudicated death from any cause. Tertiary outcomes included time to first occurrence of kidney disease progression, time to adjudicated CV death, time to first occurrence of adjudicated CV death or ESKD, and annual rate of change in eGFR (total and long-term; defined as from 2 months until final follow-up visit).

The primary outcome was analysed using a Cox proportional hazards model, adjusting for the variables that were used in the minimisation algorithm which was used to randomise patients to each treatment arm (age, sex, DM status, eGFR, uACR, and region). The utilization of the Hwang-Shih-DeCani alpha spending function, with a parameter of γ=-8, was used to address the issue of multiple comparisons in the study. This function is used to account for multiplicity in both planned and unplanned interim analyses, as was the situation for EMPA-KIDNEY. As a result of implementing this function, the 2-sided alpha spending level for the primary efficacy outcome was determined to be 0.0017. The company presented a Kaplan-Meier plot for the primary outcome considering non-CV and renal deaths as a competing risk.

The Hwang-Shih-DeCani alpha spending function is, essentially, a way of 'spending' the confidence level over time and over the various interim analyses. A gamma value of -8 is quite extreme and results in very conservative alpha spending, making it harder to declare statistical significance at each step.

Key secondary outcomes were analysed. The company specified estimands for the key secondary outcomes, as shown in table 16 in CS section B.2.4.1. Estimands help define the precise target of estimation by specifying the population, variables, and conditions under consideration. The same α-spending function was used with γ=0 to account for multiplicity and the error rates were adjusted according to the actual proportion of primary outcome events observed up to where EMPA-KIDNEY was stopped. The other secondary and tertiary outcomes were not adjusted for multiplicity.

3.2.4. Efficacy results of EMPA-KIDNEY

The company provides the clinical effectiveness results from EMPA-KIDNEY in CS section B.2.6 for the ITT population, along with corresponding sensitivity analyses which are described in Table 14.

Table 14. Sensitivity analyses performed in section B.2.6 of the company submission

	Kidney disease progression or CV death	ACH (first and recurrent)	HHF or CV death	All-cause death
Outcome type	**Primary**	**Secondary**		
Using central eGFR values only	Yes	-	-	-

Using local eGFR values only	Yes	-	-	-
Including only treatment as covariate	Yes	Yes	Yes	Yes
Multiple imputation for loss to follow-up	Yes	-	Yes	Yes
Competing risk analysis (Fine-Gray model)	Yes	-	Yes	-
Censoring patients 7 days prior to onset of COVID-19 AE	Yes	-	Yes	Yes
Including events up to 7 days prior and 28 days after onset of COVID-19 AE	Yes	-	Yes	Yes
Parametric joint gamma frailty model	-	Yes	-	-
Excluding hospitalisations due to COVID-19 AE	-	Yes	-	-

All outcomes were presented as hazard ratios (HR) with 95% confidence intervals (95% CI) except for annual change in eGFR which was presented as change from baseline and change from two months post-baseline. The results are summarised in Table 19.

During clarifications, the company provided the anonymised individualised patient data required to replicate the multivariate Cox proportional hazards model for the primary outcome. The EAG was able to replicate the analysis and produced the same HR and 95% CI as the company, carried out in RStudio (R version 4.1.0). Therefore, the EAG conclude that the survival analysis was performed appropriately and accurately.

Table 15. Summary of efficacy outcomes of EMPA-KIDNEY

		Events (%)				Rate (per 100 PY)		Empagliflozin vs Placebo			
Type	**Outcome**	**Empagliflozin N = 3,304**		**Placebo N = 3,305**		**Empagliflozin**	**Placebo**	**HR**	**95% CI**		**P**
Primary	Kidney disease progression or CV death	432	13.1%	558	16.9%	6.85	8.96	0.72	0.64	0.82	< 0.001*
Key secondary	Time to occurrence of ACH (first and recurrent combined)	1611	48.8%	1895	57.3%	24.80	29.20	0.86	0.78	0.95	0.0025*
Key secondary	Time to first occurrence of HHF or CV death	131	4.0%	152	4.6%	2.04	2.37	0.84	0.67	1.07	0.1530
Key secondary	Time to adjudicated death from any cause	148	4.5%	167	5.1%	2.28	2.58	0.87	0.70	1.08	0.2137
Tertiary	Time to first occurrence of kidney disease progression	384	11.6%	504	15.2%	6.09	8.09	0.71	0.62	0.81	< 0.001*
Tertiary	Time to adjudicated CV death	59	1.8%	69	2.1%	0.91	1.06	0.84	0.60	1.19	0.3366
Tertiary	Time to first occurrence of adjudicated CV death or ESKD	143	4.9%	217	6.6%	2.54	3.40	0.73	0.59	0.89	0.0023*
								Beta	**95% CI**		**P**
Further	Annual rate of change in eGFR: total							0.75	0.54	0.96	< 0.001*
Further	Annual rate of change in eGFR: long-term							1.37	1.16	1.59	< 0.001*

*Statistically significant
Abbreviations: ACH = all-cause hospitalisations; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HHF = hospitalisation for heart failure; HR = hazard ratio; P = p-value; PY = person-years.

3.2.5. Subgroup analyses

Subgroup analyses were conducted for the primary outcomes, key secondary outcomes, and the rate of change in eGFR outcomes. The pre-specified subgroups of interest were diabetes status (present, absent), eGFR (<30, ≥30 to <45, ≥45), and uACR (<30, ≥30 to ≤300, >300).

For the primary outcome, baseline DM status and baseline eGFR were consistent with the overall results, but there was some evidence that the proportional risk reduction may have been larger among patients with higher (>300) uACR (interaction p-value = 0.0174).

All subgroup analyses were consistent with the overall result for the key secondary outcomes (time to first occurrence of ACH, time to first occurrence of HHR or CV death, and time to adjudicated death from any cause). Subgroup analysis results for baseline DM status groups were consistent with the outcome of overall annual rate of change in eGFR from baseline to final follow-up. The remaining subgroup results for this outcome and all of the subgroups in the outcome of long-term annual change in eGFR had statistically significant interaction p-values ($p<0.05$), meaning that, for example, the effect of baseline eGFR on the dependent variable of annual change in eGFR differs significantly based on that baseline value of eGFR.

Detailed subgroup analyses can be found in CS appendix E.

The company considered patients with diabetes and patients without diabetes in subgroup analyses for the economic analysis.

3.2.6. Overall summary of EMPA-KIDNEY trial

EMPA-KIDNEY was a phase III trial with over 6,000 participants. There were 1,133 participants from the UK. Table 1 of CS section O.1.3 which summarises clinical expert responses on key details of the CS showed that two of the three experts considered that the population of CKD patients in EMPA-KIDNEY would be generalisable to the NHS clinical practice population; the other expert, pointed out that EMPA-KIDNEY included a higher-than-expected male and Asian cohort.

The Empa Kidney trial recruited 6609 patients from 241 centers in 8 countries (USA, Canada, China, Malaysia, Japan, Germany, Italy and UK), an average of 27 per center. The UK centers recruited 1133 patients, about 17% of the total, and an

average of about 21 per centre. The study was led from the Oxford Clinical Trials Unit.

Table 27 of the submission provides baseline characteristics of the recruits, separately for those with diabetes and those without. The ERG noted that overall smoking prevalence in the diabetic subgroup was 47%, which was likely to be higher than in the UK population, and that the mean HbA1c was 7.17%, which might be better than in the UK population. This might mean that outcomes in the UK might differ from those in the whole study.
36% of recruits to Empa Kidney were Asian, but there was no breakdown of this group. Presumably most were East Asians from China, Japan and Malaysia but there were presumably some South Asians from the other countries including the UK.

The statistical analysis followed the SAP form stopping rules to the Cox PH models. Results showed statistically significant improvements in the empagliflozin arm compared to the placebo arm across the following outcomes: the primary outcome of kidney disease progression or CV death, time to occurrence of ACH, time to first occurrence of kidney disease progression, time to first occurrence of adjudicated CV death of ESKD, and annual rate of change in eGFR (total and long-term). Similarly for sensitivity and subgroup analyses which were consistent with the overall result, bar the few aforementioned subgroups.

The EAG asked for the data required to replicate the Cox models used in the analysis of the EMPA-KIDNEY trial. The Cox model for the primary outcome was adjusted for six additional variables including competing risks. The EAG produced the same results as the company when replicating this analysis, thus the EAG consider the methods and results appropriate.

The EAG also asked for the individualised Kaplan-Meier data for all-cause mortality to check for the potential of adding long-term survival extrapolations to the economic model, which the company did not originally use in the model. This is discussed further in 3.4.

The submission provided details of the effect sizes used in the modelling. The changes over time in each arm are shown in Table 16. All showed reductions except for Hb on empagliflozin.

Table 16. Effect sizes used in the modelling (clarification response, reductions unless otherwise specified by +)

	Empagliflozin		Placebo	
Variable		SE		SE
HbA1c %	0.56	0.14	0.16	0.14
BMI	0.55		0.24	
Hb g/dl	+ 0.6	0.49	0.14	0.06
SBP mmHg	3.9	4.3	1.20	0.21
DBP mmHg	1.6	1.9	1.22	0.12

The following analyses from the CS report of the EMPA-KIDNEY trial were used in the company's economic analyses:

- Clinical effectiveness results (CS Section B.2.6) comparing empagliflozin to placebo in EMPA-KIDNEY. The hazard ratios were used in the indirect treatment comparison of empagliflozin versus active treatments.
- Baseline characteristics of the full EMPA-KIDNEY cohort, the diabetic subgroup only, and the non-diabetic subgroup only were used in the economic model based on which population the economic model was modelled for, either the full cohort, the diabetic subgroup, or the non-diabetic subgroup.
- The company originally used annual change in eGFR and uACR from all patients, but supplied the OC-AD analysis of these separately for the diabetic and non-diabetic subgroups during clarifications.
- Adverse events which were reported for all subgroups and appeared the same across all subgroups.

3.2.7. Overview of flozin evidence

A systematic review was carried out by the Nuffield Department of Population Health Renal Studies Group[34] and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium.

The aim was to compare outcomes of SGLT2 inhibitor trials in participant with and without diabetes. Outcomes included both renal and cardiovascular disease, and two adverse outcomes – ketoacidosis and lower limb amputation. Amputation was included because one trial of canagliflozin, the CANVAS trial,[35] reported an increased risk of amputation in the drug arm. Ketoacidosis is included because of an increased risk with the flozins[36] and it may be diagnosed late because blood glucose may not be raised.

The review was assessed as high quality using the NIH checklist for systematic reviews.[37] Of the 13 included trials, four were in diabetics with high CVD risk, five were in people with heart failure (half diabetic) and four were in CKD. The Empagliflozin Kidney trial was not then published at the time of the review but was included. Data on renal outcomes (> 50% decline in GFR, ESRF, renal death) were extracted from all 13 trials. The flozins reduced the composite renal outcome by about a third with no significant difference between the diabetes and non-diabetes groups. The ORs were 0.62 (0.56 to 0.68) for those with diabetes and 0.69 (0.57 to 0.68) without.

The risk of ketoacidosis was two-fold on flozins (OR 2.12, 95% CIs 1.5, 3.0). There was no overall risk of amputation once the CANVAS trial[35] was removed.

A very recent narrative review in the UK Drug and Therapeutic Bulletin[38] found that all trials were included in the Nuffield review.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Section B.2.9 of the CS describes the indirect treatment comparisons methods used by the company.

3.3.1. Feasibility assessments of indirect treatment comparison methods

The company considered a pairwise meta-analysis between empagliflozin and comparators specified as the NICE scope, specifically dapagliflozin, to not be feasible due to the lack of head-to-head trials comparing empagliflozin to any of these comparators. The EAG agreed with this as no direct head-to-head trials were found.

The company opted for an anchored network meta-analysis (NMA) to compare the efficacy of empagliflozin to canagliflozin, dapagliflozin, and finerenone. The treatments were anchored by placebo across all studies in the NMA.

3.3.2. Feasibility of MAIC

The company also considered a matching-adjusted indirect comparison (MAIC) between empagliflozin from EMPA-KIDNEY and dapagliflozin from DAPA-CKD as not feasible. The EAG requested the company's full feasibility assessment of a MAIC during clarifications to properly judge the appropriateness of not performing a MAIC.

The company provided the full feasibility of the MAIC method during clarifications. The company presented the viewpoint that, due to the existence of a connected network, a NMA would be the best course of action when calculating indirect estimates between empagliflozin and the other active treatments in this network. The company argued that major disadvantages of the MAIC over the NMA were due to differences in prognostic factors between participants of the two studies. They suggested that the MAIC would ignore the correlations between covariates, which are unknown in DAPA-CKD, and also that event rates in the placebo arms differ between studies, suggesting underlying effects which remain unaccounted for.

The company presented the DAPA-CKD-eligible participants of EMPA-KIDNEY and compared that to DAPA-CKD in Table 15 of the CQ responses, There were

differences in primary cause of kidney disease, e.g. proportion who had DM, and in levels of HbA1c, eGFR, and uACR.

Given the reasons listed above by the company, the EAG agree with the company that the NMA was preferable to a MAIC.

3.3.3. Search strategy

The company performed a clinical SLR and TLR to identify all RCTs and observational studies that were related to the treatment of CKD/DKD. Studies were included if they were phase III (or II/III) studies evaluating approved doses of the included treatments, with a study duration of more than 52 weeks.

Searches were conducted on October 3, 2022, and were done in EMBASE, MEDLINE, Cochrane CENTRAL Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Searches were also carried out on seven conferences of interest which took place between 2019-2022, by manual check of bibliography lists and by searching Boehringer Ingelheim clinical study reports and unpublished meta-analyses. The SLR identified 4,476 publications which, after eligibility screening, ended with 209 publications on 27 trials. The TLR identified 14 studies, all of which were excluded due to not meeting the inclusion criteria. Thirteen RCTs were ultimately selected for inclusion in the NMA. Full details of the company's search strategy are presented in CS section D.1.2 to section D.1.7.

3.3.4. Heterogeneity of studies included in the ITC

Table 17 and Table 18 compare the study design, demographic, and baseline characteristics of the studies which were included in the company's NMA. From the 13 studies, two compared canagliflozin 100mg or 300mg to placebo, five compared dapagliflozin 5mg or 10mg to placebo, four compared empagliflozin 10mg or 25mg to placebo, and two compared finerenone 10mg or 20mg to placebo. Two studies, EMPEROR-Preserved and DAPA-HF had only one drug arm.

Study participants were broadly similar in terms of age, and the majority of participants in each study were males and of White ethnicity. However, there were variations to ethnicities such as only around 3% of participants of particpants in Dekkers 2018[39] were Asian, compared to 35% of participants of CAPA-CKD. A number of studies recruited only patients who were diabetic compared to other

studies which had a mix of diabetic and non-diabetic participants. BMI for all participants was in the overweight or obese range. The range of eGFR varied from study to study. Although they were all under 90 mL/min/1.73m², they ranged from as high as 85 in DECLARE-TIME to as low as 37 in EMPA-KIDNEY. Some studies recruited only patients with a history of heart failure, others had a mix. There was also a large variation in baseline uACR. Participants in studies such as the CANVAS program had baseline uACR values around 21 (indicating a normal uACR) whilst other studies had baseline uACR values in the 800s and 900s (indicating moderately increased uACR).

Table 17. Characteristics of studies included in the company's NMA

		Treatment arms				Sample size		
Studies	**Population**	**Intervention**	**Control**	**Disease area**	**Blinding**	**Total**	**Intervention**	**Control**
CANVAS program	eGFR < 60	Canag 100 mg or 300 mg	Placebo	T2DM, HbA1c ≥7.0 and ≤10.5%, elevated risk of CVD	Double	2,029	1,100	929
CREDENCE	Full sample	Canag 100 mg	Placebo	T2DM and CKD	Double	4,401	2,202	2,199
DAPA-CKD	Full sample	Dapag 10 mg	Placebo	CKD with or without T2DM	Double	4,304	2,152	2,152
DAPA-HF	eGFR < 60	Dapag 10 mg	Placebo	HF and LVEF ≤40%	Double	1,926	1,926	
DECLARE-TIME	Only subgroup of interest	Dapag 10 mg	Placebo	T2DM	Double	17,160	8,582	8,578
Dekkers, 2018	eGFR >=12 to <45	Dapag 10 mg or 5 mg	Placebo	T2DM and impaired kidney function	Double	220	151*	69
MB102029	Moderate renal impairment	Dapag 10 mg or 5 mg	Placebo	T2DM, HbA1c ≥7.0 and ≤11%	Double	252	168*	84
EMPA-KIDNEY	Full sample	Empag 10 mg	Placebo	CKD with or without DM	Double	6,609	3,304	3,305
EMPA-REG OUTCOME	eGFR < 60 or uACR > 300	Empag 10 mg or 25 mg	Placebo	T2DM, drug naïve, high CV risk	Double	2,250	1,498	752
EMPEROR-Preserved	Full sample	Empag 10 mg	Placebo	Chronic heart failure	Double	5,988	5,988	
EMPEROR-Reduced	eGFR < 60 or uACR > 300	Empag 10 mg	Placebo	HF, LVEF ≤40%, and elevated NT-proBNP	Double	1,978	981	997
FEDELIO-DKD	Full sample	Finer 10 mg or 20 mg	Placebo	T2DM and DKD	Double	5,674	2,833	2,841
FIGARO-DKD	Full sample	Finer 10 mg or 20 mg	Placebo	T2DM and DKD	Double	7,352	3,686	3,666

Table 18. Demographic and baseline characteristics of studies included in the company's NMA

	Age		Female %		Ethnicity: White %		Ethnicity: Black %		Ethnicity: Asian %		Ethnicity: Other %		T2DM %		T2DM duration		BMI		eGFR		History of HF		uACR	
Studies	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**	**Int**	**Ctrl**
CANVAS program	67.6	67.6	40.6	43.3	81.7	82.5	2.4	2.0	10.6	10.5	5.3	5.0	100.0	100.0	16.1	15.7	32.1	32.5	49.2	49.0	18.0	17.7	21.5	21.7
CREDENCE	62.9	63.2	34.6	33.3	67.5	65.7	5.1	5.1	19.3	20.6	8.1	8.6	100.0	100.0	15.5	16.0	31.4	31.3	56.3	56.0	14.9	14.7	923.0	931.0
DAPA-CKD	61.8	61.9	32.9	33.3	52.2	54.2	4.8	4.0	34.8	33.4	8.2	8.4	67.6	7.4			29.4	29.6	43.2	43.0	10.9	10.8	965.0	934.0
DAPA-HF	70.9		27.7										51.0				28.4				100.0			
DECLARE-TIME	63.9	64.0	36.9	37.9	79.7	79.4	3.4	3.6	13.4	13.5	3.5	3.5	100.0	100.0			32.1	32.0	85.4	85.1	9.9	10.2		
Dekkers, 2018[a]	66.3 66.0	66.0	47.3 44.8	42.0	89.2 79.3	87.0	6.5 8.6	1.4	1.1 3.4	5.8	3.2 8.7	5.8	100.0	100.0	16.7 17.2	13.5	34.8 34.7	34.6	38.0 37.6	38.4			40.0 51.0	52.0
MB102029[a]	68.0 66.0	67.0	34.1 33.7	36.9	90.6 78.3	82.1	4.7 8.4	1.2	3.5 4.8	7.1	1.2 8.5	9.6	100.0	100.0	18.2 16.9	15.7			43.9 44.2	45.6			73.0 79.0	67.0
EMPA-KIDNEY	63.4	63.3	33.2	33.1	58.7	58.1	3.9	4.1	36.1	36.3	1.3	1.5	4.5	44.4			29.7	29.8	37.4	37.3	9.8	10.1	330.6	327.3
EMPA-REG OUTCOME	66.2	66.0	31.0	29.7	71.4	72.3	4.9	4.5	22.6	22.2	1.1	1.0	100.0	100.0			30.8	30.8	54.5	54.3	13.4	14.1		
EMPEROR-Preserved	71.7	71.9	44.6	44.7	76.3	75.4	4.4	4.2	13.8	13.7	5.5	6.7									100.0	100.0		
EMPEROR-Reduced	70.4	70.1	23.6	27.4	75.6	72.3	5.1	6.5	15.5	15.4	3.8	5.8					28.1	27.9	46.5	47.4	100.0	100.0	36.0	36.0
FEDELIO-DKD	65.4	65.7	31.1	28.5	62.7	63.9	4.9	4.4	25.3	25.4	7.1	6.3	100.0	100.0	16.6	16.6			44.4	44.3			833.0	867.0
FIGARO-DKD	64.1	64.1	31.4	29.7	72.5	71.1	3.1	4.0	19.4	20.2	5.0	4.7	100.0	100.0					67.6	68.0			315.0	302.0

[a] Includes the dapagliflozin 10 mg and 5 mg groups separately.
Abbreviations: BMI = body mass index; ctrl = control group; eGFR = estimated glomerular rate; HF = heart failure; Int = Intervention group; T2DM = type 2 diabetes mellitus; uACR = urine albumin-creatinine ratio.

3.3.5. NMA methods

The company used a Bayesian fixed-effects model to perform the NMA. The fixed-effects model was preferred due to the absence of heterogeneity for all outcomes except the comparison of dapagliflozin for the HHF or CV death outcome and the 3P-MACE+ and 3P-MACE outcome. The company compared the Deviance Information Criterion (DIC) of the fixed and random-effects models to ensure best fit. The EAG agreed with this approach.

There are advantages and disadvantages to choosing the Bayesian framework over the frequentist. The company's reasons for choosing the Bayesian NMA model are its advantage in interpretability, that it makes it possible to incorporate different sources of uncertainty, and that the method lends itself to decision making in a more direct way. The EAG agrees with the use of the Bayesian model and deems the company's reasons appropriate.

Priors were selected by the company in accordance with the NICE DSU TSD 2 document. The company did not provide the number of burn-in and sampling iterations used in the NMA, but supplied on request to the EAG during clarifications. They also supplied the codes and raw data to replicate the NMA and test the assumptions in the models.

There were two types of outcomes analysed in the NMA: binomial and rates. Binomial outcomes, where patients either experienced or did not experience an event such as kidney disease progression, were analysed using a regression model with binomial likelihood and a log link. Results of these models were presented as hazard ratios with corresponding 95% credible intervals Rate outcomes, where data were present as person-years, were analysed using a model with Poisson likelihood and a log link. These results were presented as incidence rate ratios with corresponding 95% credible intervals.

The company used JAGS version 4.3.0 and R version 4.0.5 to perform these analyses.

3.3.6. NMA results

Results of the NMA are presented in CS section B.2.9.5 with more detailed results presented in CS section N.2.2. This includes the overall cohort and the CKD+T2D

subgroup analysis results. The EAG asked for the results of the NMA done on patients who were not in the CKD+T2D subgroup during clarifications.

In short, empagliflozin was statistically superior to placebo in every outcome (HR or IRR < 1.00). Empagliflozin was not inferior to canagliflozin, dapagliflozin, and finerenone (95% CrI included 1.00), except in the comparison against finerenone for the all-cause hospitalization admission (rate per person-time) outcome where empagliflozin was superior (IRR = 0.92).

Empagliflozin was superior to placebo for some of the outcomes in the CKD+T2D subgroup and was non-inferior to dapagliflozin for all outcomes. Empagliflozin was also non-inferior to canagliflozin and finerenone for all outcomes except CV death (for comparison against both of these treatments) and all-cause hospital admissions (for comparison with finerenone) where empagliflozin was superior.

During clarifications, the company provided the EAG with the code and raw data required to replicate the NMA. This allowed the EAG to critique the code used for the NMA, and the ability to accurately perform the heterogeneity tests and run the NMA models. Furthermore, the company provided a corrected figures for the heterogeneity tests and NMA results for a few further outcomes during clarification. All but two conclusions remained the same.

[redacted]

The EAG was able replicate the heterogeneity tests and NMA for the overall EMPA-KIDNEY cohort and the CKD with T2DM subgroup and were able to arrive at the same pooled results and conclusions, albeit with minor changes to the 95% credible intervals, however this is expected due to the nature of the Bayesian approach to statistics, such as differences in prior specifications or computational methods which can lead to very slightly different results.

3.3.6.1. CKD without T2DM subgroup

During the clarifications stage of this appraisal, the company also provided the EAG with the codes and raw data for the new NMA of the subgroup of EMPA-KIDNEY

participants who had CKD but without T2DM. These were included as an addendum to Appendix N. The company did not originally report this NMA as there were only two trials to date which reported outcomes in this subgroup, EMPA-KIDNEY and DAPA-CKD. Table 1 of this addendum presents a comparison of the baseline characteristics of this subgroup, where median uACR levels differ wildly between the two trials. There were differences in other variables, such as eGFR, but these were not statistically significant.

Due to a lack of evidence, the only indirect comparison that came out from this NMA was that of empagliflozin 10 mg compared to dapagliflozin 10 mg. The company provided both the fixed and random effect models for CV death, HHF or CV death, and all-cause mortality.

[redacted]

The EAG similarly replicated the company's NMA for the CKD without T2DM subgroup and were able to replicate the results and credible intervals.

The following analyses from the network meta-analysis in the clinical effectiveness section of the CS was used in the company's economic analyses:

- The NMA "support[s] the assumption of equivalence of treatment effects empagliflozin and dapagliflozin in the economic assessment". Evidence that empagliflozin is equivalent to the other active treatments for kidney disease in the NICE scope is supported by the indirect treatment comparison, therefore the company focused on the comparison between empagliflozin plus standard of care versus standard of care alone, and a cost-comparison for empagliflozin versus dapagliflozin.

Table 19. Results of the company's NMA

	N trials	Placebo	Canagliflozin 100 mg	Dapagliflozin 10 mg	Finerenone 10 or 20 mg
Overall results: empagliflozin versus comparator					
Composite renal outcome – definition 1 (57% threshold)	5	0.69 (0.58, 0.82)*	1.05 (0.79, 1.38)		0.91 (0.72, 1.14)
Composite renal outcome – definition 1 (50% threshold)	6	0.66 (0.57, 0.77)*		1.13 (0.88, 1.46)	
Composite renal outcome – definition 1 (40% threshold)	5	0.72 (0.62, 0.82)*		1.23 (0.71, 2.20)	0.86 (0.73, 1.02)
Composite renal outcome – definition 2 (57% threshold)	2	0.72 (0.06, 0.85)*	1.05 (0.82, 1.34)		
Composite renal outcome – definition 2 (50% threshold)	5	0.77 (0.61, 0.98)*		1.30 (0.78, 2.17)	
ESKD/ESRD	8	0.69 (0.56, 0.86)*	1.01 (0.73, 1.41)	1.05 (0.75, 1.46)	0.83 (0.62, 1.09)
HHF (number of patients)	11	0.74 (0.65, 0.85)*	1.12 (0.88, 1.44)	1.00 (0.83, 1.20)	0.96 (0.77, 1.18)
HHF (rate per person-time)	7	0.72 (0.58, 0.91)*	1.12 (0.83, 1.52)	1.46 (0.93, 2.32)	0.93 (0.71, 1.23)
CV death (number of patients)	11	0.85 (0.68, 1.03)	0.89 (0.61, 1.26)	0.97 (0.72, 1.30)	0.97 (0.69, 1.34)
CV deaths (rate per person-time)	9	0.82 (0.69, 0.98)*	0.99 (0.76, 1.28)	0.90 (0.69, 1.18)	0.94 (0.75, 1.19)
HHF or CV death (number of patients)	10	0.78 (0.69, 0.87)*	1.14 (0.91, 1.44)	0.95 (0.83, 1.10)	0.94 (0.80, 1.11)
HHF or CV death (rate per person-time)	8	0.81 (0.70, 0.93)*	1.12 (0.89, 1.39)	0.98 (0.79, 1.21)	0.96 (0.80, 1.15)
3P-MACE+	3	0.93 (0.76, 1.14)			1.09 (0.87, 1.36)
3P-MACE+ and 3P-MACE	8	0.88 (0.73, 1.02)	1.06 (0.84, 1.35)	1.08 (0.91, 1.28)	1.01 (0.83, 1.22)

All-cause mortality (number of patients)	9	0.88 (0.74, 0.99)*	1.04 (0.81, 1.35)	1.08 (0.91, 1.28)	0.97 (0.80, 1.16)
All-cause mortality (rate per person-time)	9	0.87 (0.76, 0.99)*	1.04 (0.84, 1.28)	1.11 (0.91, 1.35)	0.97 (0.81, 1.16)
All-cause hospital admissions (number of patients)	5	0.87 (0.80, 0.94)*			0.92 (0.83, 1.03)
All-cause hospital admissions (rate per person-time)	5	0.88 (0.83, 0.94)*			0.92 (0.85, 1.00)*
CKD+T2D subgroup analysis results: empagliflozin versus comparator					
Composite renal outcome – definition 1 (57% threshold)	4	0.62 (0.43, 0.92)*	0.95 (0.61, 1.47)		0.82 (0.55, 1.24)
Composite renal outcome – definition 1 (40% threshold)	4	0.67 (0.55, 0.83)*		1.16 (0.65, 2.11)	0.81 (0.64, 1.02)
Composite renal outcome – definition 2 (40% threshold)	3	0.66 (0.55, 0.80)*		0.90 (0.60, 1.37)	
ESKD/ESRD	5	0.55 (0.26, 1.16)	0.81 (0.37, 1.76)	0.80 (0.36, 1.80)	0.66 (0.30, 1.42)
HHF (number of patients)	5	0.61 (0.42, 0.88)*	0.99 (0.63. 1.57)	0.77 (0.51, 1.15)	0.78 (0.52, 1.18)
HHF (rate per person-time)	6	0.63 (0.44, 0.90)*	0.95 (0.63, 1.45)	0.79 (0.51, 1.23)	0.79 (0.54, 1.19)
CV death (number of patients)	7	0.64 (0.48, 0.84)*	0.66 (0.47, 0.95)*	0.76 (0.48, 1.20)	0.73 (0.53, 1.00)*
CV deaths (rate per person-time)	7	0.82 (0.67, 1.00)	0.98 (0.74, 1.29)	0.83 (0.60, 1.16)	0.93 (0.72, 1.20)
HHF or CV death (number of patients)	7	0.75 (0.59, 0.94)*	1.10 (0.81, 1.49)	0.88 (0.68, 1.14)	0.90 (0.70, 1.17)
HHF or CV death (rate per person-time)	8	0.73 (0.63, 0.85)*	0.91 (0.73, 1.15)	0.89 (0.72, 1.10)	0.87 (0.72, 1.05)
3P-MACE+	3	0.75 (0.57, 0.98)*	0.96 (0.69, 1.33)	1.09 (0.82, 1.45)	
All-cause mortality (number of patients)	7	0.78 (0.64, 0.95)*	0.95 (0.71, 1.27)	0.98 (0.79, 1.22)	0.88 (0.70, 1.11)

All-cause mortality (rate per person-time)	7	0.82 (0.67, 1.02)	0.98 (0.76, 1.29)	1.00 (0.76, 1.33)	0.92 (0.72, 1.18)
All-cause hospital admissions (number of patients)	4	0.43 (0.38, 0.48)*			0.45 (0.40, 0.52)*
All-cause hospital admissions (rate per person-time)	3	0.89 (0.78, 1.01)			0.92 (0.80, 1.05)
* indicated statistical meaningfulness					

3.3.7. Critique of the indirect comparison and/or multiple treatment comparison

The company's NMA feasibility was presented in CS Appendix D. Thirteen eligible RCTs evaluating the efficacy and safety of empagliflozin as well as specific treatment comparators (canagliflozin, dapagliflozin, finerenone, and placebo) along with outcomes of interest were included in the feasibility assessment for conducting an NMA. The company assessed the feasibility of the NMA by examining:

- The treatment network connectivity.
- Heterogeneity.
- Transitivity assumption.

For the purpose of assessing and addressing the transitivity-consistency assumption, the company selected the following potential effect modifiers *a priori*: trial design/methodology (e.g., randomisation, blinding), baseline population characteristics (e.g., eGFR and uACR classifications), treatment characteristics, and outcome characteristics (time points of assessment).

The three points above will be expanded more in this section, but to summarise, the EAG considers the company's overall approach for assessing the feasibility of the NMA to be appropriate and in line with current NMA recommendations.

3.3.7.1. Treatment network connectivity

The network connectivity was examined through the characteristics of treatments, outcomes, and the existence of a common treatment. In all of the 13 studies included in the NMA, placebo was the comparator, therefore placebo was the anchoring treatment arm connecting all treatments to each other. Figure 1 presents an

illustration of the connectivity of the company's NMA when specific outcome is not taken into account.

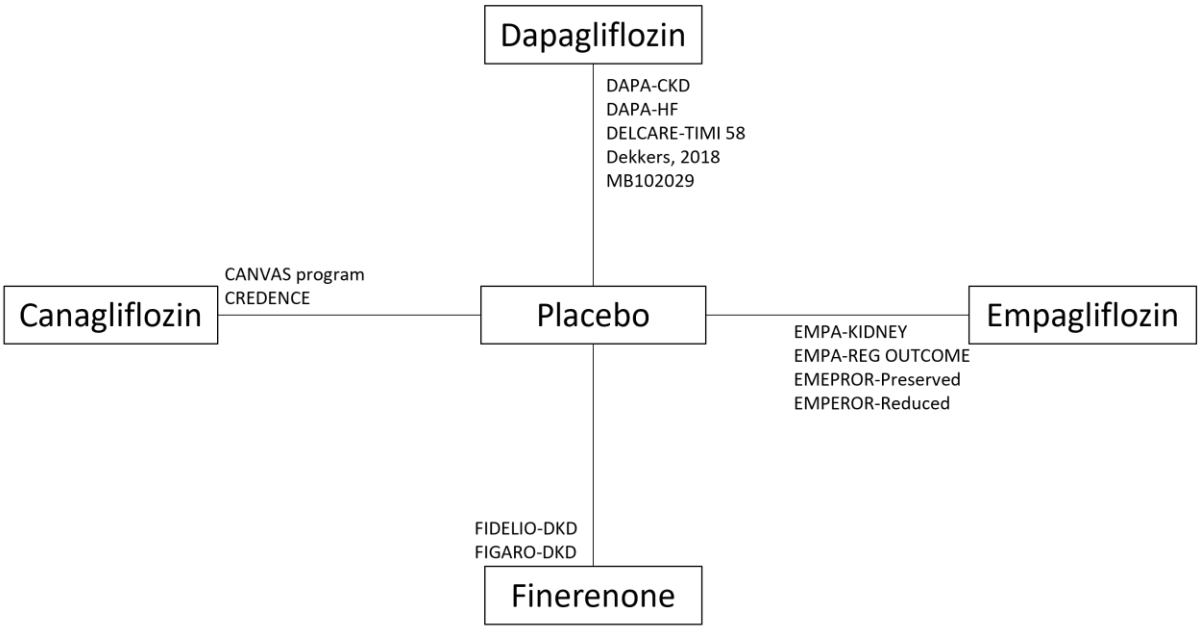


Figure 1. The full network connectivity of the 13 studies included in the company's NMA irrespective of outcome

Where studies did not report different outcomes, they were removed from the network map. At all times however placebo was the only comparator linking the active treatments together. The EAG notes that the treatment nodes were connected correctly in all of the NMA plots.

Furthermore, as there are no closed loops in the network, it is impossible to test the NMA assumption of loop-consistency and, therefore, this was not done by either the company or the EAG.

3.3.7.2. Transitivity and Heterogeneity

Transitivity was assessed in this submission by comparing the distribution of population characteristics that are effect modifiers across the treatment comparisons in the presented network.

The company acknowledged differences in inclusion criteria such as some studies which had CKD/DKD as an inclusion criterion compared to other studies which included T2DM or HF patients and further differences in target population definition.

The heterogeneity assumption of the NMA was examined by conducting a heterogeneity test on a set of pooled studies that compared the same treatments to determine if there was any clinical, methodological or statistical heterogeneity between the studies.

Statistical heterogeneity test results for direct meta-analysis comparing the four active treatments to placebo were not statistically significant except for the following comparisons:

- the comparison of dapagliflozin for the outcome HHF or CV death (number of patients) which consisted of DAPA-CKD – KDIGO moderately high, DAPA-CKD – KDIGO high, DAPA-CKD – KDIGO very high, DAPA-HR – eGFR < 60, DECLARE-TIMI 58 – eGFR < 60 or uACR > 30 (I^2 = 58%, p = 0.05).
- the comparison of dapagliflozin for the outcome 3P-MACE+ and 3P-MACE which consisted of DAPA-CKD – History of CVD, DAPA-CKD – No history of CVD, DECLARE-TIMI 58 – eGFR < 60 or uACR > 30, DECLARE-TIMI 58 – eGFR < 60 and uACR > 30 (I^2 = 90%, p < 0.01).

The EAG visually inspected the two corresponding forest plots of the meta-analysis of dapagliflozin vs placebo for the above two outcomes. For the HHF or CV death outcome, the results between studies did not differ appreciably with the exception of the odds ratio from DAPA-CKD – KDIGO high, the OR for which was significantly lower than the KDIGO moderately high and very high groups.

Similarly for the other outcome, the subgroups of DAPA-CKD did not differ significantly but the subgroups of DECLARE-TIME 58 differed significantly from the rest of the pairwise comparisons. Since comparisons of this outcome come from subgroups of two studies, the high statistical heterogeneity may be explained by differences in population characteristics between the subgroups, or the presence of confounding or contextual factors which were unaccounted for. However, performing analysis to check this, such as performing subgroup analyses of the trials to explore if certain pre-defined factors were differently distributed across the studies pooled in these direct meta-analyses, would be impossible as the company is unlikely to have access to the IPD since it does not manufacture dapagliflozin.

Given the above, the EAG is satisfied with the company's heterogeneity assessment. Post-clarification, the EAG is satisfied with the company's NMA methodology and results.

3.4. Additional work on clinical effectiveness undertaken by the EAG

The EAG compared the baseline characteristics of the DapaKidney[26] and EmapKidney trials, Details are in Appendix 1 but did not perform additional NMAs.

The EAG undertook the following statistical work to rebuild the company's analysis, both from EMPA-KIDNEY and the analysis specific to this submission. Moreover, the EAG undertook long-term survival analysis on the all-cause mortality outcome using data provided by the company during clarifications.

3.4.1. Competing risk-adjusted survival analysis for discontinuation rates

The EAG requested the data of the number of participants remaining in EMPA-KIDNEY with death from any cause as a competing risk. The company provided this data for the full cohort and the T2DM subset. The EAG were provided with time to treatment discontinuation treating ACM as a competing risk, however there were zero competing risks (deaths) that were not on the same day as discontinuation. The EAG were also provided with discontinuation where all-cause mortality (ACM) the same day as treatment discontinuations was used as competing risk. The EAG used the latter for the analysis in this section.

Table 20 presents the discontinuation rate per 100 person-years in EMPA-KIDNEY. The EAG obtained the same discontinuation rate as presented in the company submission section B.3.3.6 for the full cohort. When adjusting for the competing risk of ACM, the discontinuation rate per 100 PY decreases to [redacted] in the empagliflozin group, and [redacted] in the placebo group. Similarly, in the T2DM subgroup where the unadjusted discontinuation rate per 100 PY was [redacted] in the empagliflozin group and [redacted] in the placebo group. Adjusted, these were [redacted] and [redacted], respectively.

Table 20. Discontinuations per 100 person-years unadjusted and adjusted for the competing risk of all-cause mortality

		Unadjusted		Adjusted	
		Empagliflozin	**Placebo**	**Empagliflozin**	**Placebo**
Full cohort	N	3,304	3,305	[redacted]	[redacted]
	Discontinuations	755	848	[redacted]	[redacted]
	Total person-years	6009.71	5987.07	[redacted]	[redacted]

	Discontinuations per 100 PY	12.56	14.16	[redacted]	[redacted]
T2DM subgroup	N	1525	1515	[redacted]	[redacted]
	Discontinuations	402	458	[redacted]	[redacted]
	Total person-years	[redacted]	[redacted]	[redacted]	[redacted]
	Discontinuations per 100 PY	[redacted]	[redacted]	[redacted]	[redacted]

The above data is further discussed in the discontinuation rates in the cost-effectiveness section.

3.4.2. Naïve and corrected competing risk analysis

Figure 2 presents Kaplan-Meier survival functions for both discontinuation and the competing risk of ACM, both corrected and uncorrected (naïve). In this figure, the top of the graph (y=1) and the red line indicates the proportion of EMPA-KIDNEY participants who have discontinued the study. The distance from the bottom of the plot (y=0) to the blue line is the proportion of subjects who died for any reason. The distance between the lines is the proportion of participants who have neither discontinued or died, i.e. those who remain in EMPA-KIDNEY.

The issue with this plot is that it assumed that censored subjects are still at risk, but subjects who have had a competing event are no longer at risk, and thus the survival function is calculated incorrectly. Therefore, the estimates need to be corrected for this and those estimates are also presented in the figure.

Figure 2 presents the cumulative incidence of discontinuation and the competing risk of ACM for each treatment group separately. In both outcomes, the cumulative incidence for the placebo group is higher as the number of days from discontinuation increases. There is a clear separation at around 450 days for the discontinuation outcome. For ACM, cumulative incidence between empagliflozin and placebo groups are similar until around 800 days where placebo curve increases more quickly than the empagliflozin curve.

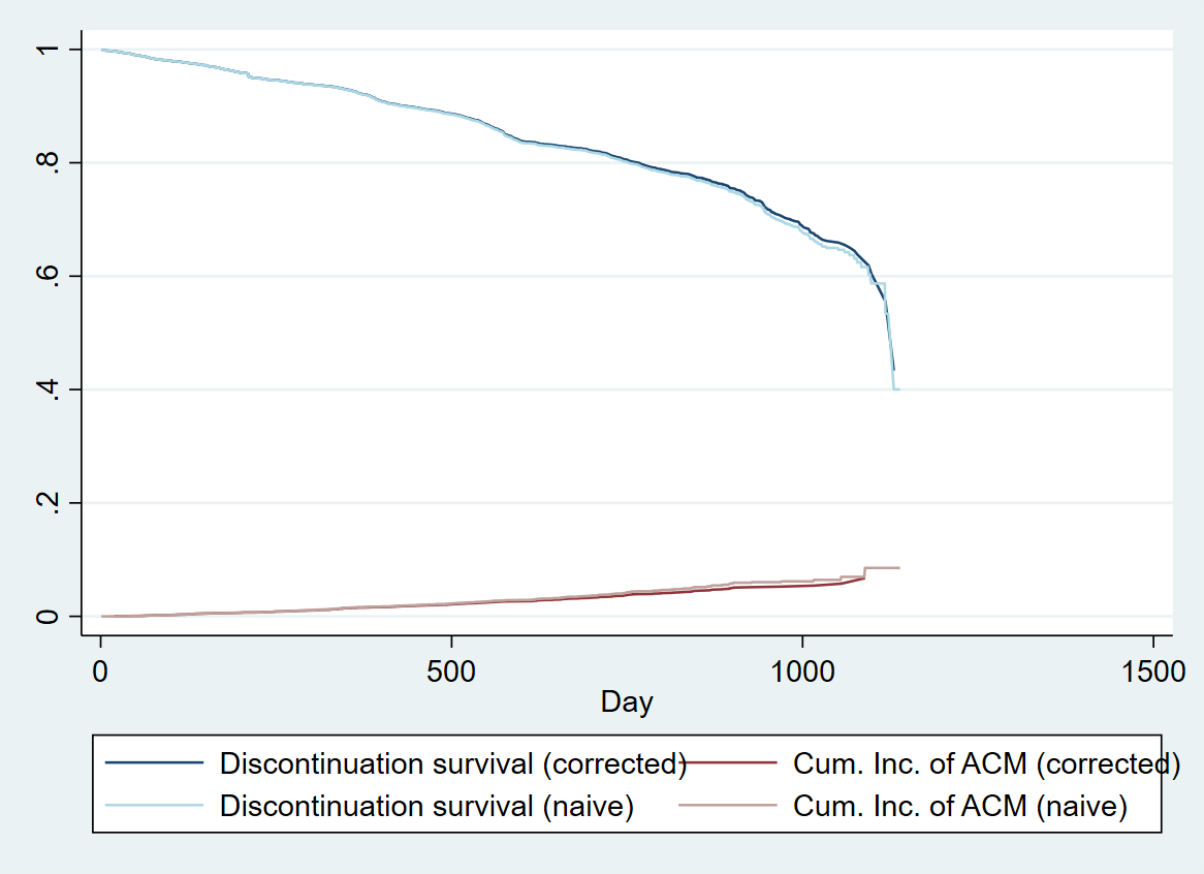


Figure 2. Survival and cumulative incidence: Naïve and corrected Kaplan-Meier estimates

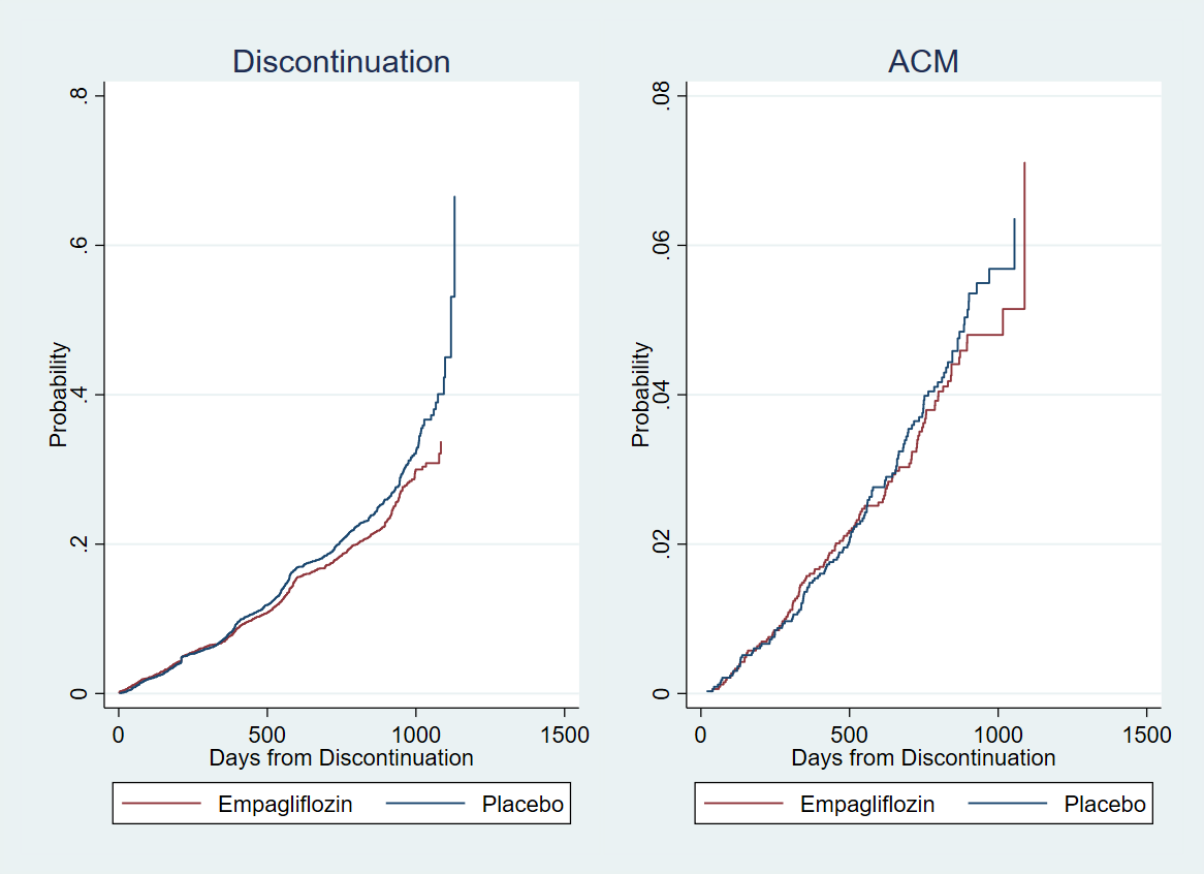


Figure 3. Cumulative incidence of discontinuation and same-day ACM by treatment group

3.4.3. Competing risks regression model

Table 21 presents the sub-hazard ratio (SHR) estimates for discontinuation in the presence of the competing risk of ACM. In all three cases (empagliflozin only, placebo only, or both), the SHR of 0.994 to 0.995 indicates that, as time goes on, the hazard of discontinuation decreases while accounting for the presence of the competing risk, including no adjustments for other confounders.

Table 21. Competing risks regression model

	Sub-hazard ratio	95% CI	P-value
Empagliflozin	0.9941	0.9936 to 0.9947	< 0.001
Placebo	0.9945	0.9939 to 0.9950	< 0.001
Both	0.9943	0.9939 to 0.9947	< 0.001

Results for the T2DM subgroup are consistent with that of the full EMPA-KIDNEY cohort.

3.4.4. Survival curves for all-cause mortality

The company provided individualised Kaplan-Meier survival data for all-cause mortality which allowed the EAG to fit parametric survival curves in order to extrapolate long-term survival for both treatment groups in this submission. The six parametric curves were the exponential, Weibull, log-normal, log-logistic, Gompertz, and the generalised gamma. Data were provided for both the full EMPA-KIDNEY cohort and the T2DM subgroup.

When modelling the full cohort, the Weibull model has the lowest AIC and BIC for the empagliflozin and placebo arms. There were no obvious turning points or sudden changes in the cumulative hazard plot for this cohort, thus the EAG constructed only one-stage parametric survival plots from time t=0. **Error! Reference source not found.** presents the curves fitted for the empagliflozin arm only.

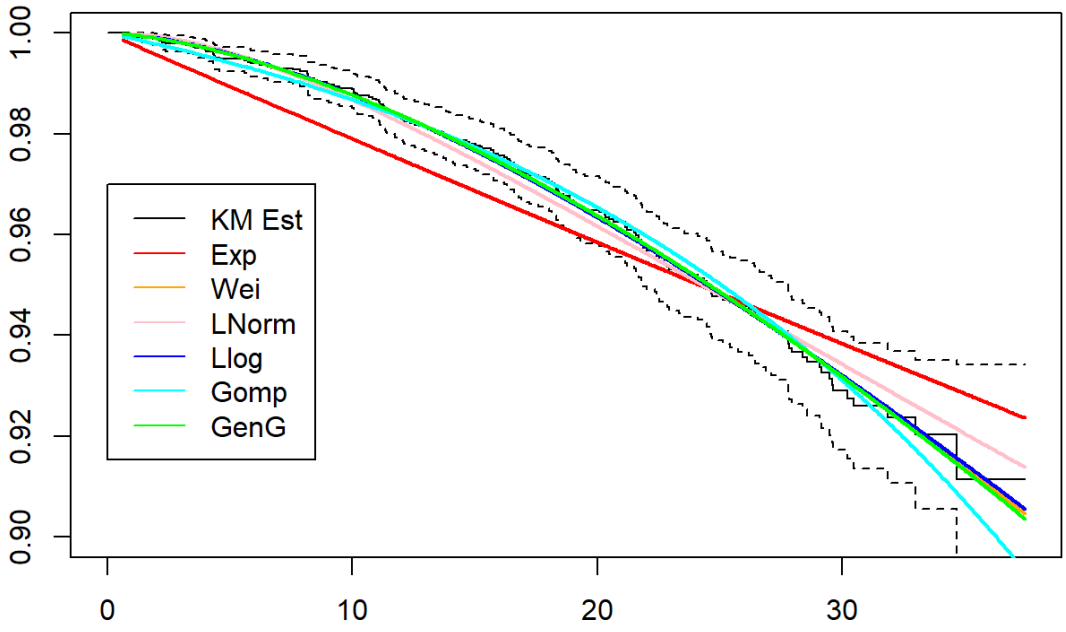


Figure 4. Parametric survival curve fitting to the empagliflozin arm of the full EMPA-KIDNEY cohort

Results when modelling the CKD+T2DM subgroup are similar to the full cohort in the empagliflozin arm. The Weibull model had the lowest AIC and BIC for the empagliflozin group. For the placebo group, the Gompertz model was the best performing curve in terms of having the lowest AIC and BIC. However, the 120-month survival estimate was implausible (0%). The second best fitting curve was the Weibull.

Figure 5 presents the six parametric curves fitted to the empagliflozin group of the T2DM subgroup.

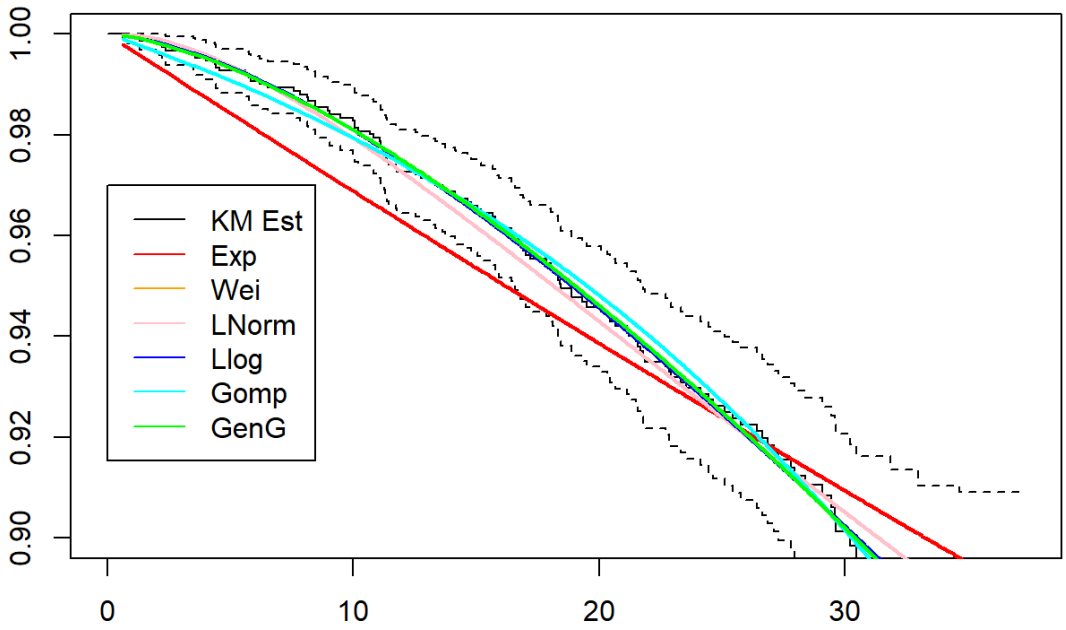


Figure 5. Parametric survival curve fitting to the empagliflozin arm of the full CKD+T2DM subgroup

The EAG performed these survival analyses as a sense-check, to ensure the long-term mortality rates used in the company's economic model were plausible given the deaths that occurred in EMPA-KIDNEY. Table 22 shows the differences in the survival estimates between the company's model and the EAG's analysis. When comparing the survival rates between what the company used and the EAG's Weibull estimation for the empagliflozin treatment group, they are similar throughout,

with the largest discrepancy at six-years where the Weibull model overestimates survival compared to the company.

Comparing survival for the placebo group, estimates between the company and the EAG's Weibull model are consistent until year two, after which the difference between the two estimates increases. At ten-years, the difference between the company's and EAG's survival estimate is 16% (amounting to 529 people). However, the Weibull model may be unsuitable, despite being the best-fitting model, as it estimates more people alive in the placebo group (60%) compared to the empagliflozin group (53%) at ten-years.

Table 22. A comparison of long-term survival estimates between the company's model and the EAG's analysis of all-cause mortality

	Company OS	**EAG Weibull OS**	**Company OS**	**EAG Weibull OS**
Year	Empagliflozin	Empagliflozin	Placebo	Placebo
0	100%	100%	100%	100%
1	97%	98%	96%	99%
2	93%	93%	92%	96%
3	90%	91%	87%	92%
6	75%	81%	75%	84%
10	56%	53%	44%	60%

3.5. Conclusions of the clinical effectiveness section

The population reflect the entry criteria of the EMPA-KIDNEY trial with race-adjusted: [redacted]

- In the company submission, the comparator was in effect dapagliflozin shown by both the company NMA and the meta-analysis by Herrington et al[34] to have a non-inferior effect to empagliflozin. The NMA showed a borderline meaningful difference between empagliflozin and dapagliflozin for the composite renal outcome definition, in favour of dapagliflozin. For patients with CKD but without T2DM, there were no meaningful differences between dapagliflozin and empagliflozin
- CKD but without T2DM. These were included as an addendum to Appendix N. The company did not originally report this NMA as there were only two trials to date which reported outcomes in this subgroup, EMPA-KIDNEY and DAPA-CKD. Table 1 of this addendum presents a comparison of the baseline characteristics of this subgroup, where median uACR levels differ wildly between the two trials. There were differences in other variables, such as eGFR, but these were not statistically significant.
- The EAG did not identify any concerns with regards to the statistical analysis of the outcomes presented in section B.2.6 of the CS. In the absence of head-to-head trials comparing empagliflozin to active treatments outlined in the NICE scope, the company performed an NMA which was anchored by the common comparator across all of the eligible studies, placebo. The EAG agreed with the company's feasibility assessment which concluded that the NMA was the most appropriate ITC method given the availability of studies and data. Results of the NMA was used in the economic assessment of empagliflozin by showing equivalence between empagliflozin and dapagliflozin, thereby allowing the company to focus on empagliflozin with SoC versus standard of care alone.
- A major concern was in the calculation of the annual change in eGFR per KDIGO categories and overall. This was only based on KDIGO health state at

baseline, however KDIGO health states can change from timepoint to timepoint, and the progression of eGFR should reflect this. Therefore, the EAG believe this should be calculated at least annually. eGFR was collected at baseline, 2, 6, 12, 18, 24, 30, and 36 months, whereas uACR was recorded at 2, 18, 24, 30, and 36 months. uACR values at baseline and 12 months should be estimated using an appropriate method such as multiple imputation. Moreover, since patients will have missing eGFR and uACR measurements at some timepoints, these can also be imputed.

3.5.1. Recent evidence

Alnsasra et al[40] provide a cost analysis comparing dapagliflozin and empagliflozin and conclude that empagliflozin is lower cost for preventing a composite of renal and cardiovascular events in people with diabetes but that dapagliflozin is better value in people without diabetes. They also conclude that dapagliflozin is better value for prevention of CVD events but empagliflozin is better value for prevention of CKD progression. Their analysis is based entirely on the results of the EmpaKidney and DapaKidney trials. They estimate the number needed to treat each year to prevent one CVD or renal event and call this the annualised NNT. They then multiply that by the cost of treating that number – CNT. They provide very little detail on how drugs costs were estimated, saying only “Our costs were calculated as 75% of the US National Average Drug Acquisition Cost for July 2022”. In Table 2, they give annual costs of $4,807 for dapagliflozin and $4,992 for empagliflozin. Costs of adverse effects are not included, which could be relevant if the frequency varied between the trials.

To calculate the aNNT, they use the difference in event rates between the drug and placebo arms in the two trial, those events being CKD progression, CVD events, and all-cause mortality. They note the annual event rates in DapaKidney to be 6.04% in the dapagliflozin arm and 3.68% in the placebo arm, giving an annualised event rate reduction of 2.36%. For the EmpaKidney trial, the corresponding figures are 8.44%, 6.08% and 2.36%. These figures give aNNTs of 42 for both trials.

The primary outcomes in the two trials were fairly similar but not identical. In the dapagliflozin trial CKD progression used a decline of 50% in eGFR compared to 40% in the empagliflozin trial. For severe CKD, the dapagliflozin trial used eGFR of <15

ml/min whereas the empagliflozin trial used < 10ml/min. The empagliflozin trial recruited patients with a wider range of baseline eGFRs and had a lower mean baseline eGFR of 37 ml/min compared to 43 ml/min in the dapagliflozin trial. There were other baseline differences such as the proportion with diabetes, 67% in the dapagliflozin trial and 46% in the empagliflozin trial (44% with T2D). These baseline differences may explain the differences in absolute risk of the outcomes. However, the aNNT is based on comparisons of outcome rates between the arms in both trials, so the authors can argue that this overcomes the different baseline risks. The authors conclude that the costs needed to prevent one event are $201,911 for dapagliflozin and $209,664 for empagliflozin. Subgroup analysis showed that the CNT was higher for diabetic patients with dapagliflozin ($201911) than empagliflozin ($134,133). Whereas for non-diabetic patients, the CNT was lower for dapagliflozin ($197,103) than for empagliflozin ($394,368). They do not attempt to estimate cost per QALY, or to factor in secondary outcomes or adverse events. They do some sensitivity analysis around costs. They recommend a full cost-effectiveness comparison between the drugs in CKD. Tn the EAG's opinion, the key question is whether using the absolute difference between the arms in the trials, overcomes the problem of the considerable differences in baseline risk factors and the minor differences in outcome definitions. In the UK, prices of empagliflozin and dapagliflozin are similar so the Alnsasry analysis would show no difference.

4. COST EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

CS Appendix G reports an SLR to identify UK evidence on the cost-effectiveness of pharmacological treatments for CKD. Additional searches were undertaken to identify utility/disutility and costs inputs for the company's cost-effectiveness model; these followed a structured process described in detail in Appendices H and I.

4.1.1. Search strategy

An appropriate selection of bibliographic databases, recent conference proceedings, reference lists and websites of relevant UK agencies (NICE, SMC, AWMSG) was searched for the cost-effectiveness SLR (CS Appendix G.1.1).

The search strategies reported in CS Appendix G.1.1.2 reflect the SLR eligibility criteria (G.1.1.3 Table 6), comprising terms for CKD, UK and constituent nations, a search filter for economic evaluations and limits to human studies and English language. For comprehensiveness, the EAG recommends searching the keywords field in MEDLINE and Embase in addition to title and abstract. The MEDLINE search (G.1.1.2 Table 3) is the same as the Embase search (G.1.1.2 Table 2), despite these databases using different subject headings (MeSH and Emtree). Some lines of the MEDLINE search therefore retrieve 0 results. For sensitivity, search strategies should be adapted for the different databases.[41] Despite these limitations, the EAG believes it unlikely that any relevant studies were missed, due to the range of sources searched.

Database searches for utility and cost data were only undertaken where suitable model input data could not be found via other appropriate sources (NICE technology assessments, NHS tariffs) (CS Appendix H Figure 2 and Appendix I Figure 3). Unfortunately, the search strategies used at this step in the process (H.1.1.2 Table 12 and I.1.1.2 Table 17) are not comprehensive, for example not including synonyms for CKD such as "chronic renal insufficiency" or "kidney failure". Therefore, there is a possibility that useful sources of utility and cost data from the published literature were missed.

4.1.2. Summary and critique of the company's submitted economic evaluation by the EAG

4.1.3. NICE reference case checklist

Table 23: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes. But since net savings are estimated the company converts these to additional net QALY gains using a willingness to pay of £20,000 per QALY. These are added to the modelled patient QALY gain to give an overall net health benefit (NHB).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	50 years. A microsimulation samples patient baseline ages with a mean 63.3 years and s.d. 14.0 years, restricted to a 20-80 year range. The 50 year time horizon is effectively a lifetime horizon for all but a small percentage of simulated patients.
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes, mainly. But only NHS costs are considered. PSS costs for aspects such as public funding of residential care for those suffering stroke are not included.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2. Company submission completeness

The EAG thinks that the economics of the company submission is poorly documented, omits key elements and provides scant detail of many other aspects of the cost effectiveness model inputs and structure. For instance, the company submission only outlines the eGFR effects and uACR effects, though presents the wrong eGFR effects for those modelled as discontinuing treatment. The presentation of the estimation of the eGFR effect inputs and uACR effect inputs to the model is also not particularly clear, which is unfortunate given their centrality to the modelling. The company submission does not contain an account of the assumed effects upon

HbA1c[1], weight, BMI and SBP[2]. The clarification response on this contains little to no real detail other than bald values and there is no presentation of their evolution during EMPA-KIDNEY. The company submission provides scant practical detail of a number of aspects of the model structure, model inputs and modelling assumptions as outlined in the ERG critique.

When reviewing the company submission the EAG thinks that it should be borne in mind that unlike most STA submissions it is in a sense "selling" two commercial products: (1) empagliflozin for CKD and (2) the iQVIA CKD model. The latter may account in part for the lack of practical detail about the model structure, model inputs and modelling assumptions. It may also result in some tension between the company and the iQVIA modelling team. At error check the company supported the iQVIA modelling team in its assertion that the cost effectiveness estimates run over 1,000 patients with its chosen random number seed of 0.200 are as valid as those with the EAG selected random number seed of 0.301.

The above has somewhat limited the EAG critique of the cost effectiveness of the company submission. But the company has been notably prompt and helpful about most of the questions asked during clarification and subsequent to clarification, particularly with regards additional analyses of the EMPA-KIDNEY data.

4.3. Model convergence

The deterministic model simulates 1,000 patients, these being sampled to reflect the patient heterogeneity of the EMPA-KIDNEY trial. The EAG thinks that running the model over 1,000 patients is insufficient for model convergence. This applies particularly to net costs, as shown below for the company base case with the company specified random number seed of 0.200[3].

[1] Document B Table 50 that presents the base case variables applied in the cost-effectiveness analysis does not state any effects for these variables.

[2] Note that the model also contains treatment effects for Hb and DBP but the EAG has not found any elements that rely upon these estimates and they appear to be placeholders for future model development.

[3] Random numbers are required within an individual patient model because the model estimates a probability of each event during each model cycle occurring for the patient currently being modelled. For instance, the probability of a CVD event for a given patient in the first model cycle might be 10%. This is then compared with a random number which is drawn between 0% and 100%. If the random number if less than 10% the patient is modelled as having a CVD event that cycle, and not if not. The computer cannot generate a true sequence of random numbers but rather simulates a sequence of numbers that viewed statistically appear to be random. For a given random number seed the same sequence of random numbers is always generated. As a consequence, the random number seed that is chosen affects the path of patients through the model. This should not matter provided that enough patients are simulated for the overall average across the patients simulated to

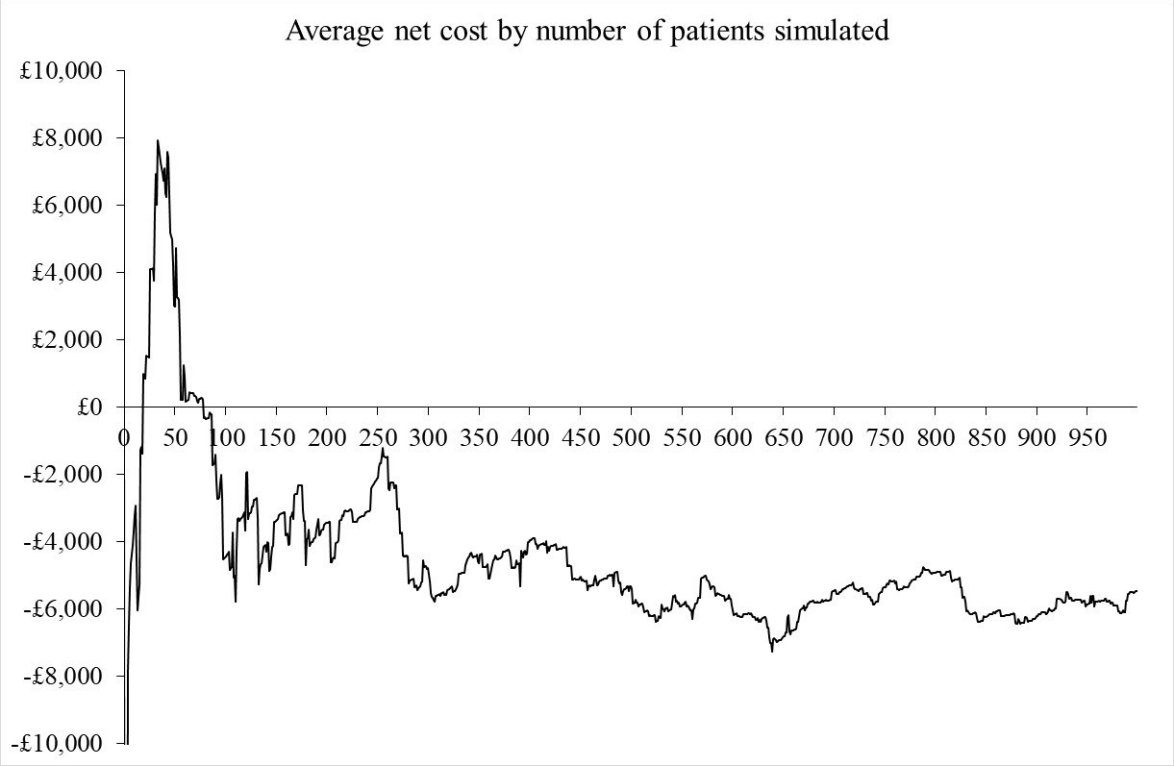


Figure 6: Company base case: Average net cost by number of simulated patients

Running the company base case 10 times with EAG arbitrarily selected random number seeds also results in quite large variation in the net cost estimates relative to the company base case, though net QALYs and net health benefits[4], NHBs, are more stable.

Table 24: Repeat company base case runs with different random number seeds

	Δ Cost	vs B.C.	Δ QALY	vs B.C.	NHB	vs B.C.
Base Case	-£5,460	..	0.849	..	1.122	..
Run 01	-£5,457	-0.1%	0.821	-3%	1.093	-3%
Run 02	-£5,239	-4%	0.862	2%	1.124	0.2%
Run 03	-£4,055	-26%	0.846	0%	1.048	-7%
Run 04	£546	-110%	1.065	25%	1.028	-8%
Run 05	£814	-115%	0.943	11%	0.902	-20%
Run 06	-£3,245	-41%	0.901	6%	1.063	-5%
Run 07	-£2,134	-61%	0.997	17%	1.104	-2%

have converged. But if the model has not converged the random number seed and by implication the sequence of random numbers that is applied in the modelling can affect results.

[4] Calculated by converting the net saving to QALYs at a willingness to pay of £20,000 per QALY. For instance, if the patient gain was 1.0 QALY and the net saving was £10,000 the £10,000 translates to an additional 0.5 QALY gain. The overall net health benefit is 1.5 QALYs because the £10,000 saved could be spent elsewhere in the NHS to generate another 0.5 QALYs. Net costs are converted to a QALY loss; the £546 and £814 being -0.027 QALYs and -0.041 QALYs respectively.

Run 08	-£3,047	-44%	0.876	3%	1.029	-8%
Run 09	-£3,804	-30%	0.917	8%	1.107	-1%
Run 10	-£4,155	-24%	0.850	0.1%	1.058	-6%

The company submitted some data on model convergence at clarification. It is unclear whether this was based upon the original model or the 01-Aug-2023 company revised model that was submitted at clarification. Within this the first patient modelled was estimated as having a total cost of around £630k when treated with placebo and £120k when treated with empagliflozin, resulting in a net cost saving over -£500k. This is quite alarming. This single patient is sufficient to affect the mean net costs over the 1,000 patients simulated. It appears that the model on occasion estimates extreme values. It is difficult to imagine how these can come about given the model structure and implementation. They are sufficiently extreme to affect average results. Running more patients through the model will not cure this if the extreme values continue to be repeated at a similar rate.

The EAG thinks that the above suggests that if a user specified random number seed is used it should not be the company selected 0.200. The EAG will change this arbitrarily to 0.301. Based upon the 01-Aug-2023 company revised model the 0.200 seed estimates net cost savings of -£6,030, net gains of 0.842 QALYs and a net health benefit (NHB) at a willingness to pay of £20,000 per QALY of 1.143 QALYs. The arbitrarily selected EAG seed of 0.301 results in estimates of net costs of £2,437, 1.078 QALY gains, an ICER of £2,260 per QALY and a NHB of 0.957 QALYs. The current company position is that model convergence is not really an issue, each model run is equally valid and that any convergence issues need to be balanced against computational time and the desirability of implementing as much of the model in Excel as is practicable. The EAG supports the company on the last point.

Due to 1,000 patients being the largest cohort permitted in the original company model, 50 cohorts of 1,000 patients can be run through the model. Rather than a user specified random number seed, a randomly selected random number seed can be applied for each model run. Within the original company model this results in 1 simulation estimating a net cost, 45 simulations estimating net savings smaller than the company base case and 4 simulations estimating net savings larger than the

company base case. Across the 50 simulations the net cost estimate is -£2,753. This is 50% of the savings estimated in the company base case.

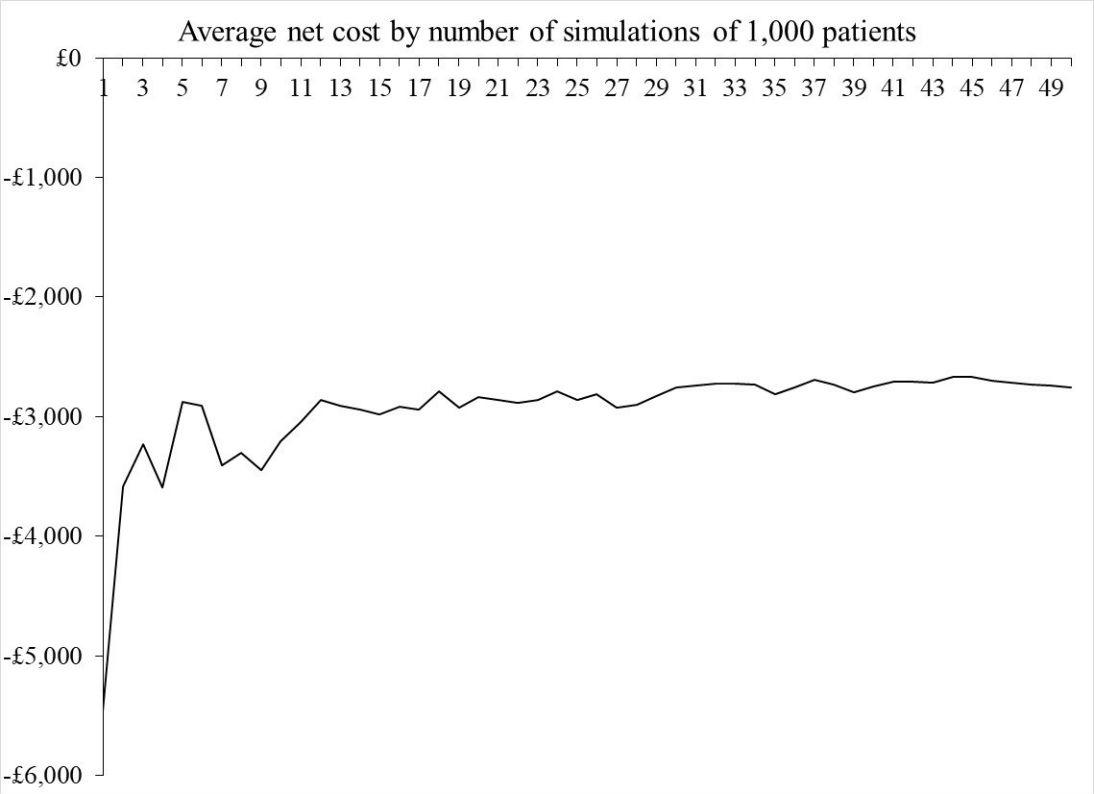


Figure 7: Company base case: Average net cost by number of cohorts of 1,000 patients

It appears that the first model run when a random seed is selected always generates the same results and a net cost of -£5,457[5]. This is very similar to the net cost of -£5,460 when the company specified user seed of 0.200 is chosen. It is only during the subsequent model runs that the net cost estimates differ and converge at a net saving that is roughly half that of the company base case.

After around 12 runs of the model, or 12,000 patients, the net costs appear to have reasonably converged. But the step between 5 model runs and 8 model runs remains a concern due to the fifth model run resulting in a net cost rather than a net saving. This also has to be viewed alongside 20% of the arbitrary model runs of

[5] The same set of "random" numbers is generated each time despite the "random" seed. The EAG thinks that it may be better practice to set the random number seed using the timer or something else that generates a different value each time it is called though this would not permit reproducibility of results. It is also peculiar that the first model run with a random seed estimates net costs that are of a similar magnitude and as much of an outlier as the deterministic model run with the company selected random seed of 0.2. For this reason during multi runs of the model the EAG will discard the first run.

Table 24 resulting in net costs rather than net savings. It may be safer to go beyond 12,000 patients.

After 20,000 patients net costs appear to be fairly stable. But it should be noted that across the 50 model runs only one resulted in net costs rather than net savings, whereas in the arbitrarily selected random seed runs of Table 24 among only 10 model runs there were two that resulted in net costs. Confidence in 20 model runs and 20,000 patients could be upset if only a few more model runs with net costs rather than net savings were randomly sampled within this, or if within runs extreme outcomes for a single patient are occasionally simulated.

During clarification the EAG asked about model convergence. This also asked whether the EAG implementation of multiple runs of the model was correct. Unfortunately, the company did not respond to this aspect of the question. As a consequence, given the complexity of the model that EAG cannot warrant that its implementation of multiple runs of the model is correct[6]. It should also be noted that within these model runs there are occasional patients who do not compute and result in an error. This may be due to the EAG implementation, or may be intrinsic to the original model implementation and related to the occasional extreme values that are simulated by the model. The EAG urges the company to check this aspect of the EAG revised model.

This gives rise to a number of different models which can all in a sense be described as the company base case.

- The original 29-Jun-2023 model run over 1,000 patients with a random number seed of 0.200: henceforth original model (RS 0.200).
- The original 29-Jun-2023 model run over 1,000 patients with various arbitrarily selected random number seeds.
- The company revised 01-Aug-2023 model run over 1,000 patients with a random number seed of 0.200: henceforth model (RS 0.200).

[6] Given the EAG model revisions and increase in computational time required, the EAG notes that the model could have multiple Excel treatment sheets. This would prevent the need for VBA loops by arm and might reduce computational time.

- The company revised 01-Aug-2023 model run over 1,000 patients with a random number seed of 0.301: henceforth model (RS 0.301).
- The company revised 01-Aug-2023 model subsequently revised by the EAG to run over 20,000 patients, each with a randomly selected random number seed: henceforth model (multirun).

The models of the first two bullets largely account for the results of this section due to this work having been completed prior to receipt of the clarification response and the company revised 01-Aug-2023 model. The cost effectiveness estimates of the following sections are based upon model (RS 0.200), model (RS 0.301) and model (multirun), whichever applies being stated in the preceding text or table heading. The effects of this model choice on the company base case results are presented in Table 25, Table 26 and Table 27 below.

Table 25: Company base case: model (RS 0.200)

	EMPA	PLAC	Net
Undiscounted LY	12.615	10.985	1.631
QALY	7.124	6.282	0.842
Cost	£89,907	£95,937	-£6,030
ICER			Dom
NHB			1.143

Table 26: Company base case: model (RS 0.301)

	EMPA	PLAC	Net
Undiscounted LY	13.276	11.117	2.159
QALY	7.402	6.323	1.078
Cost	£95,074	£92,637	£2,437
ICER			£2,260
NHB			0.957

Table 27: Company base case: model (multirun)

	EMPA	PLAC	Net
Undiscounted LY	12.847	11.091	1.756
QALY	7.234	6.325	0.910
Cost	£91,786	£94,737	-£2,951
ICER			Dom
NHB			1.057

4.4. Model structure

The company uses a complicated de novo model, developed by iQVIA. It is conceptually similar to the iQVIA Core Diabetes Model. It simulates individual patients in a micro-simulation model, sampling a cohort of 1,000 patients. The model structure implements each single patient in Microsoft Excel, with additional programming in Visual Basic as is necessary to implement patient sampling, random number generation, recording outcomes for placebo and then empagliflozin for the single patient and then collating results as additional single patients are sampled and modelled.

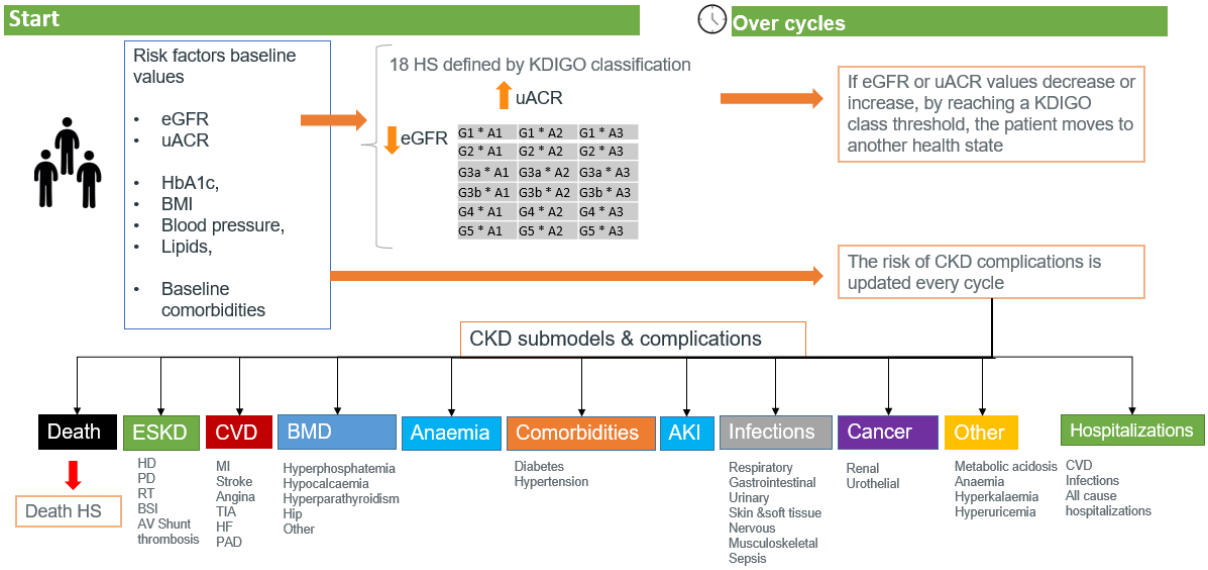


Figure 8: Company model structure: CS Document B, Figure 22, Page 90

Given the size and complexity of the model the EAG does not describe each of the individual sub-models. The company submission Document B and Appendix P present some of the model elements in terms of risk equations, though how these are implemented is largely not described.

4.5. Population

The company base case samples from the EMPA-KIDNEY all-patient population and models these accordingly.

Subgroup analyses for those with diabetes at baseline and those without diabetes at baseline are presented in an appendix. These apply subgroup specific baseline characteristics but retain the EMPA-KIDNEY all-patient population effect estimates.

No analyses are presented for those with cardiovascular disease or for those with other causes of CKD.

4.6. Interventions and comparators

The final scope specifies established clinical management with or without dapagliflozin.

- The economics does not model dapagliflozin. In the light of the company NMA equivalence with dapagliflozin is assumed. Since empagliflozin has the same list price dapagliflozin this implies that it has the same cost effectiveness as dapagliflozin.
- Empagliflozin plus standard care is compared to placebo plus standard care, as per the EMPA-KIDNEY trial. In what follows the these are described as empagliflozin and placebo, or EMPA and PLAC in table headings.

4.7. Perspective, time horizon and discounting

The model applies a 50 year time horizon. Given the mean age of 63 years and its standard deviation of 14 years this is effectively a lifetime horizon for all but a very small number of the patients modelled. Increasing the time horizon to 80 years has no material effect upon model outcomes.

The perspective for patient benefits is as per the NICE reference case. The perspective for costs is the NHS. It does not include any PSS costs for the modelled complications of CKD such as stroke.

Discounting is as per the NICE reference case.

4.8. Treatment effectiveness and extrapolation

4.8.1. Annual eGFR absolute changes

The model applies the following eGFR annual changes in ml/min/1.73m^2 by KDIGO health state, estimated from the EMPA-KIDNEY all-patient population OC-AD data using a random slope and intercept model.

Table 28: Annual eGFR change by KDIGO health state: empagliflozin

	A1	A2		A3	
G2		-2.20	(-3.26, -1.14)	-3.39	(-3.96, -2.81)
G3a		-1.60	(-2.32, -0.89)	-3.45	(-3.91, -2.98)

G3b	-0.58	(-0.96, -0.19)	-1.04	(-1.40, -0.67)	-2.90	(-3.20, -2.60)
G4	-0.32	(-0.87, 0.22)	-0.62	(-1.04, -0.19)	-2.76	(-3.08, -2.45)

Table 29: Annual eGFR change by KDIGO health state: placebo

	A1		A2		A3	
G2			-2.76	(-3.92, -1.59)	-5.14	(-5.70, -4.58)
G3a			-2.29	(-3.04, -1.55)	-4.66	(-5.14, -4.19)
G3b	-0.83	(-1.2, -0.46)	-1.56	(-1.92, -1.20)	-4.11	(-4.42, -3.80)
G4	-0.15	(-0.71, 0.40)	-0.85	(-1.27, -0.43)	-3.76	(-4.09, -3.44)

The deterministic model applies the central estimates of the above which are uniformly better for empagliflozin compared to placebo, except that for (G4, A1). The absolute annual worsening of eGFR is slower for patients with a worse eGFR and is faster for patients with a worse uACR.

For those who have discontinued treatment annual eGFR changes are sourced from Grams et al,[19] differentiated by whether the modelled patient has diabetes or not.

Table 30: Annual eGFR change by KDIGO health state: Off Tx: With diabetes

	A1	A2	A3
G1	-0.8	-2.2	-4.6
G2	-0.8	-2.2	-4.6
G3a	-0.3	-2.1	-4.6
G3b	-0.3	-1.5	-4.5
G4	-0.1	-1.1	-3.6
G5	-0.1	-1.1	-3.6

Table 31: Annual eGFR change by KDIGO health state: Off Tx: Without diabetes

	A1	A2	A3
G1	-0.1	-1.0	-3.1
G2	-0.1	-1.0	-3.1
G3a	-0.2	-1.5	-4.0
G3b	-0.2	-1.4	-3.2
G4	-0.2	-1.2	-2.8
G5	-0.2	-1.2	-2.8

4.8.2. Annual uACR multipliers

The annual uACR multipliers for those on treatment are estimated from a mixed model repeated measures analysis of EMPA-KIDNEY all-patient population OC-AD data. Due to uACR data not being collected at 12 months the 18 months estimates are applied, as per Table 32 and Table 33 below.

Table 32: Annual uACR multipliers by KDIGO health state: empagliflozin

	A1		A2		A3	
G2			1.26	(0.93, 1.69)	0.67	(0.55, 0.77)
G3a			0.87	(0.70, 1.05)	0.53	(0.46, 0.61)
G3b	1.62	(1.46, 1.84)	0.84	(0.76, 0.94)	0.62	(0.56, 0.67)
G4	2.08	(1.77, 2.44)	1.03	(0.91, 1.19)	0.68	(0.62, 0.74)

Table 33: Annual uACR multipliers by KDIGO health state: placebo

	A1		A2		A3	
G2			0.93	(0.67, 1.28)	0.75	(0.63, 0.88)
G3a			0.99	(0.81, 1.24)	0.71	(0.62, 0.81)
G3b	1.65	(1.49, 1.86)	1.09	(0.99, 1.22)	0.81	(0.74, 0.88)
G4	2.44	(2.13, 2.93)	1.51	(1.35, 1.73)	0.95	(0.86, 1.03)

The deterministic model applies the central estimates of the above, which are uniformly better for empagliflozin compared to placebo, with the exception of that for (G2, A1). These are annual multipliers that are reapplied each model cycle that the patient remains on treatment; i.e. a placebo patient in (G4, A2) with a uACR of 110 is modelled as worsening to a uACR of 110 * 1.51 = 166 mg/g in the first year, to 166 * 1.51 = 251 mg/g in the second year and to 251 * 1.51 = 379 mg/g in the third year. This moves the patient into (G4, A3) so has the knock on effect of worsening the annual rate of change of eGFR from -0.85 ml/min/1.73m^2 to -3.76 ml/min/1.73m^2 as per Table 29 above.

What is striking in the above is that those in A3 are estimated to see an improvement in their uACR whether treated with placebo or empagliflozin. This needs to be read alongside the uACR effects that are assumed for those who discontinue as briefly summarised in the following paragraph and as reviewed in greater detail in section 4.15.10 below.

For those who discontinue the model uses an undocumented company analysis of Coresh et al.[42] There are three model options, with the company choosing the lognormal uACR fold option using a cube root, with a mean of 1.000, a standard deviation of 0.93 and a functional form of the cube root of the lognomal inverse (1.00, 0.93). When anti-logged this results in a median uACR multiplier of 1.396 and a sampled average of 1.460. Within the deterministic modelling this is randomly sampled for each annual model cycle for each patient.

4.8.3. Clinical effect estimates not presented in Document B

The model also includes effects upon HbA1c, SBP and weight or BMI. These estimates are not presented in the company submission Document B.

Table 34: Clinical effect estimates not presented in Document B

	All patients		Diabetic patients		Non-diabetic patients	
	EMPA	PLAC	EMPA	PLAC	EMPA	PLAC
HbA1c	-0.56	-0.15	-0.20	-0.80	0.20	0.40
SBP	-3.92	-1.29	-6.7	-3.3	-1.4	-1.3
Weight	-1.55	-0.68	-3.47	-2.83	-1.79	-0.71

4.8.4. Annual discontinuation rates

Annual discontinuation rates of 12.6% for empagliflozin and 14.2% for placebo are estimated from EMPA-KIDNEY all-patient data undifferentiated by KDIGO health state. These are converted to annual rates in the model according to 1-Exp(-12.6%)=11.8% and 1-Exp(-14.2%)=13.2%. The modelling of the subgroups with diabetes at baseline and without diabetes at baseline retains these estimates.

4.9. Summary of elements of the model structure

This section contains a reasonable amount of the technical detail of the model, followed by section **Error! Reference source not found.** on quality of life values and section **Error! Reference source not found.** on cost inputs. Most readers will want to skip forward to section **Error! Reference source not found.** which presents the company base case results.

4.9.1. Renal replacement therapy risks

The model simulates the evolution of patients' eGFR and uACR, using these as inputs to 5 year risk of renal replacement therapy (RRT) equations taken from the literature.

Tangri et al[43] developed models to predict kidney failure among Canadian CKD patients, defined as a need for dialysis or pre-emptive kidney transplant with both being censored for mortality. A development cohort of 3,449 patients was augmented by a model validation cohort of 4,942. The mean age of the development cohort was 70 years, with 56% male and 37% diabetic. Mean eGFR was 36 ml/min/1.73^{2}m, with 67% in G3a or G3b, 27% in G4 and 6% in G5 at baseline.

During what appears to be a mean follow-up of 757 days there were 386 kidney failure events in the development cohort, 358 patients receiving dialysis and 7 patients receiving kidney transplant. Tangri et al[44] expanded this work by using several international datasets, a total of 721,357 CKD patients among whom there were 23,829 kidney failure events. While the authors are not explicit about what constituted a kidney failure event, the ERG assumes it was aligned with their previous paper, dialysis or pre-emptive kidney transplant censored for mortality.

Major et al,[45] funded by the NIHR, estimated similar models to predict kidney failure among 35,539 UK patients, this also being defined as the need for dialysis or kidney transplant. CKD patients were identified from general practice records spread across 4 English CCGs. The mean age was 76 years, with 43% male and 32% diabetic. Mean (s.d.) eGFR was 48.2 (9.8) ml/min/1.73m^2 and mean follow-up was 4.7 years.

To illustrate these risk functions the five year risks of RRT by eGFR are plotted below, for a 60 year old man with a uACR of 1,110mg/g and hypertension. These are shown for a patient without T2DM and with T2DM. Note that the company model only applies these risks when the patient eGFR is at or below 15 ml/min/1.73m^2: i.e. when the patient is in G5. The uACR of 1,110mg/g may be unrealistic for those with a good eGFR, but corresponds to the model baseline value for those in A3 and may be more reasonable for those with a poor eGFR to whom the risk equations are applied.

The company base case applies the pooled 6 variable model of Tangri et al (2016) apparently due to it being the best fit To the UK population but based on four variables only. This is the reason the company gives for its preference for Tangri et al.

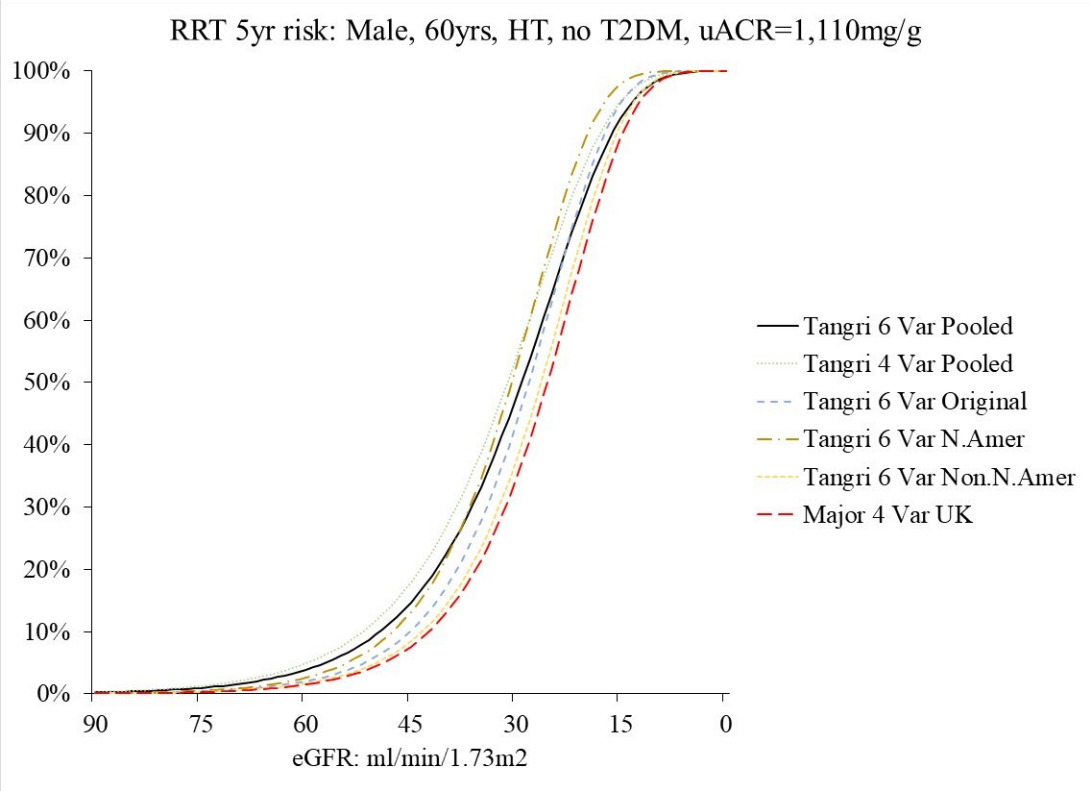


Figure 9: 5 year risk of renal replacement therapy: non-diabetic patient

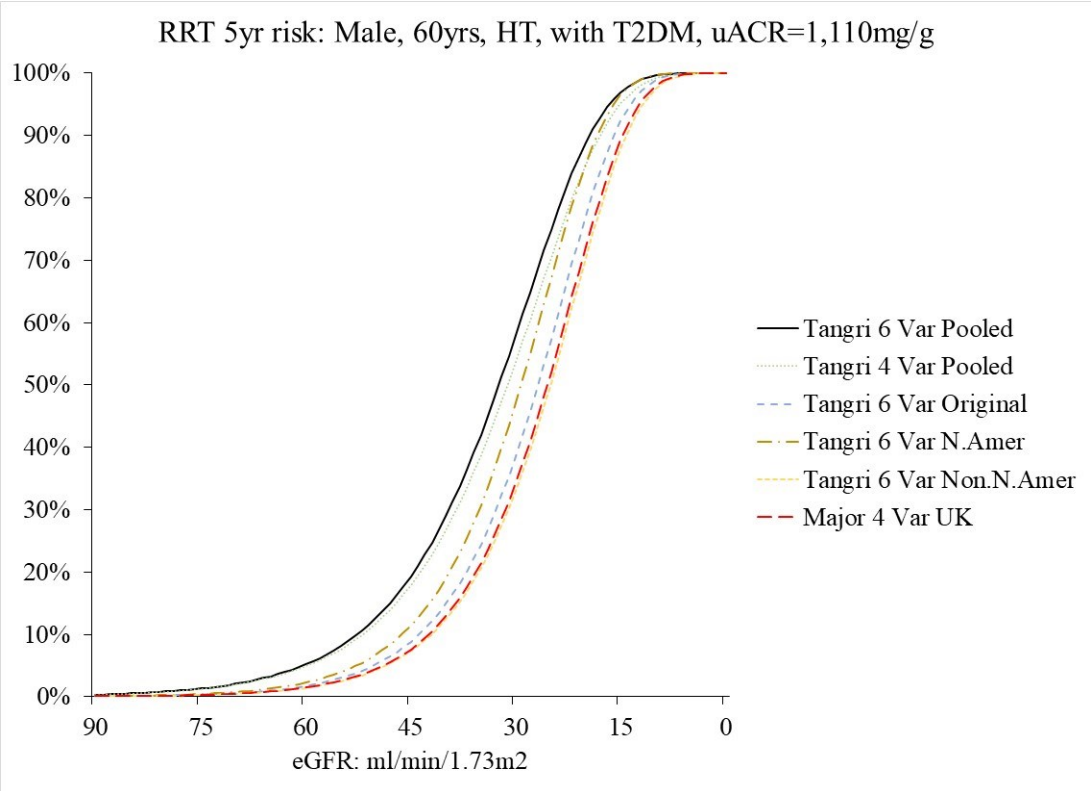


Figure 10: 5 year risk of renal replacement therapy: patient with T2DM

While the curves may initially appear reasonably closely bunched, it is the vertical separation that matters. For instance, for an eGFR of 15 ml/min/1.73m^2 the 5 year RRT risk for a non-diabetic is 92% using the company preferred curve compared to 89% using Major et al, while for a patient with diabetes they are 97% and 89% respectively.

The company assumes a constant annual rate[7] of RRT to arrive at the annual rates as outlined below.

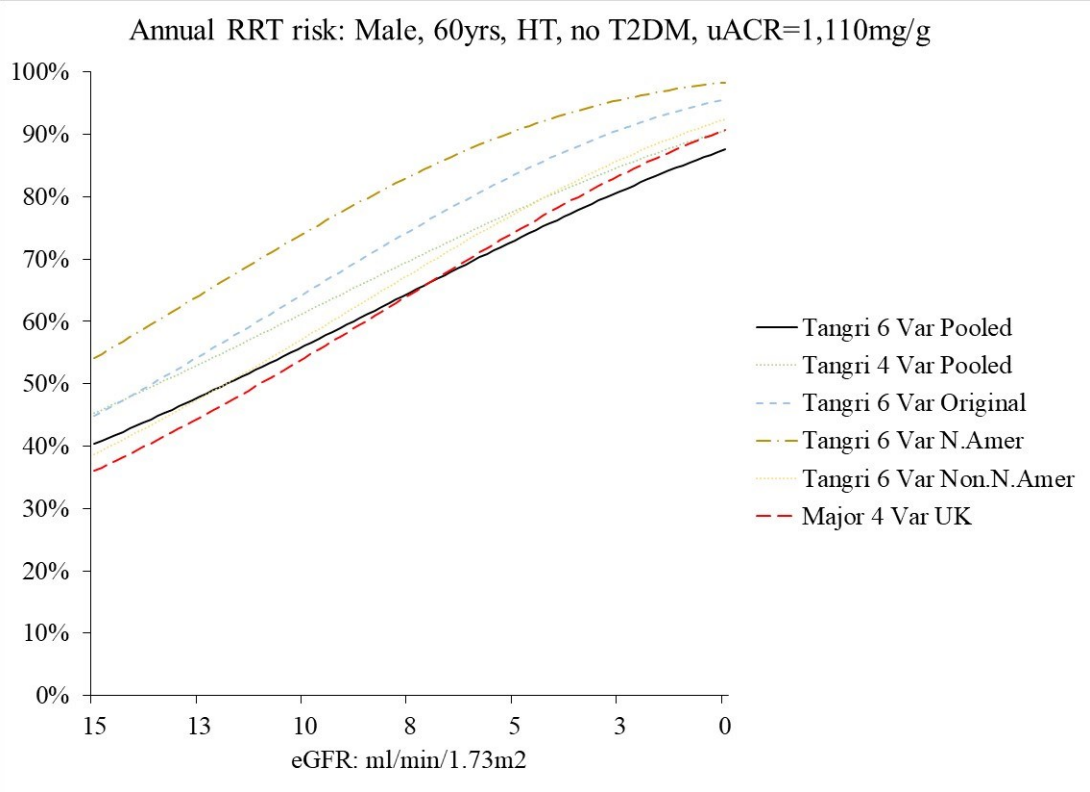


Figure 11: Annualised 5 year risk of renal replacement therapy: non-diabetic patient

[7] In effect converting the 5 year risk to an annual risk as $P_1 = 1- (1- P_5)^{(1/5)}$

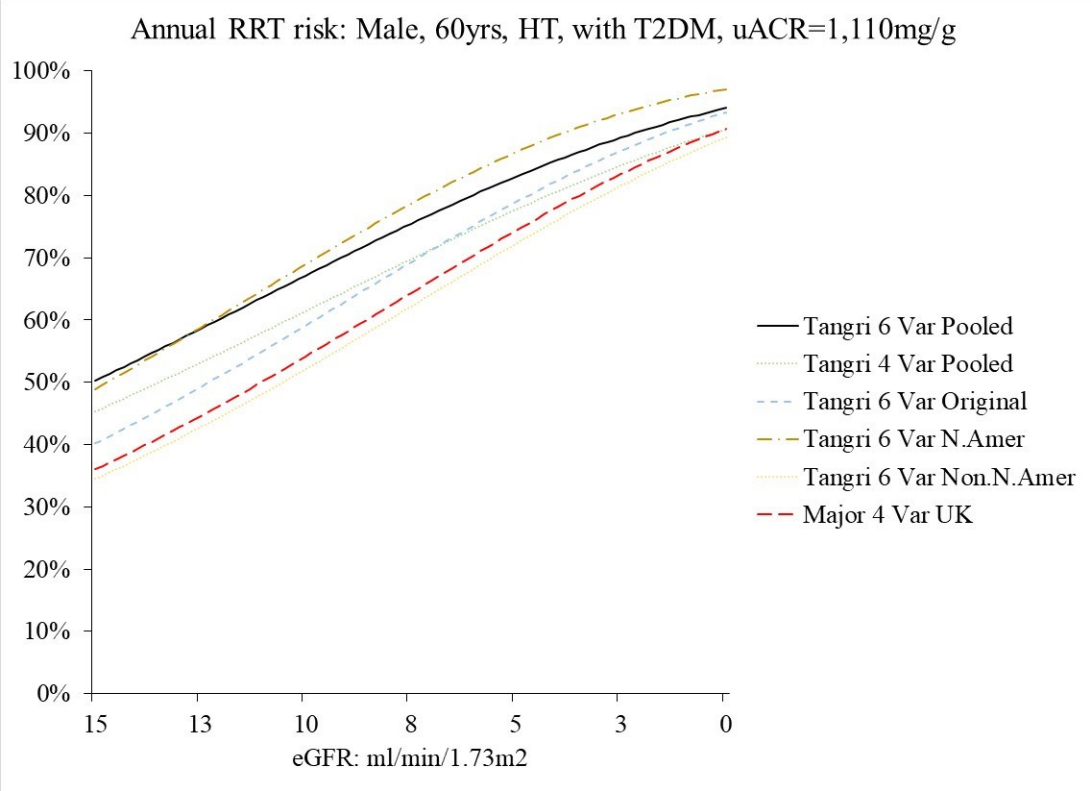


Figure 12: Annualised 5 year risk of renal replacement therapy: patient with diabetes

For those with an eGFR of 15 ml/min/1.73m^2 the annual RRT risk for a non-diabetic is 40% using the company preferred curve compared to 36% using Major et al, while for a patient with diabetes they are 50% and 36% respectively. In other words, the model assumes that in the year that their eGFR falls to 15 ml/min/1.73m^2, 40% of non-diabetic and 50% of diabetics will receive RRT, the vast majority receiving dialysis with a minority of 7.9% getting kidney transplant based upon the 2021 UKRR report. Those not receiving RRT in the year that their eGFR falls to 15 ml/min/1.73m^2 receive conservative management that year, but are reassessed for RRT using the same risk equations each subsequent annual model cycle.

The EAG critique of the annualization of these risks is presented in section **Error! Reference source not found.** below, of the eGFR threshold in section **Error! Reference source not found.** below, and of the selection of the functional form in section **Error! Reference source not found.** below.

4.9.2. CVD risks and events

The 10 year risk of CVD events was taken from the “CKD patch” equations of Matsushita et al[46] who analysed data from a systematic review of 4.1 million patients

with CKD from 35 data sets. CVD events were defined as myocardial infarction, stroke and fatal coronary heart disease. The “CKD patch” equations take into account patients’ eGFR and uACR, as well as age, sex, race, cholesterol, blood pressure and smoking status.

The 10 year risk is estimated each model cycle and annualised for application during the model cycle. Due to only myocardial infarction, stroke and fatal coronary heart disease being included by Matsushita et al, the model increases the annual risk by 1.14 to allow for unstable angina and transient ischaemic attacks. The probabilities of recurrent events is based upon an analysis of Framingham data.

The EAG is unclear whether the CKD patch equations include only myocardial infarction and stroke, or whether fatal coronary heart disease events are also included. If the latter this should be taken into account when reviewing the modelling of mortality as presented in section 4.15.13.

The EAG is also unclear whether the model structure only allows patients to have a recurrent CVD event of the same type as their 1st CVD event. If so this would unreasonably restrict patients whose 1st CVD event was angina or transient ischaemic attacks to having these recur with there being no possibility of them having the more serous myocardial infarction or stroke.

The annualization of the 10 year risks is subject to the EAG criticisms of section **Error! Reference source not found.** below.

4.9.3. Heart failure risks

The 5 year proportions reported in Grams et al[19] are converted to annual rates assuming a constant annual risk of heart failure.

Table 35: 5-year proportion with heart failure by KDIGO health state

	With diabetes			Without diabetes		
	A1	A2	A3	A1	A2	A3
G2	6%	10%	17%	1%	6%	14%
G3a	7%	13%	14%	2%	3%	11%
G3b	7%	13%	19%	3%	13%	9%
G4	24%	19%	24%	11%	9%	15%

Table 36: Annual heart failure risk by KDIGO health state

	With diabetes			Without diabetes		
	A1	A2	A3	A1	A2	A3
G1/2	1.2%	2.1%	3.7%	0.2%	1.2%	3.0%
G3a	1.5%	2.8%	3.0%	0.4%	0.6%	2.3%
G3b	1.5%	2.8%	4.2%	0.6%	2.8%	1.9%
G4	5.5%	4.2%	5.5%	2.3%	1.9%	3.3%
G5	5.5%	4.2%	5.5%	2.3%	1.9%	3.3%

The annualization of these risks is subject to the EAG criticisms of section **Error! Reference source not found.** below.

4.9.4. Fractures

The incidence of first fractures is taken from Runesson et al[47] who report the results of the Stockholm Creatine Measurement (SCREAM) project among 68,764 Swedish patients with CKD stages 3, 4 and 5 excluding patients on dialysis and patients who had had a fracture within 5 years prior to baseline. Time to first fracture, stratified by hip and non-hip, was measured against contemporaneous eGFR with rates per 1,000 patient years being reported. Runesson et al note in passing that it is recognised that patients receiving dialysis are at high risk of fractures. The model assumes that there are no fractures for G1 and G2. The annual risks are applied each year of the model.

Table 37: Annual risk of fracture

	Fractures	Hip	Other
G1/2	0.0%	0.0%	0.0%
G3a	4.5%	1.4%	3.2%
G3b	5.4%	2.1%	3.4%
G4	6.4%	2.6%	3.9%
G5	5.9%	2.2%	3.7%

4.9.5. Proportion of patients with metabolic disorders

The proportions of patients with metabolic disorders are taken from Moranne et al[48] who report results from 1,038 French patients with CKD stages G2 to G5 who were not receiving dialysis, with a mean age of 59 years, 69% male, 6% black and 75% being prescribed a least one ACE/ARB. They report proportions by eGFR ranges that differ from the KDIGO classification, typically spanning 10ml/min/1.73m^2. The company model treats these as annual risks of developing the disorder.

Table 38: Annual risk of patients developing metabolic disorders by eGFR

eGFR	Hyperparathyroidism	Anaemia	Acidosis	Hyperkalaemia	Hyperphosphatemia	Hypocalcaemia
60-89	20%	8%	4%	1%	3%	2%*
50-59	26%	7%	4%	6%	1%	1%
40-49	36%	13%	6%	4%	2%	2%
30-39	62%	17%	11%	15%	4%	3%
20-20	80%	24%	22%	26%	4%	8%
< 20	85%	88%	39%	41%	33%	17%
* This category is further split in the model but reports similar values						

4.9.6. Acute Kidney Injury

An annual incidence of AKI of 1.5% is taken from a UK study, and coupled to hazard ratios by eGFR and uACR class, A3 being split into those below 1,000mg/g, A3-, and those above it, A3+.

Table 39: AKI hazard ratios: diabetic patients

	Diabetic patients				Non-diabetic patients			
eGFR	A1	A2	A3-	A3+	A1	A2	A3-	A3+
≥ 75	0.76	0.42	0.62	0.62	0.85	0.42	1.04	1.04
60-74	0.89	2.02	1.22	1.22	0.71	0.62	1.47	1.47
45-59	1.00	1.60	2.26	2.26	1.00	1.71	2.49	2.49
30-44	1.48	2.27	5.87	5.87	1.74	2.06	2.69	2.69
< 30	3.24	3.89	1.84	1.84	4.90	6.30	7.70	7.70

The proportion of patients with an AKI who are hospitalised is also related to the patient's eGFR health state, though the majority are hospitalised and the eGFR gradient is not particularly steep.

Table 40: Proportion of hospitalised AKI by eGFR

eGFR	A1
G1	80%
G2	82%
G3a	84%
G3b	90%
G4	97%
G5	93%

The EAG has not reviewed these elements of the modelling.

4.9.7. Infections

The proportions of patients with infections are mainly taken from a Swedish paper within the literature.[49]

Table 41: Annual risk of infections

eGFR	Respiratory	Gastrointestinal	Urinary	Skin and soft tissue	Nervous system	Musculoskeletal	Sepsis
≥ 105	2.3%	1.0%	1.3%	2.8%	0.2%	0.3%	0.1%
90-104	2.1%	0.8%	1.2%	2.5%	0.4%	0.2%	0.2%
60-89	2.8%	1.0%	2.5%	2.8%	0.6%	0.3%	0.4%
30-59	6.0%	2.0%	7.6%	4.3%	1.0%	0.5%	2.0%
< 30	11.0%	3.6%	15.8%	6.2%	1.2%	1.0%	3.6%

Relative risks of hospitalisation appear to be applied, taken from a reference within the literature.

Table 42: Relative risks of hospitalisation due to infection

	A1	A2	A3
G1	1.00	1.38	1.69
G2	1.05	1.55	2.48
G3a	1.46	2.17	2.24
G3b	1.37	2.92	5.37
G4/5	3.54	3.54	3.54

Peritoneal dialysis is associated with an annual 38% risk of peritonitis, based upon the UK subset of a study within the literature. Haemodialysis is associated with a 13.7% annual risk of blood stream infections, this possibly involving some double counting with the rate of sepsis.

The EAG has not reviewed these elements of the modelling. It is unclear whether the relative risks are applied within the model and if so what the hospitalisation rate for (G1, A1) is.

4.9.8. Mortality

The model takes UK life tables and removes deaths due to ischaemic heart disease, cerebrovascular disease and renal failure due to these being within the model. It also has the option of removing deaths due to diabetes, hypertensive diseases, urinary tract cancers and metabolic disorders due to these being also associated with CKD. This yields the non-specific general population mortality estimates by age. The probability of general population CVD death is estimated from the sum of the ischaemic heart disease and cerebrovascular disease deaths conditioned by the number at risk.

For those who have not had a CVD event and are not receiving renal replacement therapy mortality multipliers are taken from Matsushita 2010,[50] a large scale meta-analysis of CKD studies with a minimum of 1,000 patients, pooling results from 105,872 patients and 730,577 patient years with uACR measurements and an additional 1.12 million patients and 4.73 million patient years with urine protein dipstick measurements.

As reported by the company, Matsushita et al split A1 into those with a uACR < 10 mg/g and those with a uACR > 10 mg/g.

Table 43: General mortality multipliers by KDIGO health state

	A1 <10mg/g	A1 >10mg/g	A2	A3
G1	1.00	1.48	1.61	3.65
G2	1.00	1.40	1.78	2.50
G3a	1.02	1.49	1.95	3.09
G3b	1.28	1.95	2.51	4.10
G4	1.97	2.65	3.66	5.08
G5	5.39	3.66	4.85	6.96

Despite Matsushita supplying estimates for A3 the company assumes that the mortality multipliers for A3 are as for A2, "*in view of ACR distribution in source cohorts*". This should be read in the light of the section 4.12.5 about model validation.

The model also includes an all-cause hospitalisation mortality multiplier but the current EAG understanding is that this has not been applied within the modelling.

For those who have had a CVD event mortality multipliers specific to CVD are sourced from Matsushita et al..

Table 44: CVD mortality multipliers by KDIGO health state

	A1 <10mg/g	A1 >10mg/g	A2	A3
G1	1.00	1.63	1.82	4.77
G2	1.03	1.48	1.73	4.01
G3a	1.09	1.58	2.18	4.23
G3b	1.52	2.38	3.13	4.97
G4	2.40	3.07	4.12	6.10
G5	13.51	7.99	5.60	9.49

In contrast to the general mortality multipliers, for the CVD mortality multipliers the company retains the estimates for A3. The current EAG understanding is that these CVD mortality multipliers are applied to patients who are modelled as having had either a stroke or an MI.

The third source of mortality risks is among those undergoing renal replacement therapy. These estimates are taken from the 2021 UK Renal Registry report, based upon Table 2.8 of "*Start and subsequent KRT modalities for adult patients*", page 27. This presents 90 day, 1 year, 3 year and 5 year data. The company applies the 1 year data to derive the following transition probabilities and annual probabilities of death. It is assumed that none over 80 years receive transplant (KT), the 1-Aug-2023 model supplied at clarification correcting an error in the reattribution of the probabilities of transplant to the other elements for these patients.

Table 45: CVD mortality multipliers by KDIGO health state: Up to 80 years

From \ To	HD	PD	KT	KT fail	Death
HD	74.0%	3.2%	5.8%		17.1%
PD	18.7%	58.0%	14.7%		8.6%
KT				2.9%	
KT fail	45.4%				54.6%

Table 46: CVD mortality multipliers by KDIGO health state: Over 80 years

From \ To	HD	PD	Death
HD	79.2%	4.0%	21.8%
PD	21.5%*	66.8%*	13.2%
* EAG inferred. May still be an error here			

It can be noted that compounding the haemodialysis annual rate of 17% results in 62% being modelled as dying by 5 years compared to the 55% of UKRR Table 2.8, while compounding the peritoneal dialysis annual rate of 8.6% results in 62% being modelled as dying by 5 years compared to the 37% of UKRR Table 2.8. But this does not take into account those on haemodialysis and peritoneal dialysis who subsequently receive transplant with its low failure rate and associated return to (G3a, A1).

The current EAG understanding is that the above mortality risks are applied in a hierarchical fashion:

- Those receiving renal replacement therapy have the renal replacement therapy mortality risks applied.
- Those not receiving renal replacement therapy but who have had a stroke or an MI in the current or a previous model cycle have the KDIGO health state specific CVD mortality multipliers applied to the general population CVD mortality risk for the patient age.
- The remainder of patients have the KDIGO health state specific general mortality multipliers applied to the non-specific general population mortality risk for the patient age.

These aspects have not been confirmed with the company.

4.10. Health related quality of life

4.10.1. KDIGO health state utilities

For its base case the company takes quality of life estimates from Jesky et al[51] who recruited 745 UK CKD patients and measured their quality of life using the EQ-5D,

evaluated using the UK social tariff during a 10 year follow-up period. The mean age was 64 years with 39% being female and 34% having diabetes. Patients were mainly in the worse KDIGO health states up to G4, tending to the bottom right of the KDIGO matrix, though numbers in G5 dropped off. Jesky et al only present quality of life by eGFR health state, pooling G1 and G2 due to low patient numbers.

Table 47: Jesky et al baseline patient distribution

	A1	A2	A3	Unknown	Total
G1/2	0.1%	0.1%	3.4%	0.3%	3.9%
G3a	1.1%	1.7%	3.2%	0.0%	6.0%
G3b	3.8%	7.9%	10.5%	1.1%	23.2%
G4	8.9%	18.5%	25.8%	3.6%	56.8%
G5	0.7%	2.6%	6.3%	0.5%	10.1%
Total	14.5%	30.9%	49.1%	5.5%	100%

Note that renal replacement therapy at baseline was an exclusion criterion. The EAG can find nothing to suggest that EQ-5D values among those who subsequently received RRT during the 10 year follow up were excluded from the analyses, further noting that 25.8% were (G4, A3) at baseline and 10.1% were in G5. The Jesky et al quality of life values for G5 may include the effects of a reasonable amount of RRT.

The values of Jesky et al can be read alongside the EMPA-KIDNEY mean EQ-5D post baseline values, also noting a general decline in the overall mean quality of life from 0.856 at baseline to around 0.817 at 36 months with there being no discernible difference between the arms. Note that during clarification the EAG did not ask for the distribution of EQ-5D values at baseline by KDIGO health state which could have usefully increased the sample size.

Table 48: KDIGO health state utilities

	Jesky et al			EMPA-KIDNEY post baseline		
	A1	A2	A3	A1	A2	A3
G1	0.85	0.85	0.85	..	..	..
G2	0.85	0.85	0.85	0.917	0.926	0.917
G3a	0.80	0.80	0.80	0.816	0.855	0.880
G3b	0.80	0.80	0.80			
G4	0.74	0.74	0.74	0.769	0.816	0.869
G5	0.73	0.73	0.73	..	..	..

While the EMPA-KIDNEY values do not populate some KDIGO health states, they suggest a somewhat better quality of life than the values of Jesky et al.

4.10.2. Renal replacement therapy quality of life

Renal replacement therapy is treated differently from the other complications, in effect being an additional model health state to the KDIGO model health states. Patients receiving, say, haemodialysis, have a base quality of life of 0.560 as taken from Liem et al.[52] The current EAG understanding is that any additional comorbidities have their disutilities applied to this; e.g. a myocardial infarction would reduce this patient's quality of life to 0.560 – 0.055 = 0.505 during that year of the model.

Table 49: Renal replacement therapy quality of life

	QoL
Haemodialysis	0.560
Peritoneal dialysis	0.580
Kidney transplant	0.710
Immunosuppressive therapy	-0.010

The quality of life for those with kidney transplant is only applied for one year, a successful transplant returning patients to (G3a, A1). These patients have an ongoing annual -0.010 disutility applied to account for immunosuppressive therapy.

It should be noted that the company model has two options for the treatment of quality of life: the base case option of "*HS utilities + one-year disutility*" and a second option of "*HS utilities, incl. ESKD submodule*". The current EAG understanding may be incorrect.

4.10.3. Complication with disutilities

The disutilities for complications are applied for the year during which they occur. The exceptions to this are the cancers which are assumed to have a lifelong effect. The disutilities are drawn from a variety of sources within the literature.

Table 50: Complication disutilities

	Disutility
CVD	
Myocardial infarction	-0.055
Unstable angina	-0.090
Stroke	-0.164

CHF hospitalisation	-0.108
Transient ischaemic attack	-0.070
Peripheral artery disease	-0.061
Peripheral vascular disease	-0.061
Hip fracture	-0.680
Other fractures	-0.680
Anaemia	-0.080
Acute kidney injury	-0.038
Renal cancer	-0.003
Urothelial cancer	-0.003
Leg amputation	-0.117
Toe amputation	-0.117
Foot amputation	-0.117

4.10.4. Complications without disutilities

A range of modelled complications are assumed not to affect quality of life. The company states that this is due to their effects already being within the KDIGO (or ESKD) health state quality of life.

These include:

Hyperphosphataemia
Hypocalcaemia
Hyperparathyroidism
Infections health state (which includes respiratory tract, gastrointestinal tract, urinary tract infection, skin and soft tissue, nervous system, and musculoskeletal system infections)
Metabolic acidosis
Hyperkalaemia
Hyperuricaemia/Gout

For hypertension, it is assumed this already affects predictions of events, so both costs and utilities are excluded as they are considered to have an impact on the occurrence of those events, therefore indirectly on costs and QALYs. Peritonitis and sepsis cost and utilities are also excluded. For AV access thrombosis, bloodstream infections, and anaemia, costs are excluded.

4.11. Resources and costs

4.11.1. Direct drug costs of treatment

The annual cost of empagliflozin is £477, which is aligned with the BNF list price and drug tariff and once daily dosing.

The direct drug cost of ongoing care with and without empagliflozin is based upon the weighted average of TA775 including ARB/ACE, statins and aspirin yielding an annual cost of £35.

4.11.2. Costs by KDIGO health state

The company sources ongoing costs by KDIGO health state from Pollock et al. Pollock et al8 analysed data from the UK subset of 5,033 patients from the DISCOVER CKD cohort study using records from the Clinical Practice Research Datalink (CPRD) linked to external databases. Unit costs were drawn from the PSSRU Unit Costs of Health and Social Care and from 2017/18 NHS reference costs, costs subsequently being inflated to 2019 values. Only NHS costs were considered. Patients with a history of transplant or undergoing dialysis were excluded.

The company excludes hospitalisation and critical care costs due to these being accounted for elsewhere within the modelling, assumes G1 annual costs will be the same as the G2 annual costs, and inflates costs to current prices.

Table 51: Annual costs by KDIGO health state

	A1	A2	A3
G1	£1,187	£1,488	£1,941
G2	£1,187	£1,488	£1,941
G3a	£1,221	£1,443	£1,901
G3b	£1,411	£1,666	£2,309
G4	£1,770	£2,075	£2,790
G5	£2,000	£2,445	£4,604

4.11.3. Costs of ESKD and renal replacement therapy

The main cost offsets in the model arise from reduced ESKD and renal replacement therapy.

[8] Sponsored by AstraZeneca

Those with ESKD not undergoing RRT are treated with conservative management at an annual cost of £6,335 based upon Agus et al.[53] This cost appeared to the EAG to be in addition to the £2,000, £2,445 and £4,604 annual KDIGO (G5, A1), (G5, A2) and (G5, A3) health states cost, but at error check the company has stated that this is not the case.

Continuous ambulatory haemodialysis and automated peritoneal dialysis costs of £29,871 and £33,388 are taken from 2020/21 NHS reference costs, converted to annual costs assuming that the NHS reference cost average adult costs of £82 and £91 are incurred every day. NHS reference costs also suggest an average unit cost of £176 for adult haemodialysis, which if required three times a week would result in an annual cost of £27,456. This is not used, the model instead sourcing a cost of £27,606 for haemodialysis from TA877 of finerenone for those with T2DM and CKD.

The costs of kidney transplant, £37,284 from a living donor and £34,700 from a deceased donor, with £6,335 annual follow up costs are stated as being estimated using the same method of TA775 of dapagliflozin for CKD.

4.11.4. Costs of CVD complications

The hospitalisation costs of CVD events are based upon NHS reference costs for non-elective long stay, while annual follow up costs are largely taken from the literature.

Table 52: CVD event costs

	Incident	Ongoing
Myocardial infarction	£3,136	£705
Unstable angina	£2,273	£421
Stroke	£6,278	£1,097
Congestive heart failure	£4,093	£941
Transient ischaemic attack	£2,854	£795
PAD or PVD	£4,650	£120

Annual follow up costs for myocardial infarction and congestive heart failure of £705 and £941 are taken from previous NICE assessments. Annual follow up costs for unstable angina, stroke and transient ischaemic attacks of £421, £1,097 and £795 were taken Danese 2015,[54] available as an abstract of a study of the UK clinical practice research datalink. It can also be noted that Danese provided long term follow up costs for myocardial infarction of £959 and for heart failure of £1,129 which

while slightly higher than the model input values are broadly in line with them. The costs of Danese included hospitalisations, visits and drugs so double count some of the KDIGO health state costs.

The company states that the follow-up costs are applied "*while the complication persists*". The EAG has not been able to find any information about how long it is assumed that complications persist in the model.

4.11.5. Costs of other complications per event

Costs of hyperphosphatemia, hyperparathyroidism and hypocalcaemia only include the direct drug costs of treating these. The costs of fractures, acute kidney injury and infection costs are mainly based upon NHS reference costs, with the remaining costs largely being taken from previous NICE assessments and from values within the literature.

Table 53: Other event costs

	Event
Hyperphosphatemia	£251
Hyperparathyroidism	£909
Hypocalcaemia	£251
Hip fracture	£4,814
Other fractures	£2,607
Acute Kidney Injury	£2,693
Respiratory infection	£129
Urinary infection	£40
Skin/soft tissue infection	£1,486
Gastrointestinal infection	£158
Muscular infection	£4,490
Nervous system infection	£3,672
Sepsis	£3,287
Renal cancer	£12,289
Urothelial cancer	£13,241
Metabolic acidosis	£1,272
Hyperkalaemia	£1,976
Gout	£2,170
Anaemia	£1,326
Leg amputation	£17,625
Toe amputation	£9,195
Foot amputation	£9,195

4.12. COST EFFECTIVENESS RESULTS

4.12.1. Company's cost effectiveness results

This section mainly uses the model (RS 0.200), provided at clarification and correcting some errors. The results of the original model (RS 0.200) are also briefly presented due to the PSA results of the company being based upon this model.

The company base case deterministic cost estimates are presented in Table 54.

Table 54: Company base case: model (RS 0.200): costs

	EMPA	PLAC	Net
Treatment	£2,572	£132	£2,440
KDIGO health state costs	£20,611	£19,904	£707
Renal replacement therapy	£25,667	£38,909	-£13,242
ESKD (non RRT)	£2,546	£2,696	-£150
CVD	£7,223	£6,541	£682
Anaemia	£4,258	£3,873	£385
Other CKD infections	£13,943	£12,472	£1,471
Metabolic complications	£8,144	£7,071	£1,072
Acute kidney injury	£1,102	£1,099	£3
Infections	£3,441	£3,065	£376
Cancers	£109	£78	£31
AEs	£291	£97	£194
Total	£89,907	£95,937	-£6,030

Increased treatment costs of £2,572 from spending an estimated 5.9 years on empagliflozin are more than offset by savings from reduced renal replacement therapy (RRT), mostly reduced dialysis costs. Infection costs in both arms are quite large, as are the costs of the other metabolic complications: hyperkalaemia, hyperuricaemia and metabolic acidosis.

The deterministic cost effectiveness results for all patients is presented in Table 55.

Table 55: Company base case cost effectiveness estimates: model (RS 0.200)

	EMPA	PLAC	Net
Undiscounted LY	12.615	10.985	1.631
QALY	7.124	6.282	0.842
Cost	£89,907	£95,937	-£6,030
ICER			Dom
NHB (WTP £20,000/QALY)			1.143

The original company model (RS 0.200) resulted in the slightly different cost effectiveness estimates of **Error! Reference source not found.**.

Table 56: Company base case cost effectiveness estimates: original model (RS 0.200)

	EMPA	PLAC	Net
Undiscounted LY	12.515	10.870	1.646
QALY	7.091	6.242	0.849
Cost	£87,946	£93,406	-£5,460
ICER			Dom
NHB (WTP £20,000/QALY)			1.122

The PSA central estimates from the original company model (RS 0.200) are presented in **Error! Reference source not found.**.

Table 57: Company PSA: original model (RS 0.200)

	EMPA	PLAC	Net
Undiscounted LY	n.a.	n.a.	n.a.
QALY	7.062	6.227	0.835
Cost	£88,690	£93,696	-£5,006
ICER			Dom
NHB (WTP £20,000/QALY)			1.085

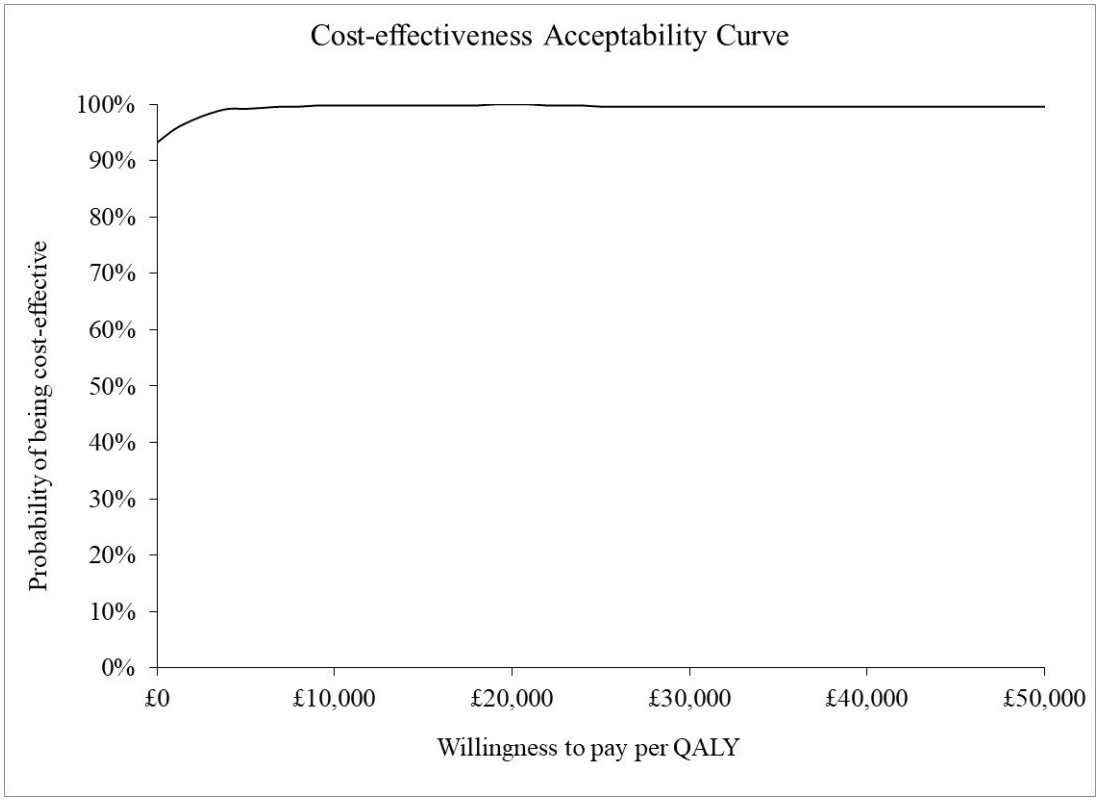


Figure 13: Company base case CEAC: original model (RS 0.200)

As explored by the EAG in section 4.3 the net cost estimates are sensitive to the random seed that is chosen. A random seed of 0.301 results in the estimated cost saving of -£6,030 changing to a net cost of £2,437, with a patient gain of 1.078 QALYs and empagliflozin ceasing to dominate but rather to have an ICER of £2,260 per QALY.

An EAG run of the company base case across 20,000 patients with a randomly selected random number seed results in the estimates of Table 58 and Table 59.

Table 58: Company base case: model (multirun): net costs

	EMPA	PLAC	Net
Treatment	£2,526	£133	£2,393
KDIGO health state costs	£20,903	£19,778	£1,125
Renal replacement therapy	£27,011	£37,552	-£10,541
ESKD (non RRT)	£2,546	£2,808	-£262
CVD	£7,407	£6,714	£692
Anaemia	£4,300	£3,900	£400
Other CKD infections	£14,002	£12,550	£1,452
Metabolic complications	£8,033	£6,966	£1,067
Acute kidney injury	£1,137	£1,064	£73
Infections	£3,511	£3,057	£454
Cancers	£165	£150	£15
AEs	£246	£64	£183
Total			-£2,951

Table 59: Company base case: model (multirun)

	EMPA	PLAC	Net
Undiscounted LY	12.847	11.091	1.756
QALY	7.234	6.325	0.910
Cost	£91,786	£94,737	-£2,951
ICER			Dom
NHB (WTP £20,000/QALY)			1.057

Net savings are more than halved compared to the company model run with a random seed of 0.200, mainly due to reduced savings from renal replacement therapy.

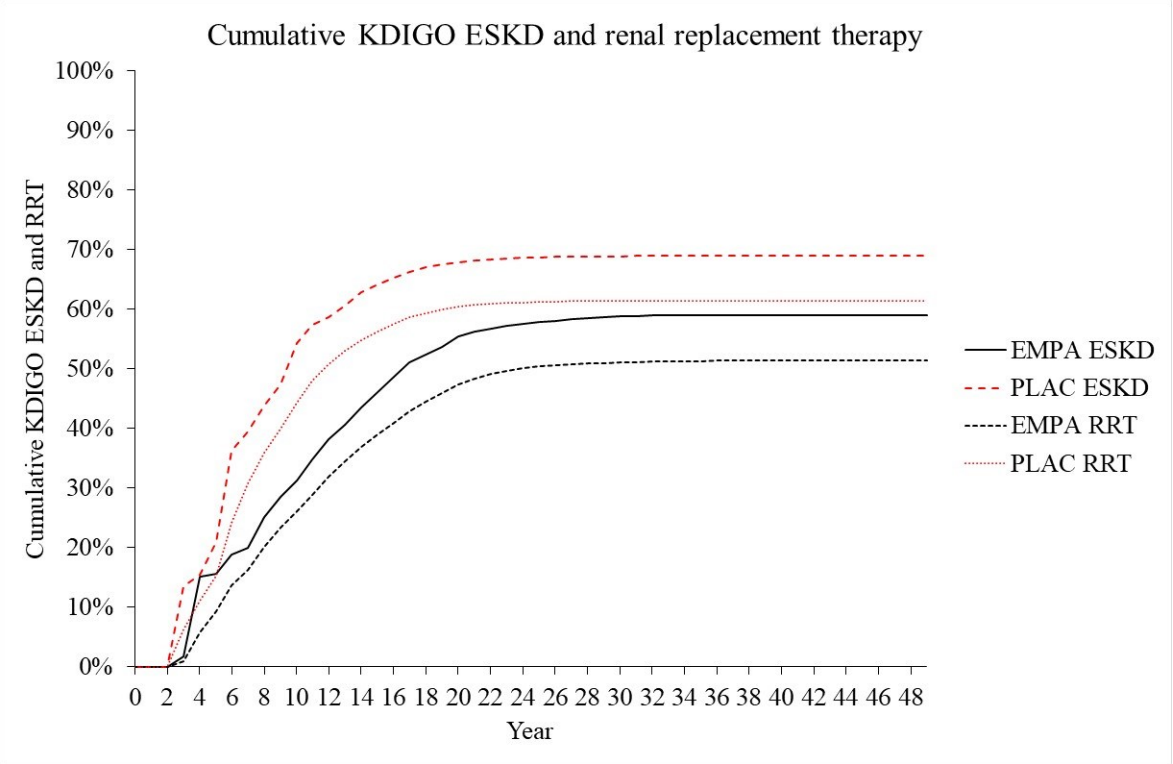


Figure 14: Company base case cumulative incidence ESKD and RRT: model (multirun)

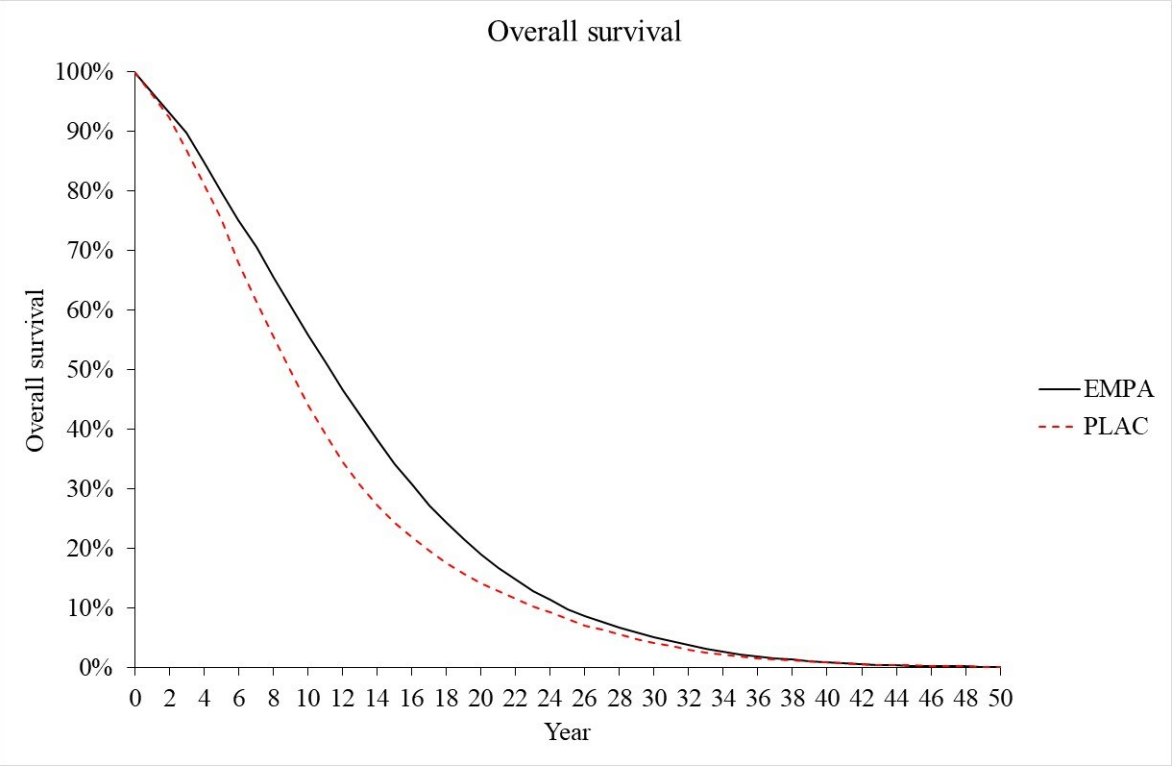


Figure 15: Company base case overall survival: model (multirun)

Overall survival is superior with empagliflozin, around 10% more remaining alive between years 7 and 17, with smaller gains before and after this resulting in an overall undiscounted survival gain of 1.8 years. Empagliflozin is estimated to remain dominant, yielding a cost saving with a QALY gain and a net health benefit of 1.057 QALYs.

The EAG has not taken the model (multirun) through to a PSA due to time constraints.

4.12.2. Company sensitivity and scenario analyses around the base case

Due to time constraints the EAG does not take these through to model (multirun) analyses and only presents the company submission Document B original model (RS 0.200) results.

The company provides an extensive set of one-way sensitivity analyses in Document B Table 55, page 135 and associated tornado diagram in Figure 29, page 138. These find the cost effectiveness estimates to be broadly stable compared to the base case ICER of -£6,431 per QALY, with only the assumed threshold for receiving a kidney transplant and the health state utility for (G5, A3) much affecting results, though the proportion of patients whose renal replacement therapy is haemodialysis also affects results to a degree.

Of the four scenario analyses only the threshold for RRT risk equations being revised to 20ml/min/1.73m^2 has much effect, worsening the ICER to -£2,338 per QALY. Applying the UK probabilities of renal replacement therapy of Major et al[45] worsens the ICER to -£5,126 per QALY. Empagliflozin is estimated to remain dominant throughout.

4.12.3. Company base case by baseline diabetes status

The company presents subgroup analyses by patients' baseline diabetes status in Appendix S. This mainly alters the patient baseline characteristics. The clinical effect estimates in terms of annual eGFR changes, annual uACR changes and discontinuation rates are taken from the all patient analysis. The EAG updates these analyses using the corrected company model supplied at clarification using the company selected random seed of 0.200, model (RS 0.200), and using the model (multirun) to ensure convergence.

Table 60: Company base case: diabetic at baseline

	Model (RS 0.200)			Model (multirun)		
	EMPA	PLAC	Net	EMPA	PLAC	Net
Undisc. LY	11.333	9.656	1.677	11.449	9.719	1.729
QALY	6.502	5.648	0.855	6.567	5.662	0.905
Cost	£85,927	£88,814	-£2,886	£85,493	£86,618	-£1,125
ICER			Dom			Dom
NHB			0.999			0.961

Table 61: Company base case: non-diabetic at baseline

	Model (RS 0.200)			Model (multirun)		
	EMPA	PLAC	Net	EMPA	PLAC	Net
Undisc. LY	13.976	12.402	1.575	14.244	12.422	1.821
QALY	7.735	6.921	0.814	7.865	6.941	0.923
Cost	£96,075	£105,832	-£9,757	£97,860	£102,210	-£4,351
ICER			Dom			Dom
NHB			1.301			1.141

Despite the on treatment clinical effect estimates being taken from the all-patient analysis, there will be some difference in eGFR and uACR trajectories due to the off treatment eGFR trajectories differing by diabetes status according to Grams. But the main source of the differences in the cost effectiveness estimates appears likely to be due to differences in baseline characteristics. Note that those with diabetes at baseline having a mean age of 68 years compared to 59 years among those without, which worsens the cost effectiveness estimate for those with diabetes.

4.12.4. Company base case by baseline KDIGO health state

The company provides sensitivity analyses around patients' baseline KDIGO health state in Appendix J, Tables 8 and 9. But the company does not take this through to a full analysis of costs and benefits by KDIGO health state at baseline. EAG analyses using the model (multirun) suggest the following cost effectiveness estimates by baseline KDIGO health state for the company base case over the 50 year modelled time horizon.

Table 62: Company base case by baseline KDIGO health state: QALYs by arm

	Empagliflozin			Placebo		
	A1	A2	A3	A1	A2	A3
G2	10.589	9.577	9.252	10.518	9.482	8.366
G3a	9.561	8.863	8.093	9.199	8.017	6.682
G3b	8.563	7.920	6.707	7.845	6.732	5.578
G4	7.289	6.576	4.991	6.326	5.330	4.644

Table 63: Company base case by baseline KDIGO health state: Total costs by arm

	Empagliflozin			Placebo		
	A1	A2	A3	A1	A2	A3
G2	£59,533	£69,084	£73,697	£56,905	£66,029	£76,992
G3a	£69,623	£77,437	£85,993	£68,390	£78,214	£91,672
G3b	£82,088	£87,190	£96,279	£81,361	£89,832	£102,505
G4	£94,638	£96,698	£109,670	£92,328	£100,182	£114,448

Table 64: Company base case by baseline KDIGO health state: net QALYs and Costs

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.071	0.096	0.885	£2,628	£3,055	-£3,295
G3a	0.363	0.846	1.411	£1,233	-£776	-£5,680
G3b	0.718	1.187	1.129	£727	-£2,642	-£6,226
G4	0.963	1.246	0.347	£2,310	-£3,485	-£4,778

Table 65: Company base case by baseline KDIGO health state: ICERs and NHBs

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£37,110	£31,905	Dom	-0.061	-0.057	1.050
G3a	£3,398	Dom	Dom	0.301	0.885	1.695
G3b	£1,012	Dom	Dom	0.682	1.320	1.440
G4	£2,399	Dom	Dom	0.847	1.421	0.586

The company base case estimates that empagliflozin results in net QALY gains across all baseline KDIGO health states. It also estimates that empagliflozin is cost saving across most baseline KDIGO health states, but is cost increasing for all patients in uACR class A1 and those in (G2, A2) at baseline.

The estimated cost effectiveness is good across all baseline KDIGO health states, with the exception of (G2, A1) and (G2, A2) which suggests ICERs above £30,000 per QALY and negative net health benefits at a willingness to pay of £20,000 per QALY. The ICERs for (G2, A1) and (G3, A1) should be interpreted with caution since as outlined in Table 28, Table 29, Table 32 and Table 33 above they are not associated with any on treatment eGFR or uACR effects. This in part illustrates the importance of the other clinical effects, HbA1c, weight, BMI and SBP, with SBP possibly particularly affecting CVD and heart failure; e.g. the net QALY gain for (G2, A1) is only slightly less than that for (G2, A2). But it seems reasonable to expect the

ICER for (G2, A1) to be worse than the ICER for (G2, A2), the latter being associated with on treatment eGFR and uACR effects so providing a lower bound for the former.

4.12.5. Model validation and face validity check

The company provides some internal and external model validation work in Appendix R. This is quite complex. The EAG provides some simpler model validation work in this section.

The company base case model (multirun) overall survival can be compared with the OS KM data of EMPA-KIDNEY, assuming a linear evolution of modelled survival between annual data points much to be in line with the company half cycle model correction.

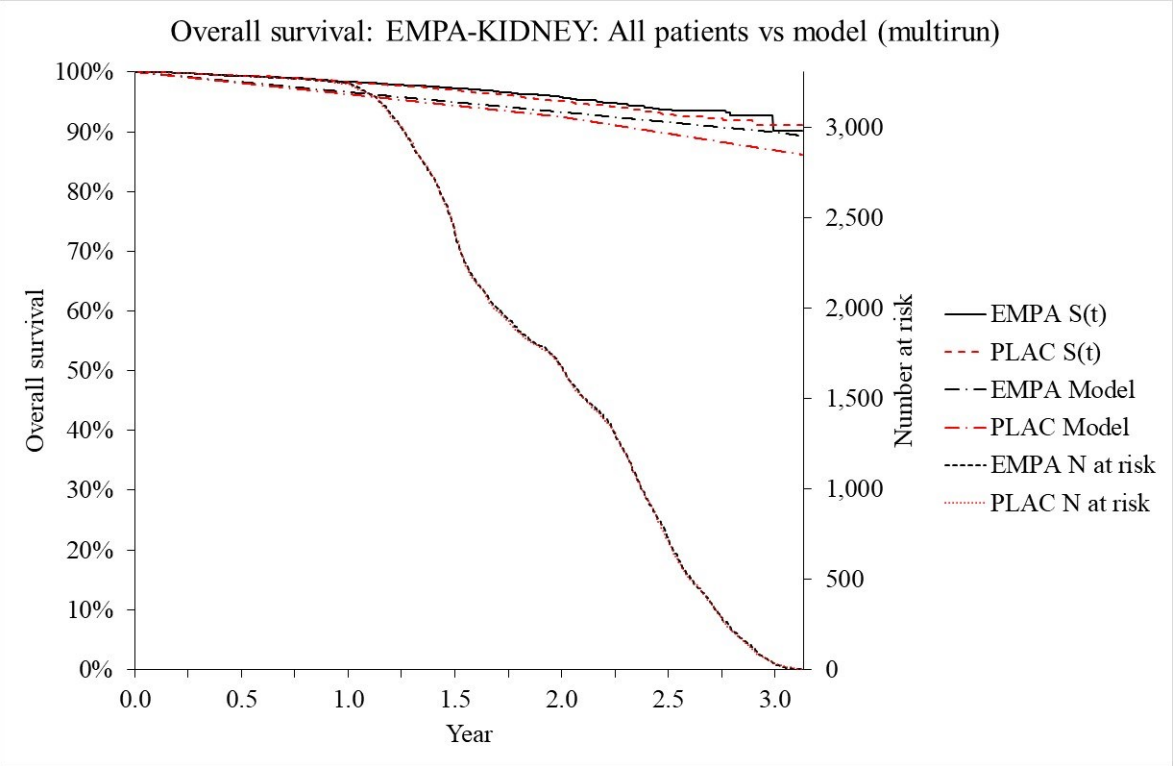


Figure 16: Company base case OS: All patients: KM data vs model (multirun)

There is little divergence between the OS Kaplan Meier curves of empagliflozin and placebo during EMPA-KIDNEY, the area between the empagliflozin and placebo KM curves being only 4.0 days survival. There is some divergence between the modelled curves starting at around 1.5 years and increasing thereafter, the area between the curves being 11.2 days survival. While 11.2 days is close to triple 4.0

days, within the context of a 3 year period the absolute difference of 7.2 days is not large.

Perhaps of more concern is that over the three years of EMPA-KIDNEY OS data the model estimates are that bit too pessimistic and tend to undershoot the Kaplan-Meier curves for both empagliflozin and placebo. For empagliflozin the KM curve terminates with 9.8% having died, though this is affected by the late step when very few patients remain at risk. The model predicts 10.7%. For placebo the KM curve shows 8.9% having died whereas the model predicts 13.8%. It is of some concern that the model estimate for placebo undershoots the observed values by an absolute 5%, overestimating deaths by 55%. This is relatively early in the model time horizon, leading to concerns around extrapolation.

It should also be born in mind that at 3 years relatively few patients are modelled as having had RRT: 1.0% for empagliflozin and 6.0% for placebo. These estimates increase quite rapidly thereafter as shown in Figure 14 above. They have a major impact upon modelled overall survival due to the high annual death rates associated with RRT most of which is dialysis: a 17.1% annual death rate for the 73% getting haemodialysis and a 8.6% annual death rate for the 19.2% getting peritoneal dialysis. This can be seen in the general steepening of the overall survival curves of Figure 15 above.

Overall survival can be presented for the company base case for the subgroups of those with and those without diabetes at baseline. Note that this applies the company base case assumptions with the exception of applying the subgroup specific annual eGFR and uACR changes, as supplied by the company at clarification.

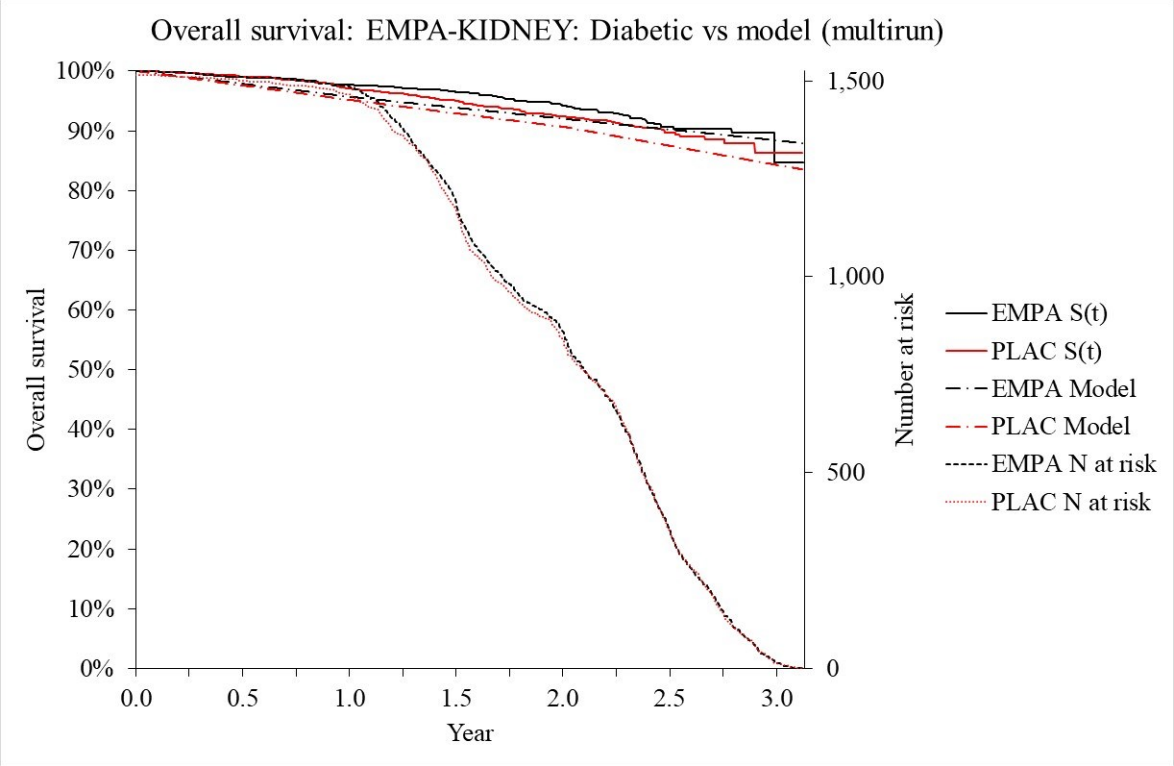


Figure 17: Company base case OS: Diabetic patients: KM data vs model (multirun)

For those with diabetes at baseline there is more separation between the Kaplan Meier curves compared to the all-patient analysis. Again, the modelled curves tend to undershoot the Kaplan Meier curves, this possibly affecting empagliflozin more than the placebo over the middle portion of the data.

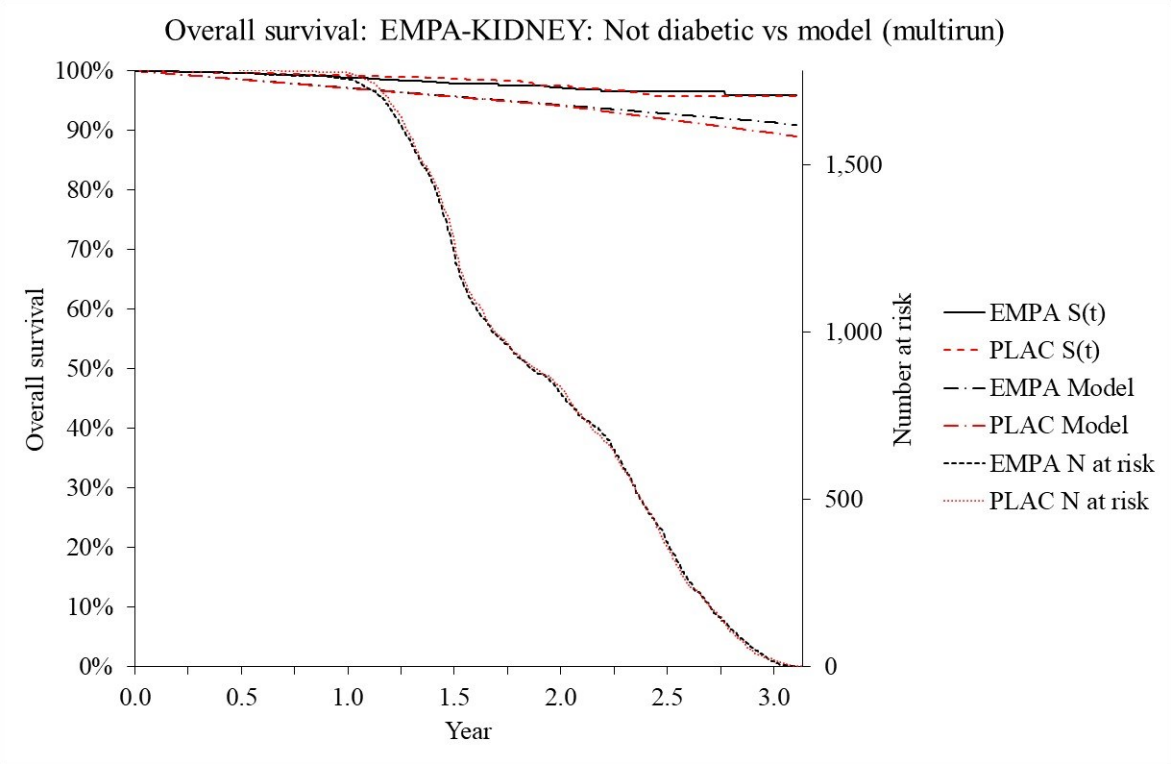


Figure 18: Company base case OS: Non-diabetic patients: KM data vs model (multirun)

For those without diabetes at baseline there is no separation between the Kaplan Meier curves. Separation between the modelled curves also only begins at around 2 years and is modest thereafter. But it is of concern is that the Kaplan Meier proportions dying by the end of follow-up are 4.1% for empagliflozin and 4.2% for placebo when the model estimates them to be 9.1% and 11.1%, more than double the observed values.

The modelled cumulative incidence of ESKD and renal replacement therapy in the placebo arm can be presented by baseline KDIGO health state at 5 years, 10 years, 20 years and 50 years estimated using the model (multirun).

Table 66: Company base case by baseline KDIGO health state: Placebo ESKD and RRT

	ESKD			Renal replacement therapy		
5 year	A1	A2	A3	A1	A2	A3
G2	0%	0%	0%	0%	0%	0%
G3a	0%	0%	0%	0%	0%	0%
G3b	0%	0%	0%	0%	0%	0%
G4	0%	55%	88%	0%	17%	77%
10 year	A1	A2	A3	A1	A2	A3
G2	0%	0%	0%	0%	0%	0%

G3a	0%	1%	48%	0%	1%	27%
G3b	0%	48%	76%	0%	24%	69%
G4	59%	79%	88%	38%	69%	80%
20 year	A1	A2	A3	A1	A2	A3
G2	7%	23%	48%	5%	19%	43%
G3a	26%	50%	64%	21%	45%	57%
G3b	53%	64%	76%	45%	56%	69%
G4	68%	79%	88%	57%	69%	80%
50 year	A1	A2	A3	A1	A2	A3
G2	28%	37%	48%	25%	34%	44%
G3a	39%	50%	64%	34%	45%	57%
G3b	54%	64%	76%	46%	56%	69%
G4	68%	79%	88%	57%	69%	80%

The modelled placebo outcomes can be compared with those reported for the CRIC study by Grams et al[19] who report up to 15 year data from the CRIC dataset of 3,939 US CKD patients.

Table 67: Model placebo ESKD vs Grams ESKD

	Model			Grams		
5 year	A1	A2	A3	A1	A2	A3
G2	0%	0%	0%	0%	3%	7%
G3a	0%	0%	0%	1%	4%	24%
G3b	0%	0%	0%	2%	13%	42%
G4	0%	55%	88%	13%	31%	70%

The model typically underestimates the incidence of ESKD at 5 years compared to CRIC., with the exception of those in (G4, A2) and (G4, A3). The EAG thinks that this is because the deterministic model structure means that all patients with a given set of characteristics work their way through the KDIGO health states at the same rate. Though note that this is with the exception of the (oddly) randomly sampled off treatment uACR effect.This progression takes time as there are no “fast progressors”, and 5 years is not sufficient for those in the better KDIGO health states to work through to G5. This is readily apparent in Figure 14 above where no patient develops ESKD before year 2, but the incidence rises steeply thereafter. The steep rise in ESKD between year 2 and year 5 is entirely accounted for by those who were in (G4, A2) and (G4, A3) at baseline. It is only after year 5 that those who were in better KDIGO health states at baseline move into ESKD, the modelled curve continuing to rise steeply after year 5. Given this, the EAG is concerned about the

overestimation of ESKD among those who were in (G4, A2) and (G4, A3) at baseline. It is possible that a similar overestimation also occurs among those who were in better KDIGO health states at baseline over the course of the modelling.

Table 68: Model placebo deaths vs Grams deaths

	Model			Grams		
5 year	A1	A2	A3	A1	A2	A3
G2	7%	9%	12%	4%	9%	12%
G3a	9%	13%	18%	6%	11%	14%
G3b	12%	17%	23%	10%	14%	19%
G4	18%	30%	50%	24%	21%	21%

Despite the model underestimating ESKD at 5 years compared to that observed by Grams et al, it appears to generally overestimate deaths at 5 years.

But the above compares the disaggregate EMPA-KIDNEY modelling with Grams. There are some differences in baseline characteristics most notably in terms of race. The distribution between eGFR classes is also different, but this does not matter for the comparison of the model with Grams by KDIGO health state of **Error! Reference source not found.** and **Error! Reference source not found.** above. The CRIC as reported in Grams et al[19] recruited patients with a baseline eGFR between 20 and 70 ml/min/1.73m^2. As such, despite Grams et al tabulating proportions in G1/2, G3a, G3b and G4/5 the EAG assumes that there were no patients in G1 or G5 at baseline.

Table 69: Baseline characteristics: Grams and EMPA-KIDNEY

	Grams	EMPA-KIDNEY
Age	57.7	63.3
Female	45%	33%
BMI	32	30
SBP	129	136
eGFR	44.3	37.4
uACR median (IQR)	52 (9-459)	331 (46-1,061)
Diabetic	48%	46%
Hypertension	86%	86%
CVD	33%	27%
Race		
White	45%*	58%
Black	42%	4%
Hispanic/Asian	13%	38%
eGFR		
G2	15%	8%
G3a	30%	13%

G3b	36%	44%
G4	19%	35%
uACR		
A1	42%**	20%
A2	30%**	28%
A3	28%**	52%
* assumed to be the residual ** estimated from median and IQR assuming lognormal distribution		

The baseline characteristics of CRIC of Grams et al can be inputted to the model (multirun) for a more reliable comparison. Patients in Grams et al were typically in better KDIGO health states and with better eGFR and uACR values. The modelling will reflect this by applying the Grams et al eGFR health state distribution and mean values for these. Grams et al did not present the distribution between uACR values. The EAG presents (1) Model A that retains the EMPA-KIDNEY uACR distribution and (2) Model B that infers a uACR distribution based upon the information provided by Grams et al assuming it was lognormally distributed. The EAG preference is for Model B.

When reporting longer term follow up Grams et al divide the CRIC patient population into low risk, 36%, medium risk, 41%, and high risk, 23%, based upon the patient reported burden of disease during follow-up. Grams et al provide up to 15 years follow up data for ESKD, treating death as a competing risk, and death by their risk groups. A weighted average of these curves can be presented alongside the company model (multirun) that attempts to replicate Grams et al.

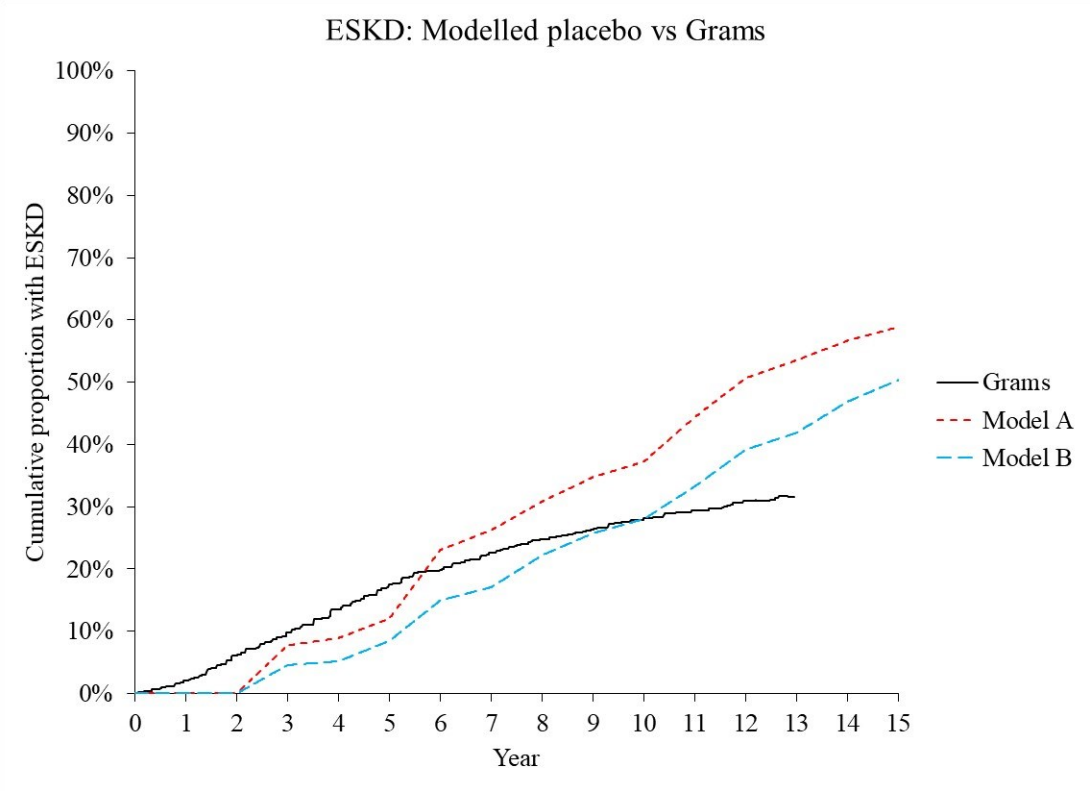


Figure 19: Company modelling Grams (multirun) vs Grams observed: ESKD

When reviewing **Error! Reference source not found.** it should be borne in mind that Grams et al present the cumulative incidence of ESKD "*taking into account the competing event of death truncated on the last event*". The model values are the unadjusted cumulative incidence of ESKD. If Grams et al had not adjusted for death as a competing risk the ESKD curve could be higher or lower depending upon whether there were a lot or relatively few deaths as competing risks. The EAG thinks that removing competing risk deaths from Grams et al would probably raise the ESKD curve, but that it is likely that Model B would still have a more aggressive trajectory.

For ESKD, much as per the earlier concerns expressed about the comparison of 5 year results of **Error! Reference source not found.** above, the model initially predicts lower rates of ESKD than were observed by Grams et al. This applies to a degree for Model A and to a larger degree for Model B. But as time progresses the model overpredicts rates of ESKD compared to Grams et al. At 13 years Model A predicts 53% cumulative ESKD and Model B predicts 42% whereas Grams et al

observed 32%: absolute over predictions of 22% and 10% and proportionately of 69% and 32%.

The modelled trajectory of ESKD at the end of the period is somewhat steeper than that of Grams and the divergence appears to be worsening. Between year 7 and 13 the annual average change for Model B is 4.1% compared to only 1.5% for Grams, the rate of change being 2.7 times greater. This is of concern as it may imply that after 15 years there will be additional effects the ESKD divergence upon RRT costs, quality of life and overall survival. The increase in the modelled cumulative ESKD does slow at around 20 years, with model B converging by year 26 at a total cumulative ESKD estimate of 67%. The EAG thinks that this 67% lies well above the Grams et al trajectory, though what the year 26 Grams et al value would be is conjecture.

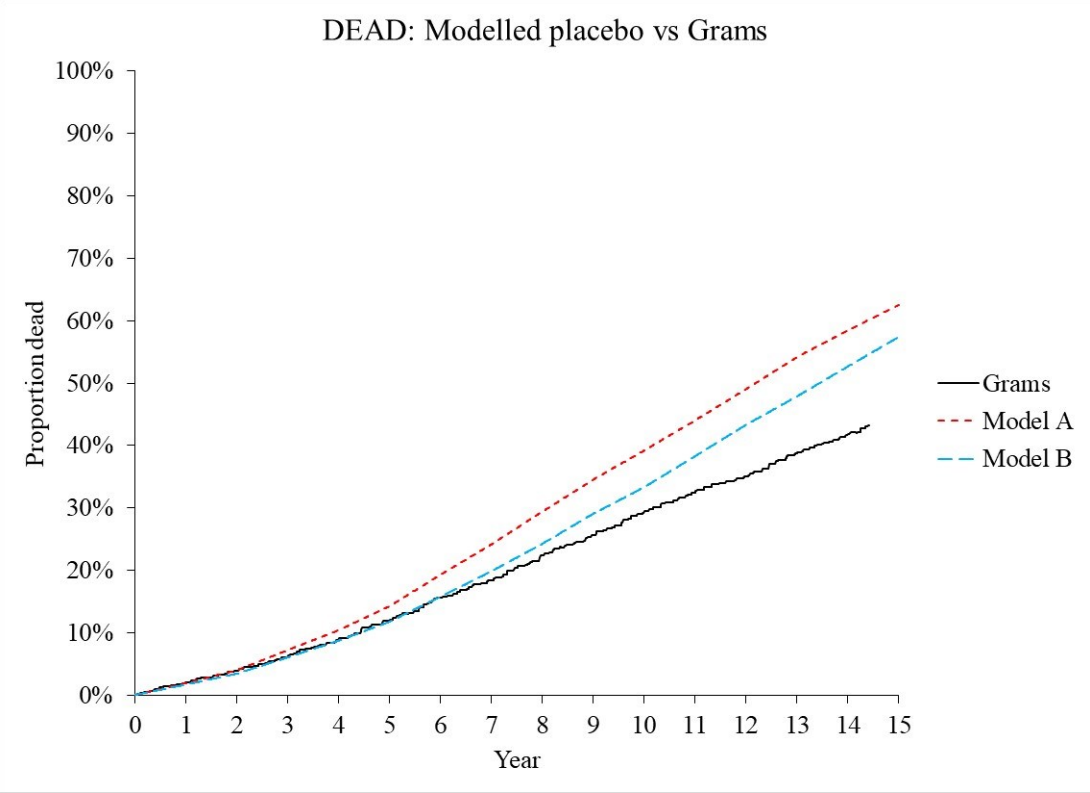


Figure 20: Company modelled Grams (multirun) vs Grams observed: Dead

Model B overall survival shows good alignment with that observed by Grams et al to around year 7. Thereafter the curves start to diverge and by the end of the 15 year period have different trajectories. At 14 years Model A predicts 58% will have died and Model B predicts 53% whereas Grams et al observed 42%: absolute over

predictions of 17% and 11% and proportionately 40% and 26%. Between year 7 and 13 the trajectory of ESKD in Model B 2.7 times as steep as Grams. This may cause modelled survival to further diverge after 14 years due to the lagged effects of ESKD and patients receiving RRT, with its associated very high annual mortality.

It is only be possible to compare the modelled disaggregate results by baseline KDIGO health state with the low risk, medium risk and high risk groups of Grams et al with additional assumptions. Each of the modelled baseline KDIGO health states would need to be assigned to low risk, medium risk and high risk groups using the KDIGO risk mapping coupled with the need for the final distribution to approximate Grams et al to categories of 36% low risk, 41% medium risk and 23% high risk. The EAG has not taken this forward because the assumptions required would to an extent be arbitrary, but can do so if required.

The modelled evolution of CKD may be too aggressive, particularly for the majority of patients without diabetes at baseline. This may result in overestimations of the proportions of patients progressing to ESKD and renal replacement therapy, and also underestimate patient survival. The impact upon net effects cannot be stated unequivocally. The EAG thinks it is likely that it overestimates both net savings and net QALY gains and biases the analysis in favour of empagliflozin.

4.13. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

4.14. EAG critique of economic modelling compared to position sought

As outlined in the company submission Document B Figure 1 page 9, the company seeks approval for empagliflozin for CKD patients, with or without T2DM, and either:

- an eGFR between 20 and 45 ml/min/1.73m^2, or
- an eGFR between 45 and 90 ml/min/1.73m^2 and a uACR of more than 200mg/g[9]

TA775 approved dapagliflozin for CKD patients, with or without T2DM, and:

- an eGFR between 25 and 75 ml/min/1.73m^2 and a uACR of more than 200mg/g

[9] Throughout the economics the company measures uACR in mg/g. The EAG retains this, noting that 200mg/g is equivalent to the 22.6mg/mmol of Document B Figure 1.

The company also seeks approval for empagliflozin for patients with CKD and T2DM for those with:

- an eGFR between 45 and 90 ml/min/1.73m^2 and a uACR less than 200mg/g

TA775 approved dapagliflozin patients with CKD and T2DM, and:

- an eGFR between 25 and 75 ml/min/1.73m^2 and a uACR of less than 200mg/g

The position sought by the company overlaps with that approved for dapagliflozin for CKD patients with:

- an eGFR between 25 and 75 ml/min/1.73m^2 and a uACR more than 200mg/g
- T2DM, an eGFR between 45 and 75 ml/min/1.73m^2 and a uACR less than 200mg/g

For these positions the EAG thinks that the main comparator is dapagliflozin. The company does not model dapagliflozin as a comparator due to assumed clinical equivalence on the basis of the company NMA and empagliflozin being the same cost as dapagliflozin.

The position sought by the company extends beyond that approved for dapagliflozin to CKD patients with:

- an eGFR between 75 and 90 ml/min/1.73m^2 and a uACR more than 200mg/g
- an eGFR between 20 and 25 ml/min/1.73m^2
- no T2DM, an eGFR between 25 and 45 ml/min/1.73m^2 and a uACR less than 200mg/g
- T2DM, an eGFR between 75 and 90 ml/min/1.73m^2 and a uACR less than 200mg/g

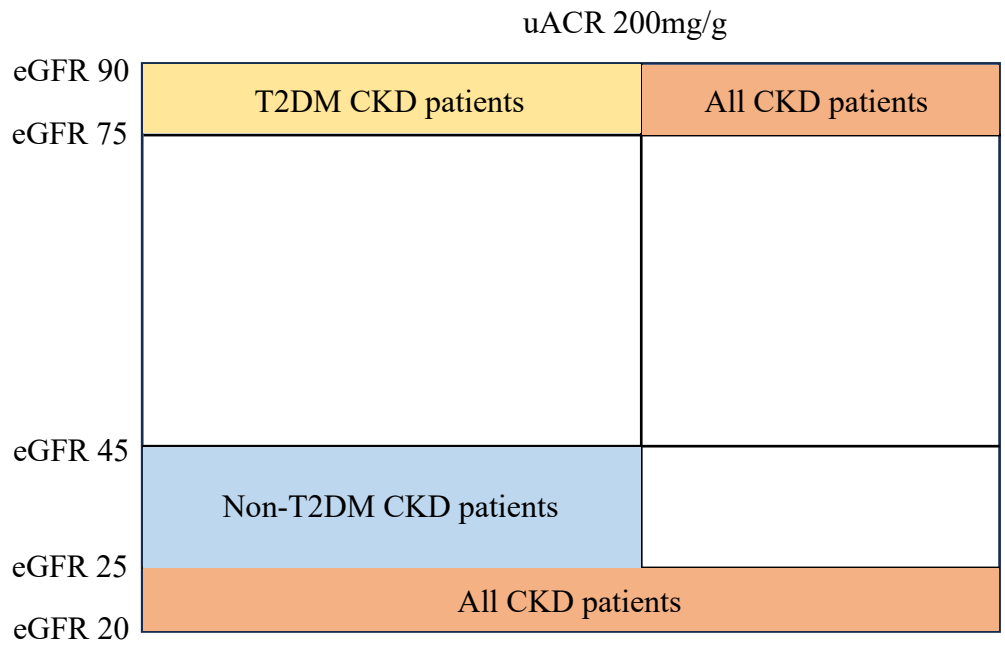


Figure 21: Empagliflozin positions sought outside current dapagliflozin position

For these positions the EAG thinks that the main comparator is usual care without dapagliflozin. The company does not present cost effectiveness analyses for these extensions. It only reports cost effectiveness results averaged across the baseline KDIGO health states (G2, A1) through to (G4, A3), though in scenario analyses it does present this separately for those with diabetes at baseline and those without diabetes at baseline and also presents some results disaggregated by KDIGO health state at baseline.

In order to move towards an assessment of empagliflozin that recognises the extensions sought compared to that approved for dapagliflozin the EAG presents subgroup analyses by baseline KDIGO health states, as in **Error! Reference source not found.** above. But this is imperfect due to the boundaries for these not being aligned with the extensions sought; e.g. eGFR state G2 is between 60 and 90 ml/min/1.73m^2 while uACR state A2 is between 30 and 300mg/g.

Given the company argument about equivalence with dapagliflozin there is an argument that for the comparison with usual care without dapagliflozin the company should present cost effectiveness estimates separately for the four groups of **Error! Reference source not found.**, possibly also splitting the eGFR 20 to 25

ml/min/1.73m^2 into those with a uACR less than 200mg/g and those with a uACR more than 200mg/g.

Note that the economics switches seamlessly between uACR boundaries of 3 and 30 mg/mmol, equivalent to 26.6 and 266mg/g, and 30 and 300 mg/g. The defining unit appears to be mg/mmol. The EAG has not been able to verify that this seamless switching between what appear to be slightly different boundaries is valid, but the website of KDIGO.ORG appears to accept this[10].

It can be further noted that TA390 approved empagliflozin as monotherapy for those with T2DM only if metformin is contraindicated or not tolerated, a sulfonylurea or pioglitazone is not appropriate and a DPP-IV would otherwise be prescribed.

TA336 approved empagliflozin as combination therapy for those with T2DM for:

- Dual therapy with metformin if a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypocalcaemia or its consequences.
- Triple therapy in combination with metformin and a sulfonylurea or in combination with metformin and a thiazolidinedione.
- In combination with insulin.

At clarification the company provided data on concomitant medication for the subgroup of EMPA-KIDNEY patients with diabetes at baseline. This suggests that a proportion of EMPA-KIDNEY patients with diabetes at baseline may be eligible for empagliflozin for treatment of their diabetes.

Table 70: Company base case by baseline KDIGO health state: Placebo ESKD and RRT

	EMPA	PLAC	ALL
Monotherapy metformin	5%	6%	5%
Other monotherapy OAD	14%	14%	14%
Dual therapy OAD	13%	10%	11%
Triple therapy OAD	2%	3%	3%
Insulin therapy	53%	55%	54%
OAD: Oral anti-diabetic			

[10] See page xii KDIGO classification of https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2023-CKD-Guideline-Public-Review-Draft_5-July-2023.pdf

4.15. EAG critique: the company model

4.15.1. ERG model rebuild

Due to the complexity of the company model structure and the extensive set of inputs taken from the literature, the EAG has not yet fully rebuilt the company model. The EAG will continue to work on this.

To date it has only rebuilt the evolutions of eGFR, uACR, HbA1c, BMI, total cholesterol and SBP, the incidence of diabetes, the incidence of CVD and its distribution across the different type of CVD events, the incidence of ESKD and the incidence of renal replacement therapy and its evolution. This has informed the review below.

The EAG has not found any major errors in terms of model structure. There are issues around the compatibility of model inputs with the model structure as reviewed in sections 4.15.4, **Error! Reference source not found.** and 4.15.6. Minor errors and undocumented modelling assumptions that have no obvious justification within the cited reference are briefly presented in section **Error! Reference source not found.** on minor issues.

4.15.2. Decision problem not fully addressed

The modelling only addresses whether it is cost effective to treat patients with empagliflozin over their entire lifetime. It is possible that it may be more cost effective to reserve empagliflozin until patients have progressed to either (1) a high risk KDIGO category, or (2) a medium risk KDIGO category.

If there are fast progressors and slow progressors this might also help differentiate between the two groups. The closest the current modelling comes to this is modelling those with diabetes and those without diabetes separately, the OC-AD data suggesting that in the placebo arm those without diabetes tend to have a slower eGFR progression than those with diabetes. This also applies to the eGFR data that the company takes from the literature for those who have discontinued treatment.

Addressing this would require extensive revision to the model structure so that those in the empagliflozin arm are untreated and have the placebo eGFR rates of progression until they worsen to either (1) a high risk KDIGO category, or (2) a

medium risk KDIGO category, at which point they would receive empagliflozin and have the empagliflozin eGFR rates of progression.

4.15.3. Modelling those with and those without diabetes separately

Given the position sought as reviewed in section **Error! Reference source not found.** above, the EAG thinks it desirable to model those with diabetes and those without diabetes as separate subgroups. This is furthered by the likelihood of treatment effect and disease progression differing between those with diabetes and those without diabetes, particularly in terms of the key model input: annual eGFR changes.

The forest plot of the company submission Appendix E Figure 5 on page 6 presents the net difference in the annual eGFR change during the chronic 2 month to 36 month period of EMPA-KIDNEY. The all patient estimate of 1.37 (1.16, 1.59), as also reported in Document B, Figure 18 on page 65, when split by baseline diabetes status results in estimates of 1.09 (0.79, 1.39) for those without and 1.68 (1.36, 2.00) for those with diabetes at baseline, with a stated p-value of 0.0085[11]. This apparent difference between those with and those without diabetes at baseline could in part be due to other baseline characteristics differing between those with and those without diabetes at baseline.

The baseline uACR is statistically significantly associated with the chronic phase annual net eGFR change. A worse baseline uACR increases the estimate.

Table 71: Chronic phase net eGFR slope by uACR and baseline patient distribution

	Chronic eGFR change		Baseline distribution	
uACR	Estimate	95% C.I.	Diabetic	Non-Diabetic
A1	0.78	(0.32, 1.23)	21.3%	19.1%
A2	1.20	(0.81, 1.59)	31.0%	25.8%
A3	1.76	(1.46, 2.05)	47.7%	55.1%

The EMPA-KIDNEY distribution across uACR health states suggests those with diabetes tend to have a better uACR distribution with fewer in A3. This might be anticipated to tend to lower the estimate for those with diabetes.

[11] Figure 5 gives this as 0.0085 but does not star it for significance. It may be a typo with the actual value of 0.085 being of borderline statistical significance, which should be read alongside the differences in the eGFR and uACR distributions for those with and those without diabetes at baseline.

The baseline eGFR is also statistically significantly associated with the chronic phase annual eGFR change.

Table 72: Chronic phase net eGFR slope by eGFR and baseline patient distribution

	Chronic eGFR change		Baseline distribution	
eGFR	Estimate	95% C.I.	Diabetic	Non-Diabetic
G2/G3a	2.01	(1.53, 2.49)	17.0%	24.7%
G3b	1.32	(0.99, 1.65)	45.1%	43.6%
G4	1.01	(0.63, 1.39)	37.9%	31.7%

The EMPA-KIDNEY distribution across uACR health states suggests those with diabetes tend to have a worse eGFR distribution with more in G4. This might also be anticipated to tend to lower the estimate for those with diabetes.

Despite the above, the estimate for those with diabetes of 1.68 is stated as being statistically significantly greater than the 1.09 for those without diabetes.

A difference in eGFR evolution between those with and those without diabetes at baseline is presupposed in the analysis of the CRIC data of Grams et al.[19] This presents long term estimates of the annual eGFR change by KDIGO health state separately for those with and those without diabetes at baseline, the company model using these estimates for its off-treatment modelling of eGFR changes.

The EAG notes the company concerns around some KDIGO health states having small patient numbers when analysed by diabetic and non-diabetic subgroups. But the EAG thinks that taken in the round, particularly with regards the positions sought where usual care without dapagliflozin is the only comparator as in **Error! Reference source not found.**, the above considerations argue for separately modelling those with and those without diabetes at baseline.

The company has supplied OC-AD central estimates for the subgroups of those with diabetes at baseline and those without diabetes at baseline, though for reasons that are not stated for uACR fold/multipliers supplied 18 month values for those with diabetes at baseline and 30 month values for those without diabetes at baseline.

Table 73: Annual eGFR change by KDIGO: empagliflozin: diabetic patients

OC-AD	A1	A2	A3
G2 G3a	[redacted]	[redacted]	[redacted]

G3b G4	[redacted]

Table 74: Annual eGFR change by KDIGO: placebo: diabetic patients

OC-AD	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]

Table 75: 18 months uACR multiplier by KDIGO: diabetic patients

	Empagliflozin			Placebo		
OC-AD	A1	A2	A3	A1	A2	A3
G2 G3a G3b G4	[redacted]					

Table 76: Annual eGFR change by KDIGO: empagliflozin: non-diabetic patients

OC-AD	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]

Table 77: Annual eGFR change by KDIGO: placebo: non-diabetic patients

OC-AD	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]

Table 78: 30 months uACR multiplier by KDIGO: non-diabetic patients

	Empagliflozin			Placebo		
OC-AD	A1	A2	A3	A1	A2	A3
G2 G3a G3b G4	[redacted]					

The central estimates of the above remain are in favour of empagliflozin, [redacted]

The EAG will present revised base cases for all patients, those with diabetes at baseline and those without diabetes at baseline. These results will also be presented by baseline KDIGO health state. As reviewed in section **Error! Reference source not found.** below, given the modelling of treatment discontinuations the EAG thinks it better to use an on treatment OC-OT analysis rather than a within trial OC-AD analysis. The OC-OT analysis has only been supplied for the all-patient analysis, as in **Error! Reference source not found.** and **Error! Reference source not found.** below. The data supplied for the subgroups of those with diabetes at baseline and those without diabetes at baseline is currently limited to an OC-AD analysis.

4.15.4. On treatment eGFR effects compatibility with model structure

At clarification the company stated "*Document B Table 29 tabulates the annual rate of change in eGFR (mL/min/1.73m2) from baseline to final follow-up for each treatment group by baseline Kidney Disease Improving Global Outcomes (KDIGO) categories*". In other words, it seems that Table 28 and Table 29 above show the annualised eGFR change by baseline KDIGO health state over the duration of EMPA-KIDNEY.

The model applies these within an annual model cycle. Crucially, if a patient changes KDIGO health state their annual eGFR changes in line with Table 28 and Table 29 above. This leads to a fundamental incompatibility between the eGFR effect estimate inputs and the model structure. The severity of this incompatibility will increase the longer the typical patient follow-up extends beyond one year.

Assuming that e.g. patients in the placebo arm who were (G3b, A2) at baseline who are subsequently modelled as falling into (G3b, A3) should have their annual eGFR change increased from the -1.56 ml/min/1.73m^2 they experienced during EMPA-KIDNEY to the -4.11 ml/min/1.73m^2 that those who were (G3a, A3) at baseline experienced during EMPA-KIDNEY is invalid and will bias results.

This cannot be addressed by the EAG. The EAG thinks that the company should re-examine the EMPA-KIDNEY eGFR data. A necessary first analysis is to present the number of patients in each arm by KDIGO baseline health state who remain in their baseline KDIGO health state at 12, 24 and 36 months. Superior to this would be to

present by KDIGO health state the number of patients in each arm who's KDIGO health state changes between the start and the end of each year. To the extent that this is not possible due to an absence of uACR measurements this should present by KDIGO health state the number of patients in each arm who's eGFR health state changes between the start and the end of each year.

If movement between KDIGO health states during EMPA-KIDNEY is consequently judged to be problematic, for the sake of simplicity and transparency the EAG thinks that the company could present the data split by arm, by year and by KDIGO health state at start of year rather than at baseline, and report N, mean eGFR change from start of year and s.d. of the mean eGFR change from start of year. This should be presented for an OC-AD analysis but given the model structure more particularly for an OC-OT analysis, preferably also split by diabetic status at baseline.

This does raise the possibility of missing data reducing the number of available annual observations; e.g. a non-trivial number of patients may only have baseline and, say, 24 months eGFR values. These patients do contribute data to the baseline to end of follow-up analysis of Table 28 and Table 29. If these patient numbers are non-trivial this argues for also presenting the eGFR change between baseline and 24 months for these patients, and likewise for other missing annual values if patient numbers are non-trivial.

This is further complicated by uACR not being recorded at 12 months but only at 2, 18, 24, 30 and 36 months. Two analyses should consequently be presented, one that assumes each patients' uACR at 12 months is their baseline value and a second that assumes their uACR at 12 months is their 18 month value. While this may appear a gross simplification it may be the best that can be presented and is a less gross simplification than that of the company base case.

Aggregation of these annual changes into a single composite matrix of annual changes by KDIGO state could then be considered. This might also be affected by consideration of how the initial 2 month "dippers" in the empagliflozin arm might affect this if the company thinks it appropriate to present an additional analysis of the 2 month to 12 month changes split by arm and patients' KDIGO health states at 2 months.

The EAG thinks this should be presented for all patients, those without diabetes at baseline or at the start of the relevant year if so recorded and those with diabetes at baseline or at the start of the relevant year if so recorded. It should also be presented for both the OC-AD analysis and the OC-OT analysis due to the concerns about the modelling of treatment discontinuations outlined in section **Error! Reference source not found.** below.

Subsequent to a simple presentation of the data, more sophisticated analyses could be undertaken. The company could consider a dynamic transition model that takes into account each patient's KDIGO health state at the start of the year, possibly pooling the analysis across arms with treatment as an effect modifier if small numbers in important KDIGO health states remain a concern. Naturally, the company is free to submit any additional analyses it sees fit or as requested by Committee.

4.15.5. Off treatment eGFR effects compatibility with model structure

The same concerns outlined in section 4.15.4 above about the eGFR effects and model structure also appear to apply to the eGFR effects for those off treatment that are taken from Grams et al.[19] Grams et al state that "*Among 3,939 participants enrolled in the Chronic Insufficiency Cohort (CRIC) Study, we evaluated multi-dimensional disease trajectories by G- and A- stages of enrolment estimated glomerula filtration rate (eGFR) and albuminuria, respectively*" and "*the goal of this study was to characterize the natural history of CKD in CRIC participants over up to 14 years of follow-up with respect to clinical events, trajectories in estimated glomerular filtration rate (eGFR)*…". Given the longer follow-up of Grams et al compared to EMPA-KIDNEY, this may also be more of an issue in the Grams et al data.

This argues for reviewing the application of the Grams et al data in the light of how much the EMPA-KIDNEY annual eGFR change estimates differ when assessed by start of year KDIGO health state compared to when assessed by baseline KDIGO health state, as suggested in section 4.15.4 above.

This also argues for applying the placebo eGFR changes by contemporaneous KDIGO health state rather than those taken from Grams et al, particularly when the

modelling of treatment discontinuations as reviewed in section 4.15.15 below is considered.

4.15.6. On treatment uACR multipliers selection and compounding

The current EAG understanding is that the on treatment uACR annual multipliers by KDIGO health state of Table 32 and Table 33 above are based upon the values observed at 18 months. At clarification in response to question B3 the company has supplied the relative changes from baseline in the uACR. Table 79[12] and Figure 22 below presents the values for the OC-AD analysis, but the picture is similar for the OC-OT analysis.

Table 79: EMPA-KIDNEY uACR relative change from baseline MMRM

	EMPA			PLAC		
Month	Mean	95% C.I.	N	Mean	95% C.I.	N
2	82%	(80%, 84%)	2,775	98%	(95%, 101%)	2,789
18	86%	(82%, 89%)	2,483	108%	(104%, 113%)	2,483
24	96%	(90%, 104%)	523	120%	(112%, 129%)	509
30	99%	(93%, 106%)	902	124%	(116%, 132%)	868
36	92%	(82%, 104%)	290	112%	(99%, 126%)	280

[12] Values taken from graph

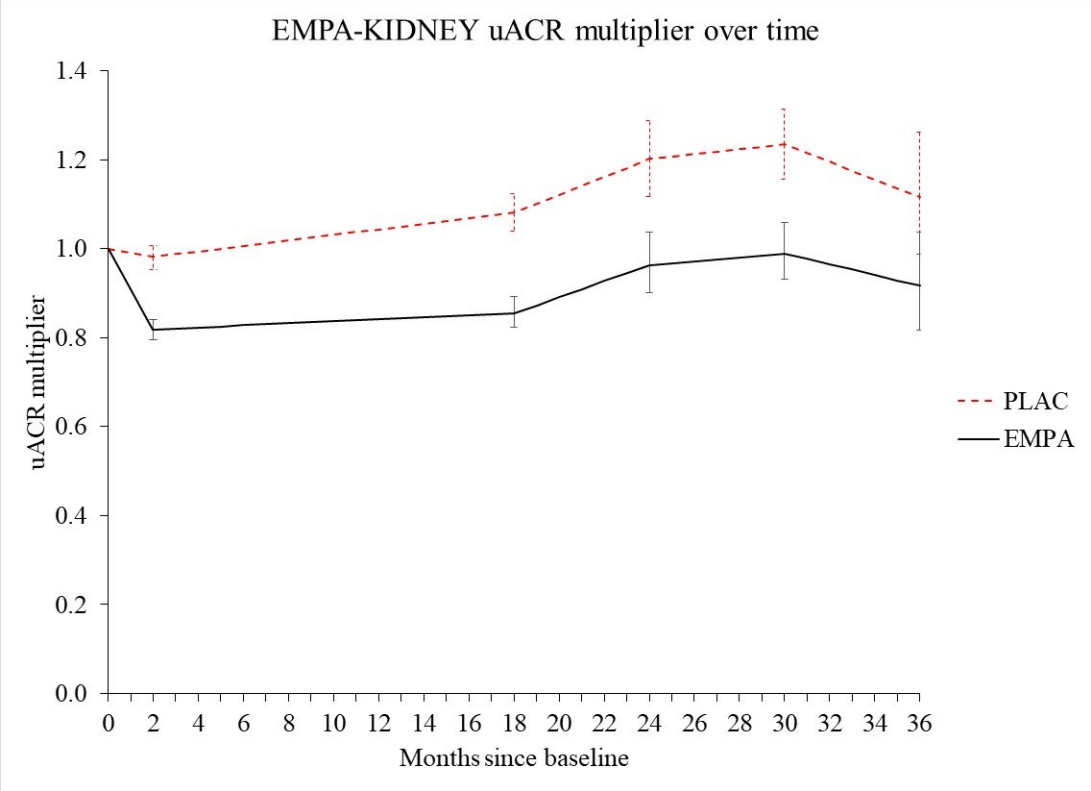


Figure 22: EMPA-KIDNEY uACR relative change from baseline MMRM

The above suggests that after an initial improvement at 2 months some of this effect is lost by 18 months, with uACR at best flatlining between 2 months and 18 months.

There are a reasonable number of observations at 24 months and at 30 months. These suggest that the uACR may worsen within both the placebo arm and the empagliflozin arm after 18 months.

The relatively small number of observations at 36 months is a concern, but there is the suggestion that by 36 months the initial treatment effect observed at 18 months has been largely maintained, but not compounded.

The EAG thinks that given data availability it is reasonable to apply the 18 month estimates of Table 32 and Table 33 for the first annual cycle of the model, but that it is not valid to reapply and compound these estimates thereafter. The most reasonable approach may be to assume a flat uACR thereafter, though given reporting rates this is more difficult to conclude for placebo than for empagliflozin.

The EAG revised base case will apply the estimates of Table 79 and Figure 22 for the first model cycle and will assume a flat uACR thereafter, including any time spent

off treatment though some rebound in the empagliflozin arm might also be a reasonable assumption. Scenario analyses of (1) annually compounding the estimates of Table 32 and Table 33 for those remaining on treatment and (2) annually compounding the estimates of Table 32 and Table 33 in conjunction with the scenario analyses for the uACR multiplier(s) for those off treatment as reviewed in section 4.15.10 below.

4.15.7. Off treatment uACR multiplier: base case: estimate

The EAG has not managed to replicate the undocumented company sampled central estimate of 1.464 from Coresh et al.[42] It is also difficult to align with what appear to be company uACR A1, A2 and A3 class specific estimates of 1.046, 1.090 and 0.939 respectively, also estimated from Coresh et al. It also needs to be read alongside the central estimates of the multipliers reported by Coresh et al in supplemental table S3, a median of 1.02 for annual studies, and in supplemental table S5, a median of 1.2 for studies with a three-year follow-up which would convert to an annual 1.062. The base case estimate may be too high.

The EAG thinks that further detail of the company estimation method is required before confidence can be placed in the company base case estimate.

4.15.8. Off treatment uACR multiplier base case: sampling

The company randomly samples the off treatment uACR multiplier, a different value being applied in each model cycle. At clarification the company stated that "*Fixing the value to the central point will limit the representation of CKD patients in the model, which are well known for being a very heterogeneous population, and therefore we believe this is not appropriate*". The EAG does not understand this, particularly in light of the deterministic modelling not sampling the on treatment uACR multipliers.

As this is a multiplicative effect rather than an absolute effect the multiplier compounds over the years. The sampling of the off treatment uACR multiplier may result in bias as outlined in **Error! Reference source not found.** below.

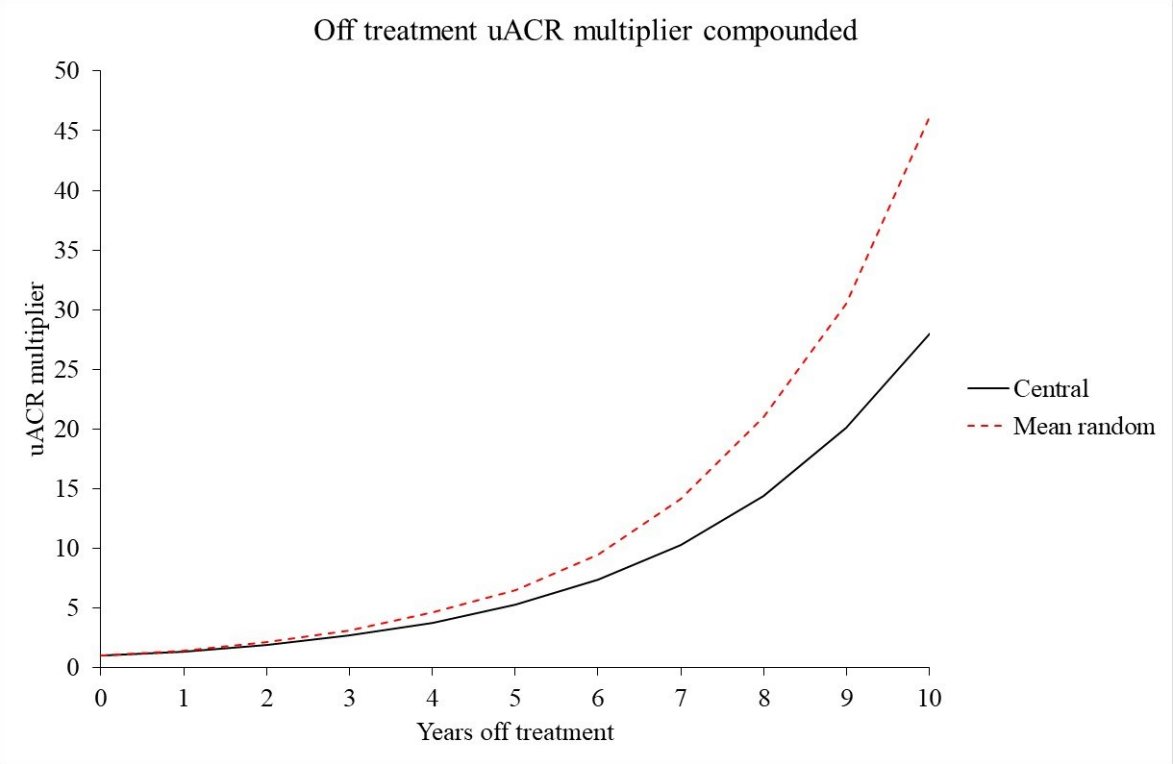


Figure 23: Off treatment uACR multiplier

The difference that results is relatively minor up to around 5 years, the mean of the randomly sampled uACR multiplier being 6.5 compared to the central value of 5.3, a discrepancy of 25%. But the difference becomes progressively worse thereafter, and at 10 years the mean of the randomly sampled multiplier is 46 compared to the central value of 28, a discrepancy of 62%. Given the logarithmic estimation the mean of the randomly sampled values, 1.464, can be seen as the best measure of central tendency rather than the central value, 1.369. But the EAG still does not understand the need to sample this for each model cycle and each patient.

4.15.9. Off treatment uACR multiplier: functional form selection

The model contains three options for the off treatment uACR multiplier functional form, all derived from the data of Coresh et al.[42]

- The base case single value log normal cube root, with a central value of 1.396 and a sampled central value of 1.464, as summarised in section 4.15.7 above.
- Three separate estimates by uACR class in A1, A2 and A3 of 1.046, 1.090 and 0.939 respectively.

- Random sampling for each patient one of the three estimates of 1.046, 1.090 and 0.939 based upon the proportion of patients in Coresh in A1, A2 and A3 of 96.7%, 2.0% and 0.3%[13]. This effectively applies the 1.046 multiplier through for virtually all; i.e. 96.7%, patients.

For illustrative purposes these can be graphed for three patients coming off treatment with uACR values of 10mg/g, 110mg/g and 1,100 mg/g, the baseline uACR midpoints in EMPA-KIDNEY for A1, A2 and A3.

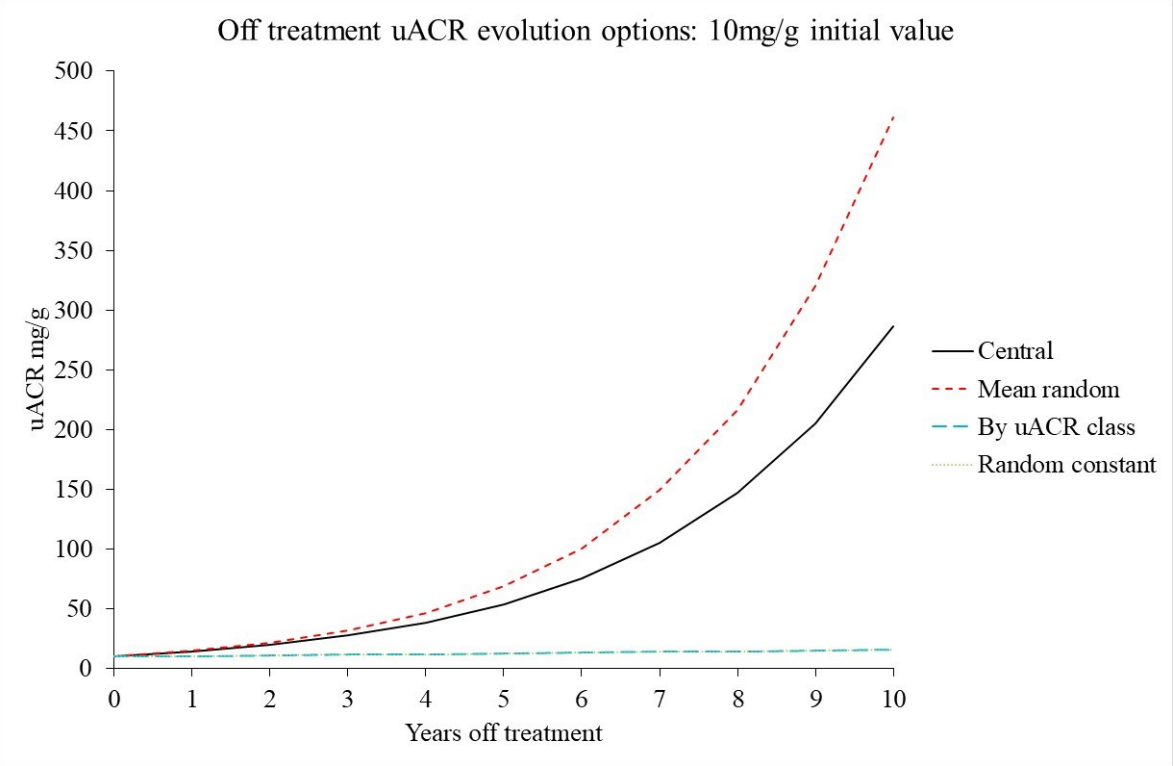


Figure 24: Off treatment uACR values for uACR 10mg/g at discontinuation

For those with a uACR within the boundaries of A1 the uACR evolution that applies estimates specific to the contemporaneous uACR class, "*By uACR class*", is effectively the same as that which applies a randomly selected constant from these uACR class values.

[13] Note that this distribution appears to be derived by assuming that all patients within a study have the study median uACR value, despite the interquartile ranges suggesting that non-trivial proportions of patients within a study had uACR values outside the uACR class of the study median.

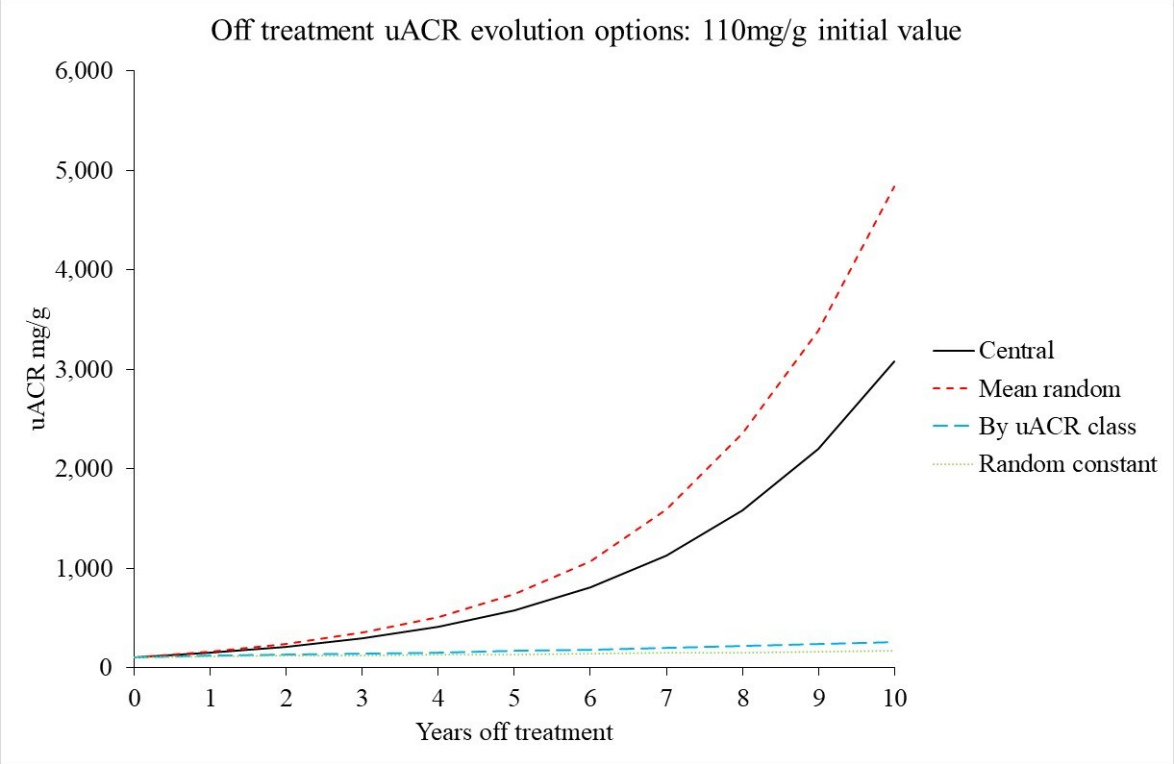


Figure 25: Off treatment uACR values for uACR 110mg/g at discontinuation

It may appear that there is again little difference between the uACR evolution that applies estimates specific to the contemporaneous uACR class, and that which applies a randomly selected constant from these uACR class values. But this is due to the vertical axis having to accommodate the other functions. By year 10 there is a 50% difference between them due to the evolution that applies estimates specific to the contemporaneous uACR class compounding the 1.090 annual multiplier rather than the 1.046 multiplier for 96.7% of patients.

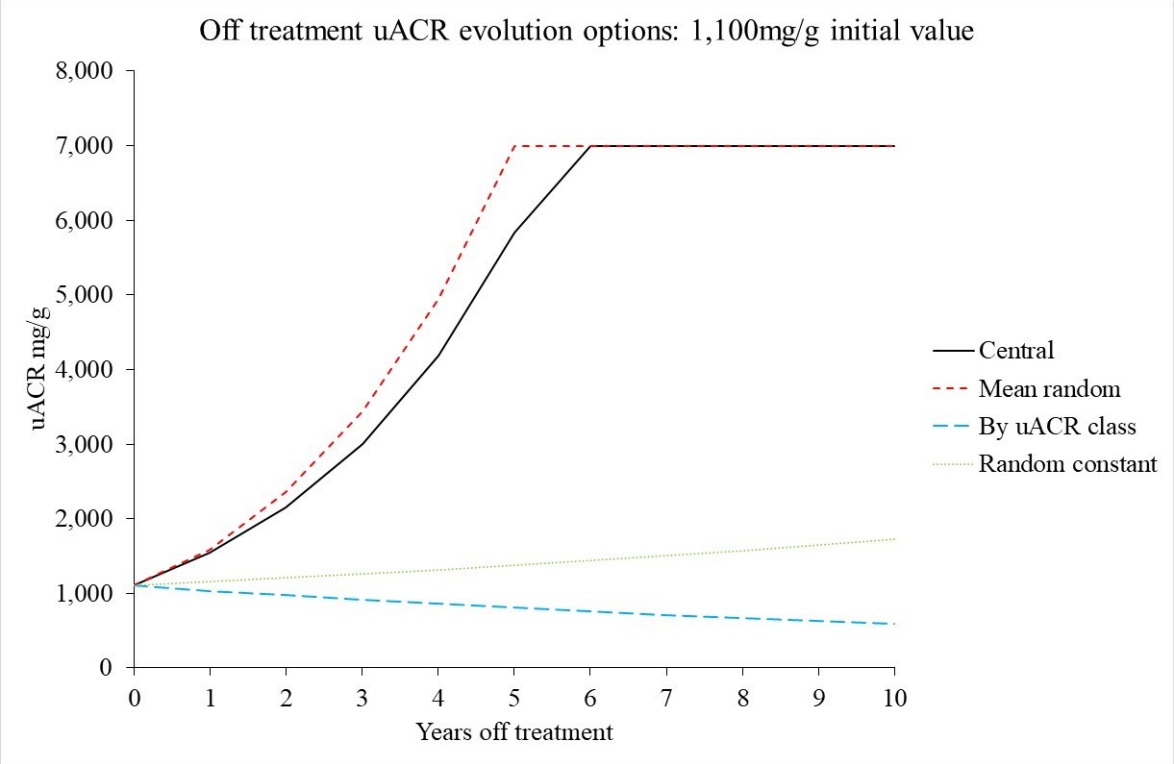


Figure 26: Off treatment uACR values for uACR 110mg/g at discontinuation

For those discontinuing treatment with a uACR of 1,100mg/g applying the single central estimate or sampling this randomly results in the uACR reaching the assumed maximum of 7,000 mg/g within 5 to 6 years. Applying the uACR class specific multipliers causes the uACR to gradually decline due to the patient remaining in A3 throughout and so having the 0.939 multiplier applied throughout. Applying the randomly selected uACR class specific value, unrelated to the patient's contemporaneous uACR value, results in a similar slope for all patients regardless of their initial uACR.

4.15.10. Off treatment uACR multiplier: EAG revised base case approach

The EAG thinks that the values applied for those off treatment should be read alongside those applied for those receiving placebo of Table 33 above. While the placebo multipliers for (G3b, A1), (G4, A1) and (G4, A2) of 1.65, 2.44 and 1.51 are somewhat higher than those the company derives for A1, A2 and A3, the other values for placebo are somewhat below them. The placebo values for A3 are similarly less than unity and are all below the 0.939 multiplier for A3 that the

company derives from Coresh et al with the exception of the 0.95 value for (G4, A3) which is very closely aligned with it.

The EAG thinks that randomly selecting one of the Coresh derived uACR specific values and applying it throughout for that patient regardless of their contemporaneous uACR value makes little sense. But it does highlight that the off treatment uACR multipliers were derived from data that apparently overwhelmingly relates to studies with a median uACR in class A1. Within Table 32 and Table 33 the uACR multipliers are somewhat greater for A1 than for A2 and A3.

If estimates for an off treatment uACR multiplier are required, given the placebo uACR multipliers of Table 33 above the EAG prefers the uACR specific values that the company derives from Coresh et al. But applying a uACR multiplier beyond the first year of the model may not be required, as reviewed in section 4.15.6 above. The EAG revised base case will set the off treatment uACR multipliers to unity, and explore a scenario that applies the Coresh derived uACR specific multipliers.

4.15.11. Treatment discontinuations and OC-AD vs OC-OT analysis

If treatment discontinuations from both empagliflozin and placebo are applied within the model alongside the eGFR changes from Grams et al[19] this suggests that the on treatment eGFR and uACR effects should not be derived from an OC-AD analysis but rather from an OC-OT analysis. The company has supplied an OC-OT analysis for the all patient eGFR changes, and an OC-AD analysis for the diabetic and non-diabetic subgroups. It has reservations around these for the diabetic and non-diabetic subgroup estimates due to some small sample sizes and difficulties achieving model convergence.

The EAG did not consistently ask for these for the uACR changes. As reviewed in section 4.15.6 above the EAG revised base case only applies the uACR changes once, so given the 18 months uACR change estimates the distinction between OC-AD and OC-OT is not really an issue.

The EAG asked for an OC-OT analysis for the subgroups of those with diabetes at baseline and those without diabetes at baseline but this was not supplied.

Table 80: Annual eGFR change by KDIGO: empagliflozin: all patients

OC-AD	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]
OC-OT	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]

Table 81: Annual eGFR change by KDIGO: placebo: all patients

OC-AD	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]
OC-OT	A1	A2	A3
G2 G3a G3b G4	[redacted]	[redacted]	[redacted]

The net effect by KDIGO class appears to be consistently less for the OC-OT analysis than for the OC-AD analysis. This is as would be expected given the higher discontinuation rate for placebo. The OC-OT analysis does result in an apparently anomalous result for (G4, A1) which could be due to random chance or discontinuation rates differing by KDIGO health state. If patients remain on empagliflozin longer there is a greater likelihood of them moving into worse uACR states with their associated faster eGFR worsening.

The EAG thinks that there is something peculiar about modelling patients as discontinuing from placebo. Placebo might be better viewed as not receiving active treatment. As a consequence, it might be more coherent to assume that those

discontinuing study treatment but remaining followed-up within EMPA-KIDNEY experience the placebo eGFR and uACR annual changes.

In the light of this the EAG revised base case for the all-patient modelling will apply the OC-OT eGFR change estimates. The EAG will also supply a scenario analysis that applies the placebo eGFR changes for those discontinuing treatment rather than the estimates taken from Grams et al.

4.15.12. Treatment discontinuations by KDIGO health state

The annual rate of treatment discontinuation is assumed to be the same across all KDIGO health states. This may not be valid. Results show some sensitivity to the discontinuation rates. Different annual discontinuation rates by KDIGO health state might better reflect EMPA-KIDNEY and could account for some of the differences in the eGFR change estimates of OC-AD and OC-OT; e.g. the central estimate for placebo (G4, A1) going from -0.39 to [redacted]. As with the eGFR change estimates, if discontinuation rates are to be differentiated by KDIGO health state, given the model structure this data would be better analysed according to the start of year KDIGO health state rather than the baseline KDIGO health state. The EAG did not ask for this data at clarification but thinks that the company should present it for all patients, for those who are diabetic at baseline and for those who are non-diabetic at baseline.

4.15.13. Mortality multipliers

The KDIGO mortality multipliers will involve mortality due to CVD and renal replacement therapy. Within the model patients who have not had a CVD or renal replacement therapy will be incurring the mortality risk of these events averaged across the relevant KDIGO category. As such, the model overestimates the mortality risk among the modelled patient cohort to some degree, this probably applying with most force to those in worse KDIGO health states.

There is no obvious means of adjusting the general mortality multipliers to remove the CVD mortality multiplier effect from the general mortality multiplier and so no obvious means of addressing this within the company model structure.

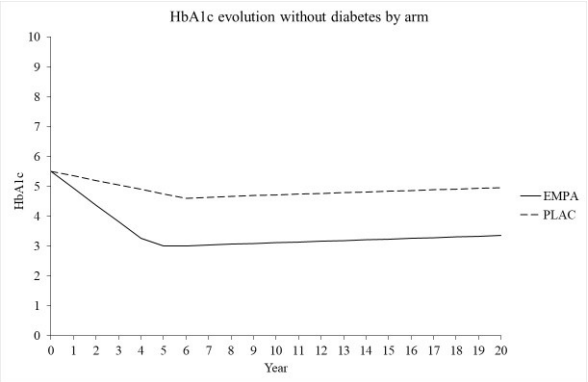
4.15.14. Duration of treatment effects other than eGFR and uACR

The annual change in HbA1c, BMI, SBP and DBP is applied every model cycle that the patient remains on treatment. For instance, the annual HbA1c improvement is -0.56% for empagliflozin and -0.15% for SoC. Similarly, the annual BMI improvement is -0.55 kgm^{-2} for empagliflozin and -0.24 kgm^{-2} for SoC. A patient remaining on treatment for 10 years sees their HbA1c fall by 5.6% with empagliflozin and 1.5% with SoC by the end of the 10 years, though a lower bound of 3.0% is placed upon HbA1c. Their BMI falls by 5.5 kgm^{-2} with empagliflozin and by 2.4 kgm^{-2} with SoC.

The modelled evolutions of HbA1c and BMI after treatment discontinuation differ depending upon whether the patient does not have or has diabetes. Those without diabetes typically have an annual increment applied equally in each arm, though possible subject to maxima and minima bounds. Those with diabetes have the updated UKPDS risk factor evolution equations applied. SBP is the exception, the company applying a risk factor evolution equation it has derived from data from one of the Framingham papers to both those without and those with diabetes.

These risk factor evolutions can be illustrated for a 60 year old white man, with the mean EMPA-KIDNEY baseline risk factor values. The annual discontinuation rate of 14% for empagliflozin and 13% for placebo suggests a median time on treatment of around 6 years. The following assumes that the patient remains on treatment for six years and then comes off treatment, though it should be borne in mind that the duration of treatment in the model is affected by other aspects such as receiving renal replacement therapy. The modelled durations of treatment differ by arm; e.g. the company base case anticipates 5.9 years on empagliflozin and 4.2 years on placebo. It also assumes that the patient does not have any events that would change the evolutions of the risk factors; e.g. developing diabetes.

Without diabetes



With diabetes

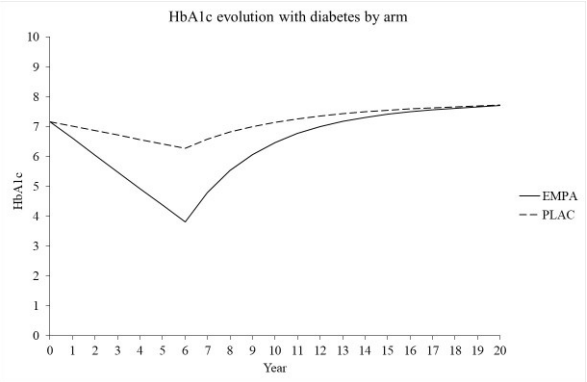


Figure 27: Modelled evolution of HbA1c

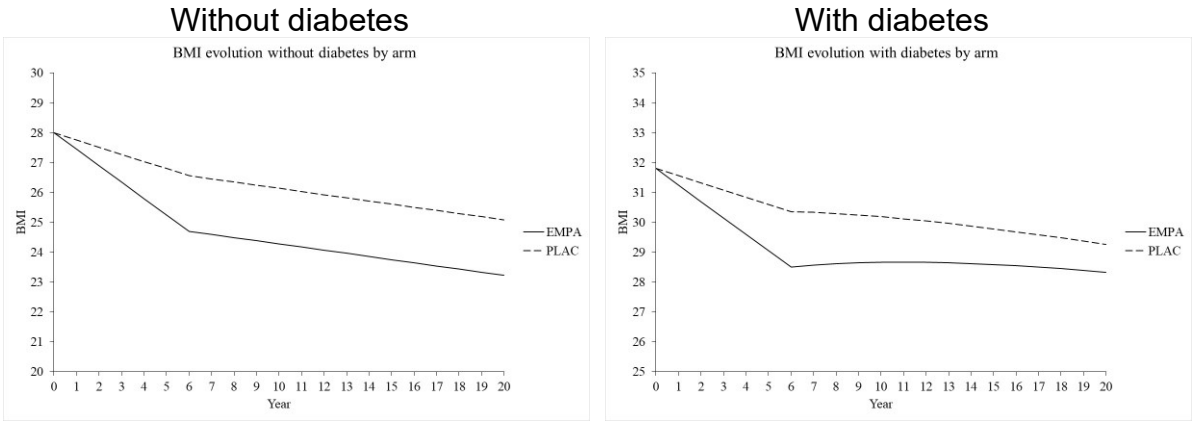


Figure 28: Modelled evolution of BMI

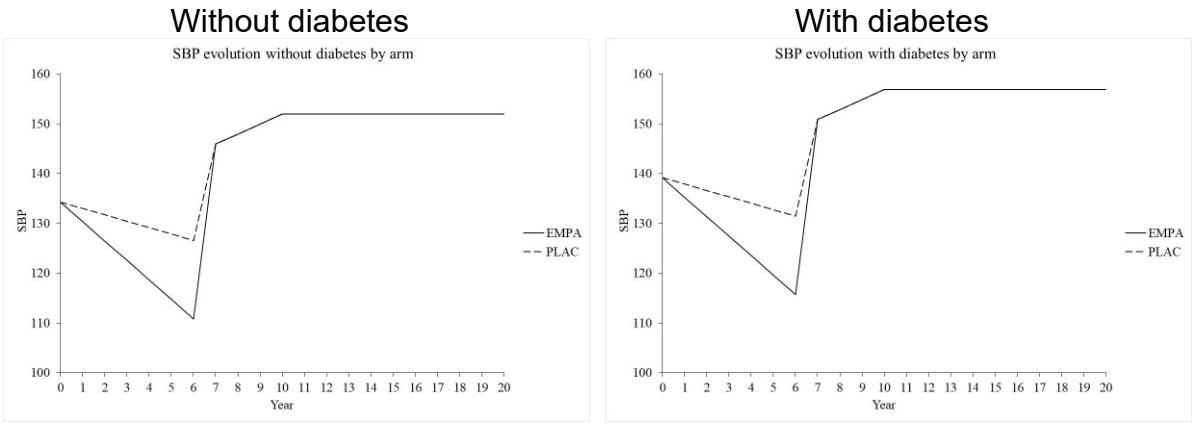


Figure 29: Modelled evolution of SBP

Note that the modelled evolution of SBP when off treatment appears quite erratic, and quite different for the different patients modelled. This aspect of the EAG rebuild may require confirmation by the company.

An initial objection to the modelled evolution of the risk factors is that the average annual rate of change observed during EMPA-KIDNEY is reapplied every annual model cycle for the duration of treatment. The company has not stated how these annual changes have been estimated, but extrapolating them beyond the mean follow-up of EMPA-KIDNEY seems questionable, particularly in the light of the assumptions made during previous assessments of empagliflozin for type 2 diabetes.

The modelled risk factor evolution after discontinuing treatment for those without diabetes is also questionable. It typically retains the full modelled net benefit at treatment cessation, rather than showing any convergence as happens among those

with diabetes. This has knock on effects within the modelling. For instance, HbA1c affects the probability of developing diabetes with diabetes in turn affecting the probability of CHD, CVD, HHF and of particular importance to the model renal replacement therapy.

EAG recollection of previous STAs of empagliflozin for T2DM is that the relevant trial treatment effects were applied only once. The debate was then how much and/or how fast the risk factors would converge between the arms, with the UKPDS risk factor evolutions tending to make them converge.

The EAG thinks that the HbA1c, BMI and SBP treatment effects should only be applied for the average EMPA-KIDNEY follow-up which given the model structure implies for only two years. But the EAG cannot revise the model to address the questionable handling of the evolution of risk factors after this period, or after treatment cessation. The EAG will present a scenario of not applying the annual treatment effects for HbA1c, BMI and SBP due to the model not having the option of assuming that these risk factors converge over time.

4.15.15. Discontinuation rates

As reviewed in section **Error! Reference source not found.** a competing risks analysis suggests discontinuation rates may be higher among those who survival than assumed for the base case: 10.8% rather than 12.6% for empagliflozin and 12.4% rather than 14.2% for placebo. The EAG will apply these estimates, while recognising that not all competing risks may have been accounted for within this.

4.15.16. Renal replacement therapy: modality by age

For those under 80 years of age the model assumes that same proportion of patients will receive HD, 73%, PD, 19%, and kidney transplant, 8%, regardless of age. For those over 80 year of age it is assumed that none receive kidney transplant.

The UKRR 2021 report shows a strong relationship between age group and renal replacement modality.

Table 82: Renal replacement modality by age group: 2021

Age	HD	PD	Transplant
18-34	57%	28%	16%
35-44	59%	27%	14%
45-54	62%	24%	15%

55-64	72%	19%	10%
65-74	77%	17%	6%
75-84	81%	18%	1%
85+	83%	17%	0%

Younger patients are considerably more likely to receive a kidney transplant, and to a lesser degree peritoneal dialysis, while older patients are more likely to receive haemodialysis.

Dialysis is expensive, annual costs of £27,606 for haemodialysis and between £29,871 and £33,388 for peritoneal dialysis, and for the company base case there is an ongoing KDIGO related annual cost of between £1,770 and £4,604. It is also associated with a low quality of life, 0.560 for haemodialysis and 0.580 for peritoneal dialysis. Maintaining a patient on dialysis has an ICER of between around £52,500 and £65,500 per QALY, or a net health benefit at a willingness to pay of £20,000 per QALY of -0.909 QALYs and -1.320 QALYs.

Kidney transplant is also expensive, between £34,700 and £37,284, but has a 97% success rate and if successful improves patients KDIGO health state to (G3a, A1). This improves their quality of life and reduces their KDIGO annual routine maintenance cost. The company model assumes that those over 80 years do not receive kidney transplant. The above suggests 75 years might be more reasonable.

It is difficult to speculate upon what the overall effect of taking into account the relationship between age and renal replacement modality would have upon the cost effectiveness estimate. Addressing it would require quite considerable reworking of the company model. The EAG cannot explore this within the time constraints of the assessment but will revise the maximum age for transplant to 75 years.

4.15.17. Renal replacement therapy: age related mortality

The model assumes the same annual mortality for those receiving haemodialysis, 17.1%, peritoneal dialysis, 8.6%, and kidney transplant in the year of transplant, 1.6%, for those up to 80 years of age. For those above 80 years of age it is assumed that there is no kidney transplant, with the probability of this subsequent to haemodialysis and peritoneal dialysis being reapportioned and so increasing the annual mortality for those receiving haemodialysis, to 21.8% and for those receiving

peritoneal dialysis to 13.2%[14]. It can be noted that the UK median age of those receiving RRT of 63.7 years is very similar to the mean of 63.3 years of EMPA-KIDNEY.

The low average mortality for kidney transplant in is in part a reflection of it being younger patients who tend to receive kidney transplants. Similarly, the high average mortality rate for haemodialysis is in part a reflection of it being the main renal replacement therapy among older patients.

There is a strong relationship between one year survival and age, as shown in Figure 30 below.

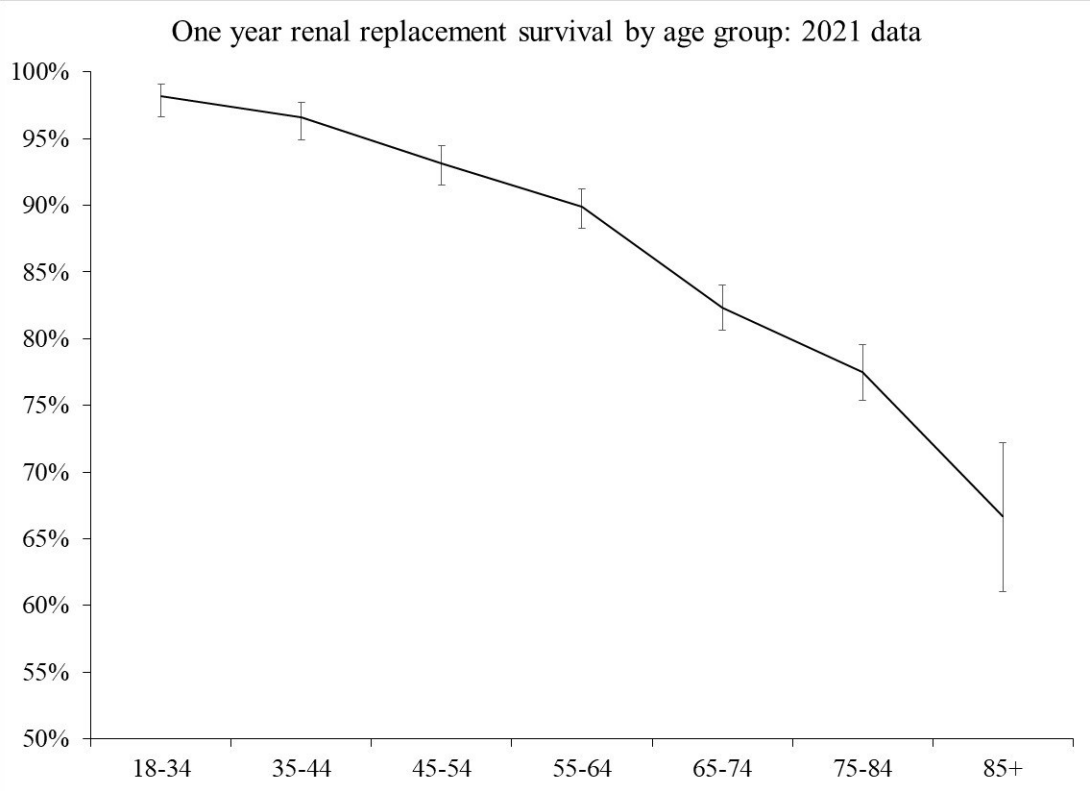


Figure 30: One year renal replacement survival by age group

Unfortunately, the UKRR 2021 report does not further disaggregate this by renal replacement modality. Were this possible, while the curve would probably not be as steep as in Figure 30 the EAG thinks that it is likely there would still be a relationship between age and one year survival due to younger patients tending to be those

[14] This aspect of the model was corrected by the company in the 01-Aug-2023 model submitted at clarification.

receiving kidney transplant. It should also be borne in mind that this is the one year survival, and the average annual survival thereafter might be quite different.

What the effect assuming too high an RRT mortality rate younger patients and too low an RRT mortality for older patients is difficult to say. Too high an RRT mortality rate means that the adverse cost effectiveness consequences of going on to dialysis will be experienced for longer. Progression to RRT is slower in the empagliflozin arm and faster in the SoC arm. It seems likely that too high an RRT mortality rate biases the analysis against empagliflozin, while too low an RRT mortality rate biases the analysis in favour of empagliflozin. The effects of this may also be non-linear in age, though this is complicated by discounting.

4.15.18. Annualization and compounding of risks

The risk functions for the various events within the model provide a probability estimate for a multi-year period.

- The probability of developing heart failure: a 5 year risk function
- The probability of developing diabetes: a 10 year risk function
- The probability of a 1st CVD event: a 10 year risk function
- The probability of receiving RRT: a 5 year risk function

These multi-year probabilities are annualised by assuming a constant annual risk according to $P_1 = 1 – (1 – P_T)^{1/T}$ where T is the number of years that the multi-year probability relates to.

It may not be reasonable to assume a constant annual risk. A 10 year probability of diabetes of 25% does not necessarily imply that the probability of developing diabetes this year is 2.8%. Risk factors tend to worsen over time and the 10 year probability of diabetes will encompass this. There are reasons to think that the annual risk of developing diabetes and the other events modelled is not constant but tends to increase over time. The model may tend to estimate that patients have events sooner than was observed within the data that the multi-year risk functions were estimate from.

Related to this but distinct from it is that the model re-estimates patients' multi-year risks each year of the model and then annualises them. For instance, the 10 year

diabetes risk for a patient may be estimated as 25% in the first year of the model, this annualising to 2.8%. When the 2.8% is compounded over 10 years this returns the 25% estimate. But the model updates the ten year risk each annual model cycle as patient's risk factors worsen. For the sake of argument suppose that there is a 1% annual increase in the 10 year risk yielding estimates of 25%, 26%, 27% … 34% and annualised estimates of 2.8%, 3.0%, 3.1% … 4.1%. When these annualised estimates are compounded they yield a 30% 10 year probability of rather than the observed 25% ten year probability. The degree of bias that results increases with the modelled rate of increase in the annual risk, this frequently being an order of magnitude greater than 1% for RRT.

It seems possible that the model estimates events occurring too early and it seems likely that the model estimates too many events occurring. The EAG thinks that both of these are likely to bias the model in favour of empagliflozin. It is not possible to quantify the extent of any bias and there is no obvious way of addressing this within the model structure.

4.15.19. Choice of eGFR threshold for RRT risk function

Related to the concerns of section **Error! Reference source not found.** above, the company assumes that the 5 year risk of RRT applies once a patient worsens to an eGFR of 15ml/min/1.73m^2. As shown in section **Error! Reference source not found.** above this means that those who worsen to an eGFR of 15ml/min/1.73m^2 are modelled as having a probability of renal replacement therapy that year of around 40% if non-diabetic and 50% if diabetic.

Much if not most of the data used to estimate the risk equations related to eGFR values that were somewhat better than an eGFR of 15 ml/min/1.73m^2. Extrapolating the risk equations to eGFR values at and below 15 ml/min/1.73m^2 may not be valid.

The 2021 UKRR report shows that for those starting haemodialysis the geometric mean (95% C.I.) eGFR was around[15] 6.8 (6.7, 6.9) ml/min/1.73m^2 while for those starting peritoneal dialysis it was 7.4 (7.2, 7.6) ml/min/1.73m^2. The implied sample standard deviations are naturally somewhat larger than the standard errors of the means, as implied by the 95% C.I.s, given sample sizes of 5,372 and 1,564

[15] Values taken from graph: Figure 2.9

respectively, but the medians (IQR) are reported as 7 (5, 9) ml/min/1.73m^2 for haemodialysis and 8 (6, 9) ml/min/1.73m^2 for peritoneal dialysis. Transplant typically occurred at better eGFR values with the geometric mean (95% C.I.) eGFR being around 9.7 (9.2, 10.3) ml/min/1.73m^2. While the data may be somewhat skewed, the UKRR figures suggest very few patients start dialysis with an eGFR of around 15 ml/min/1.73m^2, considerably less than 40%-50%. This is aligned with the NICE guidance on RRT for CKD, NG107, which states "*Consider starting dialysis when indicated by the impact of symptoms of uraemia on daily living, or biochemical measures or uncontrollable fluid overload, or at an estimated glomerular filtration rate (eGFR) of around 5 to 7 ml/min/1.73m^2 if there are no symptoms*".

While imperfect the EAG will retain the company base case assumption for its revised base case. It will present two scenario analyses that apply thresholds of 10 and of 7 ml/min/1.73m^2 for the application of the RRT risk equations.

4.15.20. Choice of RRT risk function

The company selects the function of Tangri et al because "*This version is based on the most recent data and the largest number of cohorts (pooled North America and non-North America). The 6 variable option was selected over the 4 variable option as it includes the risk factors diabetes and hypertension, and so predictions could be sensitive to these comorbidities*". The EAG thinks that the more natural selection for current purposes is the function of Major et al[45] because this uses UK data. It does have the potential downside of not including diabetes as a risk factor, but it can be noted that the Major et al data set included diabetes status so Major et al may have this prior to finalising their RRT risk function.

4.15.21. Model indeterminacy

The model aims to comprehensively model the incidences and effects of events related to CKD. But for many of the events that are modelled it is assumed that some or all of their effects upon costs and/or QALYs are captured by the KDIGO related costs and KDIGO related quality of life values taken from the literature. For instance, the effects of stroke upon inpatient costs are explicitly modelled, the follow-up costs appear to include outpatient costs[16] but in general outpatient costs are assumed to

[16] Values are taken from an abstract that notes costs were included for "*drugs, hospitalisations and visits*".

be accounted for within the KDIGO health state specific costs of Pollock et al. Similarly, quality of life effects for some complications are assumed to be accounted for within the KDIGO health state specific values of Jesky et al while others are explicitly modelled. Sepsis is modelled as an event for costing purposes but its quality of life effect is assumed to be within the KDIGO health state specific values.

The model is neither fish, modelling patients' movement through KDIGO health states and applying the KDIGO health state specific cost and quality of life values from the literature, nor fowl, explicitly modelling CKD related events and their effects. At present it sits a little unhappily between the two.

4.16. EAG critique of the handling of quality of life within the model

4.16.1. KDIGO utilities and complication disutilities: Double counting

The KDIGO health state utilities have a gradient, worse KDIGO health states having a worse quality of life. This seems likely to be due to the complications of CKD increasing as patients' KDIGO health state worsens. Applying additional disutilities for these complications is likely to double count their effect.

The quality of life values taken from Liem et al[52] for haemodialysis and peritoneal dialysis are based upon a systematic review of the literature, the values selected being restricted to the subset of papers reporting EQ-5D index values. The EAG has not reviewed all of these, only examining the largest study which accounted for 35% of the pooled haemodialysis patients and 26% of the pooled peritoneal dialysis patients. This Swiss study sent EQ-5D questionnaires to 558 haemodialysis patients and 64 peritoneal dialysis patients, with response rates of 82% and 78% respectively. The responses were valued using the UK social tariff, yielding mean quality of life values for those on haemodialysis of 0.62 and for those on peritoneal dialysis of 0.58. But these values are not adjusted for any ongoing comorbidities so will include the effects of the other complications that are modelled so double counting their effects[17]. This seems likely to apply to the other papers within the Liem et al meta analysis.

[17] This assumes that any complications modelled as concurrent to dialysis have their disutilities applied to the dialysis quality of life values.

Related to the this, the KDIGO health state specific quality of life values of Jesky et al may have also included the effects of renal replacement therapy. They note that "*Individuals requiring immunosuppression for immune related renal disease, or who has commenced renal replacement therapy (RRT) were not eligible for recruitment*" but it appears that those developing ESKD and requiring RRT would remain within the data set, their patient group with 10 year follow up in a sense reflecting the current modelled cohort flow.

The issues around the quality of life values for RRT cannot be fully addressed by the EAG, other than to supply a scenario analysis that sets the RRT quality of life to that of Jesky (G5, A3).

The EAG will present three scenario analyses: (1) assuming a flat KDIGO quality of life value of 0.85 and applying the complication disutilities, and (2) applying the KDIGO quality of life values of Jesky et al but not applying the complication disutilities also assuming those with RRT have the (G5, A3) quality of life, and (3) as per the company base case but assuming those with RRT have the (G5, A3) quality of life. These may tend to overstate any effects of double counting and so should be viewed as illustrative.

4.16.2. Dialysis quality of life values

As reviewed in the previous section the EQ-5D values for dialysis may double count the quality of life effects of the other complications of CKD. The review of Liem et al[52] also provides TTO and standard gamble utilities pooled across the values in the literature using a random effects model.

Table 83: Liem et al: Dialysis quality of life method

	EQ-5D	TTO	SG
Peritoneal dialysis	0.58	0.73	0.78*
Haemodialysis	0.56	0.61	0.75
* Simple weighted average rather than random effects model			

The EAG has not reviewed all the papers underlying these estimates. It had thought that the time trade off and standard gamble might avoid the problem of double counting the effects of other complications depending upon the health state vignettes presented. The largest study for TTO and SG among those with haemodialysis, accounting for 40% of patients, was among those on dialysis and asked them to

trade their current health state against not having "*the burden of your kidney disease*". As such, some or all of the TTO and SG papers seem as likely to include the effects of CKD complications as the EQ-5D papers. The EAG only notes the very different values from the different methods, the TTO and SG values being more aligned with the KDIGO G5 values.

4.16.3. Chronic conditions disutilities

The company model assumes that events other than RRT such as stroke only affect quality of life in the year in which they occur. The company describes this as "*conservative*" but this seems to be unlikely to be the case. The company base case model (multirun) estimates longer survival and higher complication costs in the empagliflozin arm for all complications other than RRT, where RRT is modelled as having an ongoing quality of life effect. If other complications have ongoing quality of life effects the model is probably biased in favour of empagliflozin.

4.16.4. Complications' disutilities summation vs maximum

Jesky et al performed univariate regression analyses to determine the impact of individual variables on the EQ-5D values all of which were individually statistically significant. This was augmented by a multivariate analysis that removed non-significant variables until the remaining variables achieved statistical significance. Unfortunately, the multivariate analysis included the Charlston comorbidity index which reduces the usefulness of the analysis. The EAG reports the univariate analyses central values that are most relevant for current modelling purposes, alongside the multivariate analysis final central estimates.

Table 84: Jesky et al: Quality of life by variable, including comorbidities

	Univariate	Multivariate
Age (per 10 years)	-0.034	..
Female	0.042	0.045
Unemployed	-0.263	-0.199
Retired	-0.206	-0.122
Current smoker	-0.068	-0.104
Past smoker	-0.067	-0.028
BMI	-0.009	-0.006
Charlston comorbidity index	-0.028	-0.014
Diabetes	-0.108	-0.449
COPD	-0.102	
CVD	-0.094	

IHD	-0.127	-0.056
PVD	-0.143	
Log C-reactive protein	-0.051	-0.021

The multivariate analysis is of limited direct use to the modelling due to in part to the presence of aspects that are not modelled, and also due to the inclusion of the Charlston comorbidity index. But it does appear to show that when comorbidities are examined in isolation their apparent effect is perhaps around double that when examined in conjunction with other comorbidities. The exception to this and a potential difficulty is the dominating effect of diabetes going from the univariate to the multivariate, an increase from -0.108 to -0.449.

The current EAG understanding is that the model sums the disutilities of the comorbidities experienced. The above suggests that this may overestimate the effect when patients experience a number of comorbidities. EAG recollection of the iQVIA Core Diabetes Model is that the default calculation is to apply the maximum disutility from among the disutilities of the complications experienced. The most reasonable estimate may lie somewhere between these two methods.

Time constraints mean that the EAG has not had time to explore this as a scenario. The EAG thinks it would be helpful for the model to be amended to permit a choice between summation of complications' disutilities and applying the maximum disutility of the complications' modelled.

4.17. EAG critique: costs within the model

4.17.1. KDIGO health state costs

The EAG thinks that the handling of KDIGO health state costs is unusual. The company excludes inpatient costs from the KDIGO health state costs due to the modelled events being associated with an inpatient cost, so avoiding double counting. The cost gradient across the KDIGO health state costs that are applied is mainly due to increasing outpatient costs as the KDIGO health state worsens. This increase in outpatient costs seems likely to be linked to the increased complications of CKD.

Table 85: Annual costs by KDIGO health state: Outpatient vs Total (excl. Hosp)

	Outpatient costs			Total costs (excl. Hospitalisation)		
	A1	A2	A3	A1	A2	A3
G1	..	..	..	£1,187	£1,488	£1,941
G2	£454	£566	£870	£1,187	£1,488	£1,941
G3a	£469	£535	£813	£1,221	£1,443	£1,901
G3b	£534	£633	£1,210	£1,411	£1,666	£2,309
G4	£725	£857	£1,509	£1,770	£2,075	£2,790
G5	£928	£1,195	£3,399	£2,000	£2,445	£4,604

Rather than only associating the complications of diabetes with inpatient costs, because the model attempts to include a wide range of complications of CKD to the extent of being all encompassing it would seem to be more consistent to associate the modelled complications with both inpatient and outpatient costs.

An alternative is to not associate the complications of diabetes, other than renal replacement therapy, with any costs and apply the full KDIGO health state costs of Pollock et al. The EAG will explore this as a scenario analysis. Due to Pollock et al not having estimated critical care costs for G5 due to small patient numbers this will assume the G5 critical care costs are the same as those for G4. This may seem a gross assumption, but the critical care costs for G2 through to G4 do not show any real gradient.

4.17.2. Costs of ESKD and renal replacement therapy

The cost of conservative management for those in G5 is drawn from Agus 2017.[53] This was a study of 42 UK patients who had refused dialysis and who consequently are likely to have more advanced disease than just having entered G5. The average age of patients was 80 years which also underlines that these were may have been patients refusing dialysis on grounds of infirmity. Within the model these costs are typically applied to those entering G5 prior to receipt of renal replacement therapy for whom costs might be anticipated to be somewhat lower.

It appears that the £6,335 is in addition to the £2,000, £2,445 and £4,604 annual KDIGO health state cost. While Agus et al is only available as an abstract it suggests that all NHS costs were included. As a consequence, at a minimum the KDIGO G5 health state costs should be subtracted from the £6,335 cost.

The EAG thinks that it is likely that the cost of conservative management of ESKD is too high in the model. A scenario analysis that removes the £4,604 (G5, A3) KDIGO health state cost from it would reduce the ESKD (non RRT) costs and any associated net cost savings by 73%.

At £29,871 for ambulatory peritoneal dialysis, ££33,388 for automated peritoneal dialysis and £27,606 for haemodialysis when averaged they are that bit lower than the £32,360 of TA775 of dapagliflozin which was in turn based upon the NG107 guidance covering renal replacement therapy and conservative management. The NG107 cost included a 15% allowance for access related procedures, complications, health care visits and drugs and a 13% allowance for the cost of transport. Since Pollock et al excluded those undergoing RRT from their costings it is unclear to what degree is any summing the KDIGO G5 health state costs double counts aspects such as outpatient visits.

The costs of kidney transplant, £37,284 from a living donor and £34,700 from a deceased donor, with £6,335 annual follow up costs are stated as being estimated using the same method of TA775 of dapagliflozin for CKD but differ from the £27,032 initial cost and £5,949 follow up cost of TA775, being around 33% and 6% higher.

The EAG will present a scenario analysis that reduces the costs of conservative management by an admittedly arbitrary 50% and the costs of renal replacement therapy by 15%.

4.17.3. Complication costs: Inpatient and Outpatient

The model applies the same costs for complications for those with and those without T2DM. For the incident year these are typically weighted averages of NHS reference costs for a range of non-elective long term inpatient costs, while for subsequent annual ongoing costs these are taken from references in the literature.

As a cross check, the UKPDS 84 provides a costing model that estimates inpatient and outpatient costs for those with T2DM. The total annual inpatient and outpatient costs for the complications modelled within the UKPDS 84,[55] net of those for a patient with no complications, are presented below for patients aged 60 and 70 years. This assumes that 67% are male as per the EMPA-KIDNEY baseline, but the UKPDS 84 net costs for male and female are generally closely aligned and rarely

more than 5% different. These costs are presented for the incident year and for the subsequent ongoing years.

Table 86: Complication costs: UKPDS84 IP and OP costs vs total company

	UKPDS 84					
	Age 60		Age 70		Company	
	Incident	Ongoing	Incident	Ongoing	Incident	Ongoing
Fatal MI	£602		£679			
Non fatal MI	£7,408	£995	£7,643	£1,285	£3,136	£705
Fatal stroke	£3,416		£3,482			
Non fatal stroke	£8,109	£1,058	£9,074	£1,354	£6,278	£1,097
Fatal IHD	£3,203		£3,324			
IHD	£11,253	£1,047	£11,929	£1,369		
Heart failure	£3,741	£1,725	£4,075	£2,121	£4,093	£941
Blind one eye	£2,529	£234	£2,883	£239		
Amputation	£13,095	£2,842	£13,501	£3,284	£10,082	£0

Compared to the UKPDS84 total IP and OP costs, the company cost estimates may be too low for MI, stroke and amputation during the incident year, too low for heart failure in subsequent years and considerably too low for amputations in subsequent years. A caveat to this is the large difference in incident year costs of non-fatal MI and stroke compared to fatal MI and stroke. However, the company assumes that the outpatient costs of the complications are within the KDIGO health state costs which could account for some of this.

4.17.4. Complication costs: PSS

The model does not include any PSS costs for complication costs. Some events will result in some patients incurring PSS costs, such as those entering residential care as a result of a stroke. These costs may be substantial and are likely to be incurred for the remainder of the patient lifetime. The model consequently underestimates the NHS and PSS costs of complications.

4.18. EAG Critique: Minor Issues

The EAG groups what it thinks are likely to be minor issues together when generating **Error! Reference source not found.** that outlines the effects of the EAG amendments upon the company base case. Most readers will want to skip this section and move forward to section **Error! Reference source not found.** that presents the cost effectiveness results.

4.18.1. Minor Issue: Baseline eGFR and uACR by KDIGO state

Despite eGFR being a continuous variable the model assumes that for a patient within a particular KDIGO health state their baseline eGFR is the EMPA-KIDNEY mean baseline eGFR for that KDIGO health state: 70, 49, 36 and 25 ml/min/1.73m^2 for eGFR health states G2, G3a, G3b and G4 respectively. This also applies to the modelled baseline uACR values, these being 10, 110 and 1,102 mg/g for uACR health states A1, A2 and A3 respectively. This results in the modelled baseline (eGFR, uACR) values by KDIGO health state.

Table 87: Baseline eGFR and uACR values by KDIGO health state

		uACR		
		A1	A2	A3
eGFR	G1	..	..	..
	G2	(70, 10)	(70, 110)	(70, 1,102)
	G3a	(49, 10)	(49, 110)	(49, 1,102)
	G3b	(36, 10)	(36, 110)	(36, 1,102)
	G4	(25, 10)	(25, 110)	(25, 1,102)
	G5	..	..	..

The EAG thinks that baseline eGFR and uACR should be sampled as continuous variables. At clarification the company provided the distributions for these but EAG sampling from these does not result in the stated means. As a consequence, though the EAG thinks that eGFR and uACR should be sampled as continuous variables the EAG revised base case retains the sampling of the company base case.

4.18.2. Minor Issue: Baseline characteristics: Sampling and covariances

The company model assumes that there is no association between baseline characteristics. The EAG had anticipated that due to eGFR and uACR being associated with kidney function that there would be a relationship between the two. But variance-covariance data supplied by the company at clarification and sampled using bootstrapping by the EAG suggests that there is not a significant relationship between these. The EAG will independently sample baseline eGFR and uACR as outlined in section **Error! Reference source not found.** above.

At clarification the company has provided the association between age and the dichotomous variables that are used within the model. These do appear to show an association with the complications of CKD typically increasing with age.

Table 88: Baseline proportion comorbidities by baseline age: All patients

	Baseline Age					
	≤ 40	41-50	51-60	61-70	71-80	≥ 81
Prior CVD	4%	7%	17%	30%	38%	47%
Hypertension	90%	90%	89%	85%	82%	74%
Prior heart failure	1%	2%	7%	11%	15%	18%

Table 89: Baseline proportion comorbidities by baseline age: Diabetic

	Baseline Age					
	≤ 40	41-50	51-60	61-70	71-80	≥ 81
Prior CVD	10%	12%	26%	36%	42%	49%
Hypertension	86%	88%	88%	85%	85%	81%
Prior heart failure	4%	4%	11%	13%	17%	18%

Table 90: Baseline proportion comorbidities by baseline age: Non-diabetic

	Baseline Age					
	≤ 40	41-50	51-60	61-70	71-80	≥ 81
Prior CVD	3%	5%	12%	22%	33%	44%
Hypertension	90%	90%	90%	85%	79%	68%
Prior heart failure	1%	1%	4%	7%	12%	18%

The baseline proportions with comorbidities varies by age and by subgroup. The EAG will sample these reflecting the association with age.

4.18.3. Minor Issue: Truncated sampling of baseline age

The company model typically samples baseline characteristics from EMPA-KIDNEY summary statistics, assuming they are normally distributed. To avoid sampling extreme values the company model truncates these distributions. This appears to lead to little bias within the sampling, with the exception of baseline age. This is due to an imposed 80 year maximum despite 6% of EMPA-KIDNEY patients being above 80 years at baseline. When sampled a mean age of 61.0 years results rather than the EMPA-KIDNEY mean age of 63.3.

The company model noted a maximum age of 94, whereas the actual inputted maximum is only 80. The maximum of 80 was apparently based upon Matsushita 2021., The maximum age was within EMPA-KIDNEY was 94 years. Sampling with a maximum of 94 years resulted in 5% of patients being sampled as over 85 whereas in EMPA-KIDNEY this was only 2%. While this may be a concern the EAG thinks that the sampling bias that results from assuming an 80 year maximum is more of a problem. A 94 year maximum results in a mean of 63 years, which is aligned with the

input values. When sampling according to company method the EAG prefers a maximum of 94 years for these reasons.

4.18.4. Minor Issue: Logarithm base for annual CVD risk

The company uses Log_{10} rather than Log_8 when calculating the 10 year risk of CVD (personal communication: S Ballew, 4 Aug 2023).

4.18.5. Minor Issue: English and Welsh mortality data

The EAG has not been able to match the England and Wales life table with that of the model, but the annual proportions dying, q_x, for the three year life table 2017-2019 are similar. The company may have used mortality data from a single year life table.

Of more concern is that the company has used 2020 data for excluding deaths from the complications that are modelled as having mortality effects from all cause mortality, and when calculating the general population CVD mortality risk. The 2020 data may be affected by Covid.

The EAG thinks it best to use 2017-19 life tables and 2019 deaths from the complications that are modelled. This mainly affects the estimated general population risks of death from CVD. The overall effect upon model outputs is expected to be slight.

4.18.6. Minor Issue: Conversion of proportions to hazards/rates

The model converts the proportion dying within the life tables, q_x, to a hazard or a rate according to $-Ln(1-q_x)$. This is common within health economic modelling but is not something the EAG understands the need for. For instance, within the UK life tables the proportion dying[18] within a year, q_{xt}, = $(S_t-S_{t+1})/S_t$. Converting q_{xt} to a hazard/rate and applying it to S_t does not result in S_{t+1}. But the effect is minimal.

4.18.7. Minor Issue: Age weighting quality of life

The model does not apply age weighting of quality of life values, despite having a 50 year time horizon. The EAG thinks that age weighting using the standard reference,

[18] Generally $d_x = q_x \times l_x$ and $l_{x+1} = l_x - d_x$: Methodology worksheet of UK life tables. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

Ara and Brazier,[56] should at a minimum be explored. The EAG will apply age weighting in its revised base case.

4.18.8. Minor Issue: Costs: Type 2 diabetes treatment costs

The model does not include any additional costs for the treatment of T2DM, assuming that these are within the health state cots estimated of Pollock et al.[57] This may be the case for aspects of care such as GP visits, but Pollock et al do not include medication costs, insulin costs, pump costs, test strips, etc.. These costs seem likely to be non-trivial compared to the KDIGO health state costs for the better health states; e.g. (G3a, A1) of £1,221 given that over half of EMPA-KIDNEY patients with diabetes were using insulin.

The EAG thinks it would be better practice to increase the annual costs of Pollock et al for diabetic patients by around £250 on the basis of patients mainly being restricted to those on monotherapy, SGLT2s otherwise probably forming part of their dual or triple therapy, and those on insulin. But given the additional discounted survival of perhaps around 2 years as per the company base case this in itself will not particularly affect net costs or the overall cost effectiveness estimate.

4.18.9. Minor Issue: Overestimation of metabolic acidosis

The modelling of metabolic acidosis treats the prevalence proportions reported by Moranne et al[48] as the annual risks of developing the disorder, with the disorder persisting for the remainder of the patient lifetime. This will estimate the correct prevalence for the 1st year of the model, but for each subsequent annual model cycle will incorrectly further increase the proportion of patients with the disorder. The EAG will amend the model in sensitivity analysis SA14 so that it does not assume persistence of metabolic acidosis.

The EAG also notes that the economic model states for the costs of the other metabolic disorders that "*These inputs are applied as a fixed cost per cycle (from onset of complication onwards)*". This is not obviously the case in the modelled prevalences of the other metabolic disorders but may be implemented elsewhere in the model. If this is the case the costs of the other metabolic disorders will be similarly overstated due to in effect overestimating their prevalences.

4.18.10. Minor issue: Undocumented arbitrary assumptions

The model contains some restrictions that are not documented and are not obviously justified given the references.

- The risk equation for CVD is based upon a weighted average of 90% of the calculated baseline risk and 10% of the calculated contemporaneous risk.
- The risk equations for CVD and CVD death have the patient's age as an input. The model caps this at 80 years; i.e. those modelled as being older than 80 years have the risks of an 80 year old applied to them.
- The risk equation for CVD death has the patient's uACR as an input. In general, the model caps the patient's uACR at 7,000mg/g. For the CVD risk of death the model caps this at 300mg/g; i.e. patients in A3 have an A2 risk applied to them.
- General mortality multipliers from Matsushita for A3 not being applied, with those for A2 being applied instead for patients modelled as being in A3.

The EAG explores the effect of removing these model restrictions in section **Error! Reference source not found.** under scenario SA15.

4.18.11. Minor Issue: HbA1c effect units

The EAG has replicated the company approach of inputting HbA1c effects in mmol/mol. This may be an error. It might be correct to convert the stated HbA1c effects to %, though this suggests minimal effect upon HbA1c. The EAG amends the model in sensitivity analysis SA16 to apply the HbA1c effects converted to %, doing so for both the all patient analysis and the diabetic at baseline analysis, the latter being where the effect of this is likely to be greatest.

4.19. Exploratory and sensitivity analyses undertaken by the EAG

4.19.1. EAG modelling caveat

The model is large and complicated with most implemented in Excel but some, necessarily, in Visual Basic. The EAG has attempted to revise the model as outlined below and supplies the company with full documentation of the model changes with full cell referencing. The EAG urges the company to check that the EAG changes are implemented correctly, even if it disagrees with the intended changes.

Throughout section **Error! Reference source not found.** the EAG modelling uses the model (multirun), in effect sampling 20,000 patients as reviewed in section 4.3 above. At clarification the EAG asked the company to state whether the model (multirun) was a correct implementation of this but received no reply.

4.19.2. EAG preferred modelling assumptions

The EAG makes the following changes to the company base case.

- EAG01: Using OC-OT eGFR change estimates rather than OC-AD estimates.
- EAG02: Apply the uACR multipliers in the first year but not thereafter.
- EAG03: Use the probabilities of RRT estimated from UK patient data
- EAG04: Only apply the effects on HbA1c, BMI and SBP for two years

The EAG also makes what it thinks are minor changes to the model, grouped under EAG05 in

- A maximum baseline age of 94 years rather than 80 years.
- Sample baseline comorbidities by age group and diabetes status.
- Apply 2017-19 England and Wales life tables and 2019 complication specific mortality data..
- Correct the CKD patch equation logarithm base for uACR from 10 to 8
- Apply age weighting of utilities.
- Add diabetic treatment costs to the KDIGO health states when modelling those with diabetes.

For the subgroup modelling of those with diabetes and those without diabetes at baseline the EAG applies the subgroup specific eGFR

Table 91: EAG's preferred assumptions: model (multirun): Net QALYs and net costs

Preferred assumption	EAG report	ΔQALYs	ΔCosts
Company base-case (multirun)	4.3, **Error! Reference source not found.**	0.910	-£2,951

Preferred assumption	EAG report	ΔQALYs	ΔCosts
Submitted company model (RS 0.200)	4.3, **Error! Reference source not found.**	0.842	-£6,030
EAG01: OC-OT rather than OC-AD	**Error! Reference source not found.**	0.858	-£2,579
EAG02: uACR multiplier only year 1	4.15.6-4.15.10	0.373	£1,164
EAG03: UK RRT probabilities	**Error! Reference source not found.**	0.918	-£1,975
EAG04: 2 year effect HbA1c, BMI, SBP	4.15.14	0.775	-£4,363
EAG05: Minor changes	**Error! Reference source not found.**	0.971	-£2,201
Cumulative: EAG01 to EAG06	..	0.225	£495

Table 92: EAG's preferred assumptions: model (multirun): ICER and NHB

Preferred assumption	EAG report	ICER	NHB
Company base-case	4.3, **Error! Reference source not found.**	Dominant	1.057
Submitted company model (RS 0.200)	4.3, **Error! Reference source not found.**	Dominant	1.143
EAG01: OC-OT rather than OC-AD	**Error! Reference source not found.**	Dominant	0.987
EAG02: uACR multiplier only year 1	4.15.6 - 4.15.10	£3,119	0.315
EAG03: UK RRT probabilities	**Error! Reference source not found.**	Dominant	1.017
EAG04: 2 year effect HbA1c, BMI, SBP	4.15.14	Dominant	0.993
EAG05: Minor changes	**Error! Reference source not found.**	Dominant	1.081
Cumulative: EAG01 to EAG06	..	£2,201	0.200

The effect of limiting the HbA1c, SBP and BMI effects to only 2 years is counterintuitive. The EAG will explore this before Committee.

4.19.3. EAG base case: All patients: OC-OT

Net costs averaged across all patients and KDIGO health states at baseline are as follows.

Table 93: EAG base case: model (multirun): net costs: All patients

	EMPA	PLAC	Net
Treatment	£2,417	£145	£2,272
KDIGO health state costs	£19,500	£18,969	£531
Renal replacement therapy	£18,419	£21,548	-£3,129
ESKD (non RRT)	£3,093	£3,116	-£23
CVD	£6,446	£6,519	-£73
Anaemia	£3,990	£3,769	£221
Other CKD infections	£13,279	£12,955	£324
Metabolic complications	£7,660	£7,428	£232
Acute kidney injury	£1,007	£1,080	-£73
Infections	£3,348	£3,296	£52
Cancers	£158	£160	-£2
AEs	£233	£70	£162
Total	£79,549	£79,054	£495

This results in the following cost effectiveness estimates.

Table 94: EAG base case: model (multirun): All patients

	EMPA	PLAC	Net
Undiscounted LY	13.182	12.836	0.347
QALY	6.881	6.656	0.225
Cost	£79,549	£79,054	£495
ICER			£2,201
NHB (WTP £20,000/QALY)			0.200

Modelling by baseline KDIGO health state with the model (multirun) yields the following.

Table 95: EAG base case by baseline KDIGO: net QALYs and Costs: All patients

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.007	-0.024	0.436	£2,844	£768	-£795
G3a	0.007	0.202	0.339	£2,790	£1,485	-£2,370
G3b	0.108	0.305	0.324	£1,080	£2,802	-£2,397
G4	-0.014	0.307	0.235	£5,643	£5,479	-£1,061

Table 96: EAG base case by baseline KDIGO: ICERs and NHBs: All patients

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£407k	Dom'td	Dom	-0.135	-0.063	0.476
G3a	£424k	£7,367	Dom	-0.133	0.127	0.458
G3b	£10,021	£9,179	Dom	0.054	0.165	0.443
G4	Dom'td	£17,844	Dom	-0.296	0.033	0.288

The results for (G2, A1) and (G3, A1) largely reflect the HbA1c, SBP and BMI effects. The results for (G2, A2) and (G4, A1) are particularly striking as they suggest that empagliflozin is dominated by placebo. For (G4, A1) this arises at least in part from eGFR changes of [redacted] for empagliflozin compared to [redacted] for placebo for (G4, A1) in the OC-OT analysis. The result for (G2, A2) is more difficult to account for and could be the result of adverse events such as amputations. But the QALY differences are quite small. The general pattern is of a poorer cost effectiveness towards the upper left of the KDIGO distribution and a better cost effectiveness towards the bottom right of the KDIGO distribution.

4.19.4. EAG base case: Patients with diabetes at baseline: OC-AD

Net costs averaged across diabetic patients and KDIGO health states at baseline are as follows.

Table 97: EAG base case: model (multirun): net costs: Diabetic patients

	EMPA	PLAC	Net
Treatment	£2,349	£138	£2,211
KDIGO health state costs	£18,911	£17,864	£1,046
Renal replacement therapy	£12,344	£16,250	-£3,906
ESKD (non RRT)	£2,380	£2,634	-£254
CVD	£8,312	£8,107	£205
Anaemia	£3,311	£3,310	£0
Other CKD infections	£11,907	£11,619	£288
Metabolic complications	£7,017	£6,719	£298
Acute kidney injury	£692	£751	-£59
Infections	£3,100	£2,986	£113
Cancers	£151	£146	£5
AEs	£225	£66	£159
Total	£70,697	£70,590	£107

This results in the following cost effectiveness estimates.

Table 98: EAG base case: model (multirun): Diabetic patients

	EMPA	PLAC	Net
Undiscounted LY	11.635	11.061	0.573
QALY	6.216	5.887	0.329
Cost	£70,697	£70,590	£107
ICER			£326
NHB (WTP £20,000/QALY)			0.324

Modelling by baseline KDIGO health state with the model (multirun) yields the following.

Table 99: EAG base case by baseline KDIGO: net QALYs and Costs: Diabetic patients

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.004	0.732	0.559	£2,756	-£3,188	-£849
G3a	0.008	0.453	0.415	£2,691	£1,328	-£2,542
G3b	0.097	0.468	0.381	£1,504	£2,482	-£664
G4	0.204	0.400	0.395	£4,027	£3,227	-£1,749

Table 100: EAG base case by baseline KDIGO: ICERs and NHBs: Diabetic patients

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£636k	Dom	Dom	-0.133	0.892	0.601
G3a	£348k	£2,930	Dom	-0.127	0.387	0.542
G3b	£15,579	£5,301	Dom	0.021	0.344	0.414
G4	£19,745	£8,068	Dom	0.003	0.239	0.482

The pattern of generally worse cost effectiveness to the upper left of the KDIGO health state distribution and better cost effectiveness to the bottom right of the KDIGO health state distribution is largely maintained for the modelling of those with diabetes at baseline. But the above cost effectiveness estimates should be viewed as exploratory due to them being based upon OC-AD data rather than OC-OT data.

4.19.5. EAG base case: Patients without diabetes at baseline: OC-AD

Net costs averaged across non-diabetic patients and KDIGO health states at baseline are as follows.

Table 101: EAG base case: model (multirun): net costs: Non-diabetic patients

	EMPA	PLAC	Net
Treatment	£2,465	£150	£2,315
KDIGO health state costs	£19,830	£19,676	£154
Renal replacement therapy	£25,207	£27,191	-£1,985
ESKD (non RRT)	£3,856	£3,298	£558
CVD	£5,423	£5,874	-£451
Anaemia	£4,485	£4,242	£243
Other CKD infections	£13,841	£13,750	£92
Metabolic complications	£7,965	£7,931	£35
Acute kidney injury	£1,217	£1,283	-£67
Infections	£3,565	£3,631	-£67
Cancers	£139	£142	-£3
AEs	£245	£69	£176
Total	£88,238	£87,237	£1,001

This results in the following cost effectiveness estimates.

Table 102: EAG base case: model (multirun): Non-diabetic patients

	EMPA	PLAC	Net
Undiscounted LY	14.421	14.456	-0.035
QALY	7.391	7.294	0.098
Cost	£88,238	£87,237	£1,001
ICER			£10,254
NHB (WTP £20,000/QALY)			0.048

Modelling by baseline KDIGO health state with the model (multirun) yields the following.

Table 103: EAG base case by baseline KDIGO: net QALYs and Costs: Non-diabetic patients

	Net QALYs			Net Costs		
	A1	A2	A3	A1	A2	A3
G2	0.048	-0.189	0.430	£2,248	£1,689	-£1,622
G3a	0.007	0.017	0.347	£2,477	£2,074	-£2,070
G3b	0.155	0.160	0.363	£330	£1,368	-£391
G4	-1.317	0.067	0.217	£30,185	£966	-£89

Table 104: EAG base case by baseline KDIGO: ICERs and NHBs: Non-diabetic patients

	ICERs			NHBs		
	A1	A2	A3	A1	A2	A3
G2	£46,805	Dom'td	Dom	-0.064	-0.274	0.511
G3a	£366k	£120,448	Dom	-0.117	-0.086	0.451
G3b	£2,131	£8,533	Dom	0.138	0.092	0.382
G4	Dom'td	£14,424	Dom	-2.826	0.019	0.221

The results for (G2, A2) reflect the central eGFR annual change central estimates of [redacted] for empagliflozin and [redacted] for placebo, with the results for (G4, A1) similarly reflecting eGFR change central estimates of [redacted] for empagliflozin and [redacted] for placebo.

Again, the pattern of generally worse cost effectiveness to the upper left of the KDIGO health state distribution and better cost effectiveness to the bottom right of the KDIGO health state distribution is largely maintained for the modelling of those without diabetes at baseline. But again, the above cost effectiveness estimates should be viewed as exploratory due to them being based upon OC-AD data rather than OC-OT data.

4.19.6. EAG scenario analyses: All patient: OC-OT

Time constraint mean that the EAG can only present scenario analyses for the all patient OC-OT analysis. The effects of these are likely to be similar for the subgroup modelling of those with diabetes at baseline and those without diabetes at baseline that uses OC-AD data. These scenarios will hopefully help Committee decided it preferred set of assumptions, alongside whether it is better to use an OC-AD analysis or an OC-OT analysis.

- SA01: Use OC-AD data.
- SA02: Baseline mean age ±5 years.
- SA03: Duration of eGFR effects of 2, 5 and 10 years.
- SA04: Reapply the uACR treatment effects each year while on treatment.
- SA05: Reapply the uACR treatment effects each year while on treatment and apply the Coresh et al[42] uACR specific estimates.
- SA06: No HbA1c, SBP or weight effects due to the modelled evolution of these after treatment discontinuation.
- SA07: Apply the placebo eGFR effects for those discontinuing treatment.
- SA08: eGFR thresholds for the application of the RRT risk equations of 10 and 7 ml/min/1.73m^2.
- SA09: Flat KDIGO quality of life with all health states being 0.85.
- SA10: No disutility from the modelled complications, also setting the Renal replacement therapy quality of life the same as the quality of life for (G3, A3).
- SA11: Renal replacement therapy quality of life the same as the quality of life for (G3, A3).
- SA12: Reducing the costs of conservative management by 50% and the costs of renal replacement therapy by 15% due to possible double counting.
- SA13: Apply the full KDIGO health state costs of Pollock et al, and remove the event costs other than those for RRT.
- SA14: Not assuming that metabolic acidosis lasts the patient lifetime due to the model structure and inputted data.

- SA15: Remove the apparently arbitrary modelling assumptions.
- SA16: Apply the HbA1c effects as % changes rather than mmol/mol, this appearing to suggest virtually no annual treatment effect upon HbA1c.

This results in the following cost effectiveness estimates.

Table 105: EAG scenario analyses: model (multirun): All patients

	Δ QALY	Δ Cost	ICER	NHB
Base case	0.225	£495	£2,201	0.200
SA01: OC-AD data	0.254	£22	£88	0.253
SA02a: Mean age +5 years	0.216	£762	£3,529	0.178
SA02b: Mean age -5 years	0.224	£58	£258	0.222
SA03a: eGFR effects 2 years	0.177	£1,318	£7,450	0.111
SA03b: eGFR effects 5 years	0.201	£754	£3,751	0.163
SA03c: eGFR effects 10 years	0.219	£597	£2,723	0.189
SA04: On Tx uACR ongoing	0.855	£354	£414	0.837
SA05: SA04 + Off Tx uACR	0.796	-£331	Dominant	0.813
SA06: No HbA1c, SBP, BMI	0.206	£195	£943	0.197
SA07: Placebo eGFR Off Tx	0.226	£743	£3,281	0.189
SA08a: RRT starts at eGFR of 10	0.225	£788	£3,508	0.185
SA08b: RRT starts at eGFR of 7	0.225	£883	£3,919	0.181
SA09: Flat KDIGO QoL	0.241	£495	£2,058	0.216
SA10: No complication disutility	0.213	£495	£2,322	0.189
SA11: RRT QoL as (G5, A3)	0.213	£495	£2,321	0.189
SA12: 85% RRT, 50% ESKD cost	0.225	£975	£4,333	0.198
SA13: Pollock costs throughout	0.225	£2,018	£8,967	0.124
SA14: Acidosis does not persist	0.225	£553	£2,459	0.197
SA15: No arbitrary assumptions	0.250	£1,469	£5,876	0.177
SA16: HbA1c effects in %	0.222	£401	£1,804	0.202

The EAG is confused by SA10 and SA11 effectively resulting in the same results. It has cross checked the implementation of these and has rerun the analyses. It would be grateful if the company could also cross check the implementation of these scenario analyses.

Using the OC-AD data improves the cost effectiveness estimates. The EAG thinks that this argues for OC-OT data being supplied for the subgroups of those with and without diabetes at baseline.

Baseline age has the anticipated effect with cost effectiveness worsening with age.

As would be expected, shortening the duration of eGFR clinical effects worsens the cost effectiveness estimate. Undoing the EAG changes to the uACR fold multipliers improves the cost effectiveness estimate.

Not including the HbA1c, SBP and BMI effects, which the EAG base case already limits to 2 years duration, reduces the net QALYs by around 10% but also reduces the net costs.

Assuming the placebo effects for those off treatment rather than the estimates from the literature has little effect.

Applying different threshold values at which the RRT risk functions begin to apply surprisingly has little to no effect upon net QALYs but increases net costs.

Different treatments of quality of life values have little effect.

Alternative costs for those in G5 and those getting RRT has a reasonable effect upon net costs.

None of the above scenario analyses when viewed in isolation are likely to affect conclusions about the estimated cost effectiveness of empagliflozin across the all patient group. For this group the main concern may be about the reliability of the cost effectiveness estimates as outlined in the validation section 4.12.5, coupled with a secondary concern about whether the most reasonable base case is a combination of some of the above scenario analyses.

The above scenarios are mainly intended to help Committee decide its preferred base case assumptions if it thinks those with diabetes at baseline and those without diabetes at baseline should be analysed separately, as explored in section 4.15.3, and more particularly if they should be analysed by baseline KDIGO health state given the extension to the position sought where standard care without dapagliflozin is the comparator, as explored in section **Error! Reference source not found.**. It is easy to imagine some scenarios combined with KDIGO health state specific analyses resulting in quite high ICERs.

4.20. Conclusions of the cost effectiveness section

The modelling only addresses whether it is cost effective to treat patients with empagliflozin over their lifetime compared to not treating them with empagliflozin. It does not address whether it is more cost effective to reserve empagliflozin treatment

until patients progress to (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state.

The company model is a bit of a mixed bag that accounts for some complications through KDIGO health state specific utilities and costs, some elements through complication specific costs and disutilities and some elements through a mixture of both. In many ways the most coherent approach might be to model the complications of CKD as per the current modelling as necessary to estimate renal replacement therapy and mortality, while accounting for the effects of the other complications of CKD solely through the KDIGO health state specific utilities and costs.

The model appears to underestimate the initial proportion of patients reaching ESKD due to all patients progressing through the model health states at much the same speed. But after a few years the modelled annual incidence of ESKD increases rapidly and is more aggressive than long term follow up data suggests. It seems likely that the model overpredicts the proportion of patients who experience ESKD and in turn receive renal replacement therapy. The model also appears to over predict deaths compared to long term follow up data. The EAG thinks that this biases the model in favour of empagliflozin.

The company base case applies the eGFR and uACR changes from an analysis of all EMPA-KIDNEY patients follow up data. But the model also includes treatment discontinuations. When modelling those on treatment the EAG thinks that analysis of on treatment EMPA-KIDNEY patients data should be applied. For the EAG revised all patient modelling this reduces the net health benefits (NHBs) by around 20%. This data has not been supplied separately for those with diabetes at baseline and those without diabetes at baseline.

The company base case reapplies the 18 month uACR fold multiplier each annual model cycle that patients are modelled as remaining on treatment. Data supplied at clarification suggests that uACR was relatively flat after 18 months and it may be more appropriate to assume a flat uACR thereafter.

The company analysis of the EMPA-KIDNEY data is split according to patients' baseline KDIGO health state. But the model requires data split by patients' start of year health state. The two may be fundamentally incompatible. At a minimum the company needs to present data on how many EMPA-KIDNEY patients changed their

KDIGO health state while on treatment to enable an assessment of the severity of this issue.

The EAG review has identified a number of areas where additional analyses of the EMPA-KIDNEY data may be warranted. These are matters for Committee to decide but the company may wish to review the practicality and desirability of these:

- OC-OT analyses of eGFR and uACR data for those with diabetes at baseline and for those without diabetes at baseline.
- Discontinuation rates by KDIGO health state for all patients, for those with diabetes at baseline and for those without diabetes at baseline.
- A presentation of the numbers of patients changing KDIGO health state during EMPA-KIDNEY by arm for all patients, those with diabetes at baseline and those without diabetes at baseline and if this non-trivial a reanalysis of eGFR changes and uACR changes by start of year KDIGO health state in an OC-OT analysis.

The EAG review has identified some area where further clarification is would be helpful.

- That mortality is applied in the hierarchical fashion as outlined in section 4.9.8.
- That the costs of the metabolic disorders is only applied in the year that they are occur and not since the year that they occur as outlined in section 4.18.9.
- Those in G5 on conservative therapy have a quality of life decrement of zero and not a quality of life of zero.

The EAG review has identified a number of areas where the model amendments might help generalise the model.

- The option to only use the KDIGO health state specific quality of life and costs, coupled with the renal replacement therapy costs should be explored further An option for quality of life being based upon the worst complication disutility rather than the summation of all complications' disutilities.
- Permitting KDIGO health state specific discontinuation rates.
- Sampling baseline eGFR and uACR as continuous variables.

Given the complexity of the model it would be much appreciated if all further company changes to the model could be made to the EAG amended model, with full cell referencing and documentation of the changes made.

4.21. SEVERITY MODIFIERS

The company does not consider severity modifiers.

REFERENCES

1. Baker L. Renal disease. In: Kumar P, Clark M, editors. *Clinical Medicine*. London: Saunders; 1998.
2. Warrell DA, Cox TM, Weatherall D, Benz Jr EJ, Firth JD, eds. *Oxford textbook of medicine*. Oxford University Press; 2003.
3. Kidney Disease: Improving Global Outcomes, CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;**3**(1):1-150.
4. Healthdirect. *Chronic kidney disease*. Healthdirect Australia; 2023. URL: https://www.healthdirect.gov.au/chronic-kidney-disease (Accessed 30 August 2023).
5. Messow CM, Isles C. Meta-analysis of statins in chronic kidney disease: who benefits? *QJM* 2017;**110**(8):493-500. http://dx.doi.org/10.1093/qjmed/hcx040
6. Thomas S, Krimholtz M, Viberti G. Treatment of diabetic nephropathy: the role of strict glucose control. In: Boner G, Cooper M, editors. *Management of diabetic nephropathy*. London: Martin Dunitz; 2003:99-104.
7. Ravid M, Rachmani R. Treatment of diabetic nephropathy: antihypertensive treatment. In: Boner G, Cooper M, editors. *Management of diabetic nephropathy*. London: Martin Dunitz; 2003:105-28.
8. Robertson LM, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* 2007(4):CD002181. http://dx.doi.org/10.1002/14651858.CD002181.pub2
9. Waugh NR, Robertson A. Treatment of diabetic nephropathy: low-protein diet. In: Boner G, Cooper M, editors. *Management of diabetic nephropathy*. London: Martin Dunitz; 2003:129-34.
10. National Institute for Health and Care Excellence. *Type 2 diabetes in adults: management: NICE guideline [NG28]*. NICE; 2015. URL: https://www.nice.org.uk/guidance/ng28 (Accessed 21 August 2023).
11. Kanumilli N, Peach E, Barone S, Arnold M, Tangri N. WCN23-0626 REVEAL-CKD: prevalence of undiagnosed stage 3 chronic kidney disease in England. *Kidney Int Rep* 2023;**8**(3 Suppl):S121-2. http://dx.doi.org/10.1016/j.ekir.2023.02.273
12. Abdul Sultan A, Heerspink H, Arnold M, Pollock C, Garcia Sanchez JJ, Carrero JJ*, et al.* POS-503 Evaluating chronic kidney disease progression: a report from the discover CKD retrospective cohort. *Kidney Int Rep* 2021;**6**(4 Suppl):S218-9. http://dx.doi.org/10.1016/j.ekir.2021.03.531
13. Heerspink H, James G, Nolan S, Carrero JJ, Arnold M, Pecoits-Filho R*, et al.* Evaluating clinical outcomes in patients (pts) with CKD with rapid and non-rapid eGFR decline: a report from the DISCOVER CKD retrospective cohort. *Am J Kidney Dis* 2022;**79**(4 Suppl 2):S31. http://dx.doi.org/10.1053/j.ajkd.2022.01.106
14. Idris I, Zhang R, Mamza JB, Ford M, Morris T, Banerjee A*, et al.* Significant reduction in chronic kidney disease progression with sodium-glucose cotransporter-2 inhibitors compared to dipeptidyl peptidase-4 inhibitors in adults with type 2 diabetes in a UK clinical setting: An observational outcomes study based on international guidelines for kidney disease. *Diabetes, Obesity and Metabolism* 2022;**24**(11):2138-47. http://dx.doi.org/10.1111/dom.14799
15. Rhee JJ, Han J, Montez-Rath ME, Kim SH, Cullen MR, Stafford RS*, et al.* Cardiovascular outcomes associated with prescription of sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with diabetes and chronic kidney disease. *Diabetes, Obesity and Metabolism* 2022;**24**(5):928-37. http://dx.doi.org/10.1111/dom.14657

16. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S*, et al.* Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**(9):839-48. http://dx.doi.org/10.1056/NEJMoa1616011
17. Verma S, McGuire DK, Bain SC, Bhatt DL, Leiter LA, Mazer CD*, et al.* Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: Results of the LEADER and SUSTAIN 6 trials. *Diabetes Obes Metab* 2020;**22**(12):2487-92. http://dx.doi.org/10.1111/dom.14160
18. Granata A, Maccarrone R, Anzaldi M, Leonardi G, Pesce F, Amico F*, et al.* GLP-1 receptor agonists and renal outcomes in patients with diabetes mellitus type 2 and diabetic kidney disease: state of the art. *Clin Kidney J* 2022;**15**(9):1657-65. http://dx.doi.org/10.1093/ckj/sfac069
19. Grams ME, Surapaneni A, Appel LJ, Lash JP, Hsu J, Diamantidis CJ*, et al.* Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study. *Nephrol Dial Transplant* 2021;**36**(9):1685-93. http://dx.doi.org/10.1093/ndt/gfaa364
20. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. http://dx.doi.org/10.1136/bmj.l4898
21. ClinicalTrials.gov. *EMPA-KIDNEY (the study of heart and kidney protection with empagliflozin)*. 2023. URL: https://clinicaltrials.gov/ct2/show/study/NCT03594110 (Accessed 21 August 2023).
22. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S*, et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117-28.
23. ClinicalTrials.gov. *EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with preserved ejection fraction (EMPEROR-Preserved)*. 2022. URL: https://classic.clinicaltrials.gov/ct2/show/NCT03057951 (Accessed 21 August 2023).
24. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M*, et al.* Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021;**385**(16):1451-61. http://dx.doi.org/10.1056/NEJMoa2107038
25. Wanner C, Inzucchi SE, Zinman B, Koitka-Weber A, Mattheus M, George JT*, et al.* Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial. *Diabetes Obes Metab* 2020;**22**(12):2335-47. http://dx.doi.org/10.1111/dom.14158
26. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F*, et al.* Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020;**383**(15):1436-46. http://dx.doi.org/10.1056/NEJMoa2024816
27. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U*, et al.* Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**(15):1425-35. http://dx.doi.org/10.1056/NEJMoa2004967
28. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM*, et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**(24):2295-306.
29. Meraz-Muñoz AY, Weinstein J, Wald R. eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined. *Kidney360* 2021;**2**(6):1042-7. http://dx.doi.org/10.34067/kid.0001172021
30. Beldhuis IE, Martens P, Ter Maaten JM. Early changes in renal function after sodium-glucose cotransporter 2 inhibitor initiation in EMPEROR-Reduced: the end

of the dilemma? *Eur J Heart Fail* 2022;**24**(10):1840-3. http://dx.doi.org/10.1002/ejhf.2659
31. Bolignano D, Zoccali C. Effects of weight loss on renal function in obese CKD patients: a systematic review. *Nephrol Dial Transplant* 2013;**28**(suppl_4):iv82-iv98. http://dx.doi.org/10.1093/ndt/gft302
32. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L*, et al.* Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;**7**(5):344-55. http://dx.doi.org/10.1016/s2213-8587(19)30068-3
33. Campagna D, Alamo A, Di Pino A, Russo C, Calogero AE, Purrello F*, et al.* Smoking and diabetes: dangerous liaisons and confusing relationships. *Diabetology & Metabolic Syndrome* 2019;**11**(1):85. http://dx.doi.org/10.1186/s13098-019-0482-2
34. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;**400**(10365):1788-801. http://dx.doi.org/10.1016/s0140-6736(22)02074-8
35. Neal B, Perkovic V, Zeeuw Dd, Mahaffey KW, Fulcher G, Stein P*, et al.* Rationale, design, and baseline characteristics of the CANagliflozin cardioVascular Assessment Study (CANVAS)—a randomized placebo-controlled trial. *Am Heart J* 2013;**166**:217–23.
36. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of FAERS data. *Diabetes Metab Res Rev* 2017;**33**(8). http://dx.doi.org/10.1002/dmrr.2924
37. National Heart Lung and Blood Institute (NHLBI). *Study quality assessment tools*. Bethesda, ML: National Institutes of Health; 2021. URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Accessed 29 August 2023).
38. Karagkounis D. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors. *Drug Ther Bull* 2023;**61**(7):103-7. http://dx.doi.org/10.1136/dtb.2022.000057
39. Dekkers CCJ, Wheeler DC, Sjostrom CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-Transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. *Nephrol Dial Transplant* 2018;**33**(11):2005-11.
40. Alnsasra H, Tsaban G, Solomon A, Khalil F, Aboalhasan E, Azab AN*, et al.* Dapagliflozin versus empagliflozin in patients with chronic kidney disease. *Front Pharmacol* 2023;**14**:1227199. http://dx.doi.org/10.3389/fphar.2023.1227199
41. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C*, et al.* Technical supplement to chapter 4: searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M*, et al.*, eds. Cochrane handbook for systematic reviews of interventions. Version 6.3 Cochrane; 2022.
42. Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC*, et al.* Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 2019;**7**(2):115-27. http://dx.doi.org/10.1016/S2213-8587(18)30313-9

43. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D*, et al.* A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011;**305**(15):1553-9. http://dx.doi.org/10.1001/jama.2011.451
44. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC*, et al.* Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA* 2016;**315**(2):164-74. http://dx.doi.org/10.1001/jama.2015.18202
45. Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ. The kidney failure risk equation for prediction of end stage renal disease in UK primary care: an external validation and clinical impact projection cohort study. *PLoS medicine* 2019;**16**(11):e1002955.
46. Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A*, et al.* Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. *EClinicalMedicine* 2020;**27**:100552. http://dx.doi.org/10.1016/j.eclinm.2020.100552
47. Runesson B, Trevisan M, Iseri K, Qureshi AR, Lindholm B, Barany P*, et al.* Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine Measurement project. *Nephrol Dial Transplant* 2020;**35**(11):1908-15. http://dx.doi.org/10.1093/ndt/gfz142
48. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP*, et al.* Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;**20**(1):164-71. http://dx.doi.org/10.1681/asn.2008020159
49. Xu H, Gasparini A, Ishigami J, Mzayen K, Su G, Barany P*, et al.* eGFR and the risk of community-acquired infections. *Clin J Am Soc Nephrol* 2017;**12**(9):1399-408. http://dx.doi.org/10.2215/cjn.00250117
50. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE*, et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**(9731):2073-81. http://dx.doi.org/10.1016/s0140-6736(10)60674-5
51. Jesky MD, Dutton M, Dasgupta I, Yadav P, Ng KP, Fenton A*, et al.* Health-related quality of life impacts mortality but not progression to end-stage renal disease in pre-dialysis chronic kidney disease: a prospective observational study. *PLoS One* 2016;**11**(11):e0165675.
52. Liem YS, Bosch JL, Hunink MM. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. *Value in Health* 2008;**11**(4):733-41.
53. Agus A, Phair G, Brazil K, Burns A, Roderick P, Thompson C*, et al.* Cost of conservative management in patients with end stage kidney disease who decline dialysis: lessons from a multi-centre observational study in the UK. Health Economics Association of Ireland Meeting, abstract no. 33.
54. Danese M, Gleeson M, Kutikova L, Griffiths R, Azough A, Khunti K*, et al.* Costs of cardiovascular (CV) events in the United Kingdom (UK) using real-world data. *Value in Health* 2015;**18**(7):A387.
55. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). *Diabet Med* 2015;**32**(4):459-66. http://dx.doi.org/10.1111/dme.12647
56. Brazier JE, Green C, Kanis JA, Committee Of Scientific Advisors International Osteoporosis Foundation. A systematic review of health state utility values for osteoporosis-related conditions. *Osteoporosis International* 2002;**13**:768-76.

57. Pollock C, James G, Garcia Sanchez JJ, Carrero JJ, Arnold M, Lam CS*, et al.* Healthcare resource utilisation and related costs of patients with CKD from the UK: a report from the DISCOVER CKD retrospective cohort. *Clin Kidney J* 2022;**15**(11):2124-34.

Appendices

Appendix 1: Trial comparison of Empagliflozin Kidney and Dapagliflozin Kidney[26] trials

Baseline characteristic*	Empagliflozin 10 mg	Dapagliflozin
Age (years), mean (SD)	64	62
Female sex, N (%)	33%	33%
White	59%	52%
Black	4%	5%
Asian (no breakdowns between SA and EA given)	36%	35%
Body mass index¶ (kg/m^2), mean (SD)	30	29
Systolic BP	136	137
Diastolic BP	78	78
Diabetes	**46%**	**68%**
CVD Yes	**26%**	**38%**
Smoker	**44%**	**13%**
GFR		
Mean – mL/min/1.73m^2 (SD)	37	43
<30 mL/min/1.73m^2	**34%**	**14%**
≥30 to <45 mL/min/1.73m^2	44%	46%
≥45 mL/min/1.73m^2	**21%**	**41%**
uACR		
Geometric mean (95% CI)	219 (205-234)	
Median (IQR)	331	965
<30	20.1%	
≥30 to ≤300	28.1%	
>300	51.8%	
Treatments		
Renin-angiotensin system inhibitor	85.7%	98%
Any diuretic	41.2%	43%
Any lipid-lowering medication	66.3%	65%
Cause of CKD		
Diabetic kidney disease	31.2%	NR
Hypertensive or renovascular disease	21.4%	NR
Glomerular disease	25.8%	NR
Other	11.7%	NR
Unknown	9.9%	NR

The Dapagliflozin Kidney trial reported that 68% of recruits had diabetes and that 37% had various forms of cardiovascular disease, but did not give details of the causes of CKD.

There were differences in proportions in the key empa and dapa trials. Figures rounded to one DP.

eGFR	Empa Kidney	Dapa
>90	0	0
60-89	8%	
60-75		11%
45-59	13%	30%
30-45	44%	46%
15-29	36%	
25-29		14%
<15	0	0

The company make much of their broader inclusion criteria with a broader top band of 60-89 compared to Dapa's 60-75 but the extra range of 75-89 probably only had <4% of patients. However, the additional bottom band of 15-24 gave them more severely impaired patients. The main differences in proportions are in the 45-59 and <30 bands.

There were marked differences in the uACR proportions in the empa and dapa trials;

uACR	Empa Kidney	Dapa
<30	20%	0
30-299	38%	10%
300 and over	52%	90%

Single Technology Appraisal

Empagliflozin for treating chronic kidney disease [ID6131]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Insert deadline for response** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Clarity on the intended population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the Summary (page 12), Executive Summary (page 14), and also in the Remit of the appraisal (Page 34), it appears as if the following is the Scope of the appraisal: "empagliflozin for treating adults with chronic kidney disease (CKD) (patients with or without type 2 diabetes mellitus [T2DM], with a broad range of estimated glomerular filtration rate [eGFR] from 20 to 90 mL/min/1.73m2, and varying levels of albuminuria."	Suggested addition: "Specifically, the intended population is adults with CKD having individually optimised standard of care, and having: [redacted]	We request the more specific population is given here, as detailed in the Decision Problem (Table 12, Page 42). The suggested addition provides clarity on the intended population for the reader.	No factual error, no revision required.

Issue 2 eGFR measurements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 1.4, Issue 1 (Page 18) the following is stated: "*Unclear when each patient had an eGFR measurement*"	Please delete the following: "Unclear when each patient had an eGFR measurement"	The current statement is not accurate eGFR was assessed at each visit, as per protocol. This information was provided in response to Clarification Question B33 and is available in the CTR.	Accepted.

Issue 3 Model validation and face validity check (a)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 1 (on Pages 18, 124) is factually inaccurate: "The company model when run using the baseline characteristics of a long-term follow-up study in the literature predicts too much ESKD and too little survival. There are reasons to think that this may worsen beyond the 15-year duration	The company disagrees that model validation demonstrates overprediction of ESKD and mortality. Given the company's validation results, this EAG Issue should be removed.	The company believe that the EAG's conclusion of overprediction ESKD is a factual inaccuracy as it is not supported by the company's model validation exercise using the Tangri 2016 North America or non-North America external cohorts for ESKD. Further, the EAG's conclusion of overprediction of death is not supported when using the Matsushita	No factual error, no revision required.

of the long-term follow-up study. This seems likely to bias the model in favour of empagliflozin”		2010 cohort. Finally, life expectancy by age and eGFR class provided acceptable predictions when applying the Turin 2013 cohort.	

Issue 4 Model indeterminacy and speculation regarding the model structure

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The following wording in section 4.15.21 Model Indeterminacy (page 162) is inappropriate informal language and contains opinion about the company’s cost-effectiveness model that is not formed on the basis of evidence: “[redacted]	Page 162 - [redacted] and the remaining text be revised as follows: “The model is both modelling patients’ movement through KDIGO health states and applying the KDIGO health state specific cost and quality of life values from the literature as well it is also explicitly modelling CKD related events and their effects.” Page 30 - The comment should be removed and replaced with the following:	This text contains speculation that is factually inaccurate and is unsupported by neither the company evidence submission and responses to 2 rounds of clarifications nor the published literature regarding. It is further using informal language to convey an opinion that is not supported by evidence.	The EAG have removed: “*It seems possible that as the model is further developed by the iQVIA team it will move towards the latter, but*”

[redacted] The EAG's Issue 17 (on Page 30) use factually inaccurate wording as follows: " [redacted] "	"The model structure incorporates a combination of complications whereby specific quality-of-life impacts (disutilities) and costs are associated to them, and complications whose quality-of-life and costs impacts are accounted within KDIGO health state specific values. This approach reflects the literature available to the Company at the time of model development."		

Issue 5 EAG rebuilding the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The following text from section 4.15.1. EAG Model Rebuild (page 137) states that EAG (Warwick University, plus its contractors) intend to rebuild the model: “Due to the complexity of the company model structure and the extensive set of inputs taken from the literature, the EAG has not yet fully rebuilt the company model. The EAG will continue to work on this. To date it has only rebuilt the evolutions of eGFR, uACR, HbA1c, BMI, total cholesterol and SBP, the incidence of diabetes, the incidence of CVD and its distribution across the different type of CVD events, the incidence of ESKD and the incidence of renal replacement therapy and its	[redacted]	[redacted]	No factual error. No revision required.

evolution. This has informed the review below. The EAG has not found any major errors in terms of model structure. There are issues around the compatibility of model inputs with the model structure as reviewed in sections 4.15.4, 4.15.5 and 4.15.6. Minor errors and undocumented modelling assumptions that have no obvious justification within the cited reference are briefly presented in section 4.18 on minor issues."		[redacted]	

Issue 6 Incorrect Assertions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[redacted]	[redacted]	[redacted]	The EAG thanks the company for the clarification. It will amend the text from the EAG report from: "*The EAG thinks it likely that the clarification response about model convEAGence, as explored in the section 4.3 below, was written from the iQVIA modelling team's perspective. It suggests, regardless of the user specified random number seed, that the model convEAGes when run over 1,000 patients. The company may not be as relaxed about whether the random number seed is 0.200 or 0.301, or whether the model needs to be run over more than*

[redacted]			*1,000 patients for it to reliably convEAGe*" To: "*At error check the company supported the iQVIA modelling team in its assertion that the cost effectiveness estimates run over 1,000 patients with its chosen random number seed of 0.200 are as valid as those with the EAG selected random number seed of 0.301*."

Issue 7 Description of company submission completeness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 88, the following is stated: “[redacted]”	[redacted]	The statement on [redacted] is not factual. Details should be specified, or the statement deleted. The statement [redacted] is not correct. For patients who discontinue, eGFR decline rates from published literature are applied. The statement “[redacted]” is not factual. The EAG may not agree with the assumptions,	No factual error, no revision required.

[redacted] .”		but they are provided in the submission. Re the statement “[redacted]” These are favourable to empagliflozin. The company took a conservative approach of not assuming treatment benefit on these endpoints. The statement “[redacted]” is not factual.	

Issue 8 Annual eGFR change by yearly KDIGO health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 1.4, Issue 1 (Page 18) the following is stated: "The annual eGFR change by yearly-KDIGO health state should be calculated and used in the economic model."	The statement should be replaced with following "The annual eGFR change by yearly-KDIGO health state might be beneficial to use in the economic model, but it was not feasible to generate these outputs, that represents a data driven limitation".	While the company agrees that this type of data can be of value, this additional analysis is not feasible. The company had communicated in response to Clarification Question B41 question, that it is not possible to determine changes in KDIGO risk category over time (decline or improvement) for individual patients as change in eGFR category didn't trigger collection of confirmatory values 90 days apart.	If it is not possible to perform this analysis the model structure is fundamentally at odds with the clinical inputs, and the degree to which this is a problem cannot be quantified.

Issue 9 Additional subgroups

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 3 (on Pages 12, 15, and 19) is as follows: "The modelling does not explore whether it is more cost effective to reserve empagliflozin treatment until patients progress to either (1) a high risk KDIGO health state, or (2) a moderate risk KDIGO health state. This also relates to the possibility of there being fast progressors and slow progressors."	This EAG Issue should ideally be removed. If kept in the report, please: a) Change the title of the Issue (Page 19) to "Additional subgroups now suggested by the EAG" or similar. And b) add (to Pages 12, 15, and 19): "the company wishes to clarify that these subgroups were not detailed in the Scope issued by NICE and were not suggested or requested during clarification questions. Furthermore, as empagliflozin is cost-effective overall, further subgrouping is not necessary or appropriate."	The EAG Issue, as presented, suggests that these are subgroups that were requested by NICE but not provided by the company, which is not correct. Furthermore, this is beyond the Scope of the appraisal. Patients at earlier and later stages of disease, nor patients who may be fast or slow progressors, were not subgroups detailed in the Scope issued by NICE and were not suggested or requested during clarification questions. Furthermore, as empagliflozin is cost-effective overall, further subgrouping is not necessary or appropriate. The title of the Issue ('Decision Problem not fully addressed') is not	No factual error, no revision required.

		appropriate as these subgroups were not included in the Scope issued by NICE.	

Issue 10 Model convEAGence and extreme patient values

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 4 (on Pages 12, 15, 20, 89-94) is factually inaccurate: "The company model is run over 1,000 patients. This is not sufficient for the net cost estimate of the model to convEAGe. Other estimates are more stable. Validation work presented by the company at clarification shows that the model occasionally simulates a patient with extreme values. One patient was simulated as having a total cost of around £630k when treated with standard care compared to a total cost of	This EAG Issue should be removed.	The EAG issue as presented suggests the model does not convEAGe at 1,000 patients which is incorrect as per evidence provided during clarification questions. The company provided evidence of model convEAGence at 1,000 patients during its response to clarifications question B5 through narrative and figures (i.e., 10, 11, 12, 13). Extreme healthcare costs have been observed in clinical practice for patients receiving several renal transplants over their lifetime and the modelling of occasional extreme values is an inherent benefit to the patient-level simulation model, which purposely incorporates	No factual error, no revision required.

around £120k when treated with empagliflozin and a net saving of over £500k. This is quite alarming and the EAG cannot think how this can sensibly come about within the model structure. It is sufficient to affect the average across the 1,000 patients simulated. Running 20,000 patients through the model. This addresses convEAGence issues but does not address the model occasionally simulating extreme patient values if this persists over the 20,000 patients.”		this observed heterogeneity. Further, extreme values may arise in both the empagliflozin and stand of care arm and their occurrence is not limited to standard of care only as the example provided suggests. Therefore, the EAG wording suggests the presence of extreme values is erroneous. Further, the company is not aware of recommendations in the literature to remove extreme patient values from cost-effectiveness analyses conducted through patient-level simulation models. The benefit of these models is that they account for observable patient heterogeneity, and such as extreme values are occasionally observed in real-world clinical practice.[1]	

[1] Sageshima et al. (2022) How to deal with kidney retransplantation – second, third, foruth and beyond. Transplantation 106(4): pp.709-721. https://journals.lww.com/transplantjournal/abstract/2022/04000/how_to_deal_with_kidney_retransplantation_second,.15.aspx

Issue 11 Modelling of those with diabetes and those without diabetes separately

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 5 (as detailed on Page 21) includes the following: "*The company presents cost effectiveness estimates for those with diabetes at baseline and those without diabetes at baseline in Appendix S. But this only varies baseline characteristics. Clinical effectiveness estimates are not subgroup specific*."	Suggested addition: *"*On request, the Company provided clinical effectiveness estimates for patients with and without diabetes (observed-case, all data [OC-AD], the primary dataset for trial outputs), enabling the EAG to determine cost-effectiveness estimates."	The current statement gives the impression that the company has not provided clinical effectiveness estimates per diabetes subgroup. As detailed in response to Clarification Questions, the company have explained that the treatment effect applied to patients while on treatment was based on the overall population, rather than specific treatment effects for subgroups. This approach was adopted due to limitations in the dataset size and the fact that diabetes is not considered a treatment effect modifier. However, on request, the Company did provide clinical effectiveness estimates per diabetes subgroup.	No factual error. No revision required.

		Observed-case, all data (OC-AD) results were provided. The primary analysis was based on the RS of participants using all available data from the follow-up period (OC-AD), thus following the intention-to-treat analysis approach. There is a eGFR rebound effect after treatment discontinuation, it will not be captured in OC-OT scenario. During the Clarification Question call with NICE and the EAG, potential solutions and challenges in modelling patients with and without diabetes were discussed. The company was told not to provide additional model versions at this stage.	

Issue 12 eGFR decline estimates after treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 5 (as detailed on Page 21) includes the following: *"The model assumes these estimates differ between those with diabetes and those without diabetes for those discontinuing treatment."*	Suggested amendment: "*"The model assumes eGFR decline rates (e.g., disease progression) differ between those with diabetes and those without diabetes for those discontinuing treatment."*	The current statement gives the impression that treatment effects are applied beyond treatment discontinuation, which is not correct. The model assumes different eGFR decline rates (e.g., disease progression) between patients with and without diabetes for those discontinuing treatment, but not treatment effects. No treatment effects are assumed beyond treatment discontinuation.	The EAG will amend the text from: The model assumes these estimates differ between those with diabetes and those without diabetes for those discontinuing treatment To For those discontinuing treatment the model assumes the eGFR changes differ between those with diabetes and those without diabetes, based upon values taken from the literature.

Issue 13 Net health benefits among those with diabetes at baseline compared to those without diabetes at baseline

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 5 (as detailed on Page 21) includes the following: *"Based upon OC-AD eGFR and uACR subgroup specific data suggests that the net health benefits are as much as 6-7 times greater among those with diabetes at baseline compared to those without diabetes at baseline."*	Suggested addition: "*It should be noted that EAG cost-effectiveness estimates, using their preferred assumptions, indicate that empagliflozin is highly cost-effective in CKD patients both with and without diabetes*."	Whist EAG cost-effectiveness estimates, using their preferred assumptions, indicate higher net health benefits for patients with compared with those without diabetes at baseline, this should be presented within the context that empagliflozin is highly cost-effective in both groups. For CKD patients with diabetes at baseline, the EAG estimate an ICER of £326/QALY and NHB of 0.324. For patients without diabetes at baseline, the EAG estimate an ICER of £10,254 and NHB of 0.048.	No factual error, no revision required.

Issue 14 Renal replacement therapy probability function and eGFR cap

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's Issue 12 on Page 26 includes the following incorrect wording: "The company annualization of the risk function suggests that between around 40% and 50% of patients with an eGFR of 15 ml/min/1.73m^2 will receive renal replacement therapy that year." The EAG's Issue 12 on Page 26 includes the following wording that requires additional clarity: "These probabilities are applied when patients fall into G5 with an eGFR below 15 ml/min/1.73m^2."	The EAG's sentences on page 26 and page 100 should be removed due to factual inaccuracy. The EAG's footnote on page 102 should be corrected to the following: "In effect converting the 5-year risk to an annual risk as P_1 = 1- (1- P_5)^(1/5)". The subsequent graphs (Figure 11 and 12) and narrative (page 103) should be corrected using this formula. On page 26, the following should be added to the statement on probabilities being applied when applied when patients fall into G5 with an eGFR below 15 ml/min/1.73m$^{2:}$ "The original risk equations assume eGFR threshold of 30 ml/min/1.73m^2; the company lowered this threshold to 15 ml/min/1.73m$^{2"}$	Page 26 – The EAG appears to have misinterpreted the annualization of the risk function. The correct interpretation is that there is a cumulative ESKD incidence of 40-50% over 20 years. Page 100 – The Company provided justification for choice of the Tangri et al (2016) pooled 6 variable model over the 4 variable Major et al (2019) model during further clarification question number 6: "The risk equation used to predict renal replacement therapy (RRT) initiation in the base case is the pooled, 6 variable (6v) equation by Tangri et al. 2016. This version is based on the most recent data and the largest number of cohorts (pooled North America and non-North America	The EAG will revise the text from: $P_1 = P_5$^(1/5) To: P_1 = 1- (1- P_5)^(1/5) And from: *", though the reason for the choice of Tangri et al rather than Major et al is unclear*" To *". Major et al. is specific to the UK population but based on four variables only. This is the reason the company gives for its preference for Tangri et al*."

The EAG includes the following incorrect wording on Page 100: "The company base case applies the pooled 6 variable model of Tangri et al (2016) apparently due to it being the best fit, though the reason for the choice of Tangri et al rather than Major et al is unclear." The EAG includes the following incorrect wording and footnote on Page 102: "The Company assumes a constant annual rate of RRT to arrive at the annual rates as outlined below. In effect converting the 5-year risk to an annual risk as $P_1 = P_5$^(1/5)…"		countries). The 6 variable option was selected over the 4 variable option as it includes the risk factors diabetes and hypertension, and so predictions could be sensitive to these comorbidities. An alternative source, Major et al. 2019, is specific to the UK population but based on four variables only, thus it was not retained in the base case. Scenario analysis using the UK-specific Major et al. 2019 risk equation results in similar results to the base case scenario with Tangri et al. 2016 pooled 6v." Page 102 – The EAG has misstated the formula the Company used to arrive at annual rates of RRT. The EAG's formula states $P_1 = P_5$^(1/5). Assuming P_5 = 73%, this gives P_1 = 94% using the EAG's formula. The subsequent graphs 11 and	

		12 that appear to have been created using the EAG's misstated formula should be corrected, along with the associated commentary on page 103. However, the Company's formula is P_1 = 1- (1-P_5)^(1/5). Assuming P_5 = 73%, this gives P_1 = 23%. Therefore, the EAG has misstated the formula.	

Issue 15 Duration of on treatment uACR fold multiplier

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 8 (as detailed on Pages 12, 15 and 24), includes the following: "The model reapplies these for each annual model cycle that a patient remains on treatment. Information supplied at clarification	Suggested addition "During Clarification Questions, the company provided a scenario in which uACR treatment effects were applied for 12 months only" The following should be deleted: "Clarification about why 30 month rather than 18 month OC-AD data was	Treatment effects based on observations from EMPA-KIDNEY at 18 months were used consistently, in line with available data. However, an alternative scenario was provided during clarification questions.	No factual error, no revision required. However the EAG is now uncertainwhether 30 month OC-AD uACR data for those without diabetes at baseline was supplied at clarification (based upon the footnote

suggests that based upon the 36 month data the reapplication of these uACR fold multipliers." And "Clarification about why 30 month rather than 18 month OC-AD data was supplied for those without diabetes at baseline."	supplied for those without diabetes at baseline."		to Table 28 in the first clarification response). This is independent of the company scenario analyses.

Issue 16 Off treatment uACR fold multiplier

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 9 (as detailed on Pages 13 and 15), includes the following: "There is a lack of information about the company estimate for the off treatment uACR fold/multiplier. It seems misaligned with other estimates."	The following should be deleted: "There is a lack of information about the company estimate for the off treatment uACR fold/multiplier " The second sentence should be amended as follows: "The uACR fold/multiplier was informed by the CKD PC registry"	This is not correct, uACR fold source is CKD PC registry, that is clearly stated in the dossier.	No factual error, no revision required. The EAG is referring to the detail of the statistical analysis, its inputs, goodness of fit statistics, reasons for model choices etc., not the source paper of the inputs to the undocumented statistical analysis.

Issue 17 Full follow-up OC-AD data or on treatment OC-OT data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 10 (as detailed on Page 25) includes the following: "*The model assumes a proportion of patients come off treatment each year. These patients are modelled differently than those on treatment, applying eGFR and uACR change estimates derived from the literature. Consequently, the modelling of those on treatment should be based upon an analysis of the on treatment EMPA-KIDNEY data, an OC-OT analysis*."	Suggested amendment: *"The model assumes a proportion of patients come off treatment each year. These patients are modelled differently than those on treatment, applying eGFR and uACR change estimates derived from the literature. No treatment effects are applied to patients after treatment discontinuation in the model.* *Separately, the EAG expresses a preference for modelling of those on treatment based upon an analysis of the on treatment EMPA-KIDNEY data, an OC-OT analysis, for the following reasons X, Y, Z."*	If the EAG would like to stress that OC-AD should be replaced with OC-OT, it should be noted that is independent from disease progression estimates following treatment discontinuation. The current statement is confusing to the reader as it is mixing two different things: (a) that patients who discontinue treatment in the model are applied eGFR and uACR changes based on estimates from the literature (and no treatment effects) and (b) patients who are on treatment receive treatment effect estimates based on an observed-case all-data (OC-AD) analysis of EMPA-KIDNEY, but the EAG has a preference for using	No factual error, no revision required.

		observed-case on-treatment (OC-OT) data instead	

Issue 18 Duration of treatment effects

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 11 (as detailed on Page 25) includes the following: *"EAG recollection is that this is in contrast to previous empagliflozin submissions for T2DM which limited the effects on, say, HbA1c to the trial duration."*	This issue should be removed.	The statement is not correct. In the empagliflozin T2D submission the company used the assumption of treatment effect on HbA1c while on treatment.	The EAG will revise the text from: *"EAG recollection is that this is in contrast to previous empagliflozin submissions for T2DM which limited the effects on, say, HbA1c to the trial duration."* To. *"EAG recollection is that this is in contrast to previous empagliflozin submissions for T2DM which limited the effects on, say, HbA1c to the trial duration; e.g. an annual -0.5% change over a 2 year trial*

			duration would be assumed to apply for 2 years hence a -1.0% change at 2 years but no further improvement thereafter. The current modelling repeatedly applies this to yield a -1.0% change at 2 years, a -2.0% change at 4 years, a -3.0% change at 6 years, etc… until the 3.0% HbA1c floor is achieved"

Issue 19 Treatment benefit after discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG's Issue 11 (as detailed on Page 25) includes the following: "*For those discontinuing treatment the model may also retain the full benefit at discontinuation for the remainder of the time horizon for those without*	This issue should be removed.	The statement is not correct. Following treatment discontinuation, treatment effect in not maintained. It should be noted that the model is an individual patient simulation model, and so individual patient trajectories	No factual error, no revision required. Again this is unclear. If a constant annual change is assumed to apply at treatment discontinuation this will maintain the full benefit at treatment

diabetes. This may not be reasonable."		change across each model cycle.	discontinuation for the remainder of the model, subject to any ceilings and floors for the relevant risk factor; i.e. if the patient were at 5% with empagliflozin and 6% with placebo and discontinued at the same time point an annual +0.5% annual increase would cause HbA1c to rise in both arms but the net gain of 1.0% would be maintained for the remainder of the time horizon.

Issue 20 Costs of ESKD and renal replacement therapy

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
The EAG incorrectly states the following in Section 4.11.3 (Pages 115): "Those with ESKD not undEAGoing RRT are treated with conservative	The EAG's sentence on Page 115 is factually incorrect and should be replaced by the following sentence: "Those with ESKD not undEAGoing RRT are treated with conservative	The EAG has stated that costs for conservative therapy in ESKD are additional to annual KDIGO health state costs in G5 health states leading to double count. This is factually	The EAG will revise its wording from: This cost appears to be in addition to the £2,000, £2,445 and £4,604 annual KDIGO (G5, A1), (G5, A2)

management at an annual cost of £6,335 based upon Agus et al.[53] This cost appears to be in addition to the £2,000, £2,445 and £4,604 annual KDIGO (G5, A1), (G5, A2) and (G5, A3) health states cost."	management at an annual cost of £6,335 based upon Agus et al."	incorrect – only conservative therapy in ESKD costs are accounted for and the G5 KDIGO health state costs are not incorporated in the RRT submodule.	and (G5, A3) health states cost." To This cost appeared to the EAG to be in addition to the £2,000, £2,445 and £4,604 annual KDIGO (G5, A1), (G5, A2) and (G5, A3) health states cost, but at error check the company has stated that this is not the case.

Issue 21 Costs of CVD complications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG incorrectly states the following in Section 4.11.4 (Page 115-116): "Annual follow up costs for myocardial infarction and congestive heart failure of £705 and £941 are taken from previous NICE assessments. Annual follow up costs for unstable angina, stroke, and transient	The following wording should be deleted: "The costs of Danese included hospitalizations, visits and drugs so double count some of the KDIGO health state costs."	The EAG has stated that Danese double counts KDIGO health state costs due to hospitalisation costs. This is factually incorrect as costs of hospitalisation and critical care are excluded from KDIGO health state costs. Therefore, no double counting occurs.	No factual error, no revision required. The double counting is due to "visit" costs. These are quite substantial in the KDIGO costings and may be similarly substantial in the Danese costings.

ischaemic attacks of £421, £1,097 and £795 were taken Danese 2015,54 available as an abstract of a study of the UK clinical practice research datalink. It can also be noted that Danese provided long term follow up costs for myocardial infarction of £959 and for heart failure of £1,129 which while slightly higher than the model input values are broadly in line with them. The costs of Danese included hospitalisations, visits and drugs so double count some of the KDIGO health state costs.”			

Issue 22 Model validation and face validity check (b)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG incorrectly states the following in Section 4.12.5 (Page 128)	The wording should be amended to state the following:	The EAG incorrectly states that all patients with a given set of characteristics move	The EAG will amend the text from:

“The model typically underestimates the incidence of ESKD at 5 years compared to CRIC., with the exception of those in (G4, A2) and (G4, A3). The EAG thinks that this is because the deterministic model structure means that all patients with a given set of characteristics work their way through the KDIGO health states at the same rate.”	“The model typically underestimates the incidence of ESKD at 5 years compared to CRIC., with the exception of those in (G4, A2) and (G4, A3).”	through KIDIGO states at the same rate due to the deterministic of the model. This is incorrect. The Company wishes to clarify that it is unlikely for patients to have the same set of baseline characteristics due to the patient-level simulation structure of the model. Additionally, uACR natural progression is random and heterogenous for each patient due to this and patients will not have the same uACR path through the model. uACR affects even predictions in the model including ESKD.	The EAG thinks that this is because the deterministic model structure means that all patients with a given set of characteristics work their way through the KDIGO health states at the same rate.” To The EAG thinks that this is because the deterministic model structure means that all patients with a given set of characteristics work their way through the KDIGO health states at the same rate. Though note that this is with the exception of the (oddly) randomly sampled off treatment uACR effect.”

Issue 23 Annualization and compound of risks

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
The EAG incorrectly states the following in Section 4.15.18 (Page 159):	The wording should be amended to state the following:	The Company wishes to clarify that Matsushita (2020) was used to estimate the	The EAG will amend the text from:

"The probability of a 1st CVD event: a 5-year risk function."	"The probability of a 1st CVD event: a 10-year risk function."	probability of a 1st CVD event. This was a 10-year risk function and not a 5-year risk function as currently stated.	The probability of a 1st CVD event: a 5-year risk function To The probability of a 1st CVD event: a 10-year risk function

Issue 24 Description of ITC results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 65, the following is stated: "First, there is a borderline meaningful difference between empagliflozin and dapagliflozin for the composite renal outcome definition 2 using the fixed-effects model, in favour of dapagliflozin.	The wording should be amended to state the following: "First, there is a borderline meaningful difference between empagliflozin and dapagliflozin for the composite renal outcome definition 2 using the fixed-effects model (which was not observed in the random effects model), in favour of dapagliflozin.	To provide an accurate representation of the findings.	No factual error. No change required.

Issue 25 Description of ITC results in patients with CKD but without T2DM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 82, the following is stated: "The NMA showed a borderline meaningful difference between empagliflozin and dapagliflozin for the composite renal outcome definition, in favour of dapagliflozin. For patients with CKD but without T2DM, Dapagliflozin demonstrated a non-meaningful benefit over empagliflozin across all of the outcomes and models (fixed and random-effects)."	The wording should be amended to state the following: "The NMA showed a borderline meaningful difference between empagliflozin and dapagliflozin for the single outcome of a composite renal outcome definition (composite endpoint with 50% eGFR decline), in favour of dapagliflozin. For patients with CKD but without T2DM, there were no meaningful differences between dapagliflozin and empagliflozin"	The definition of the renal outcome should be included. The current statement re a 'non-meaningful benefit' is not appropriate. Instead 'no meaningful differences' should be reported.	No factual error, no revision required.

Issue 26 EMPEROR trial results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 47, the following eGFR decline rates are reported for the EMPEROR-Reduced and EMPEROR-Preserved studies, respectively: "GFR declined by 0.55 ml/min on empagliflozin 10mg and by 2.23 on placebo." "GFR fell by 1.75 ml/min on empagliflozin and by 2.62ml/min on placebo."	These should be amended as follows: [EMPEROR-Reduced]: GFR declined by 0.55 ml/min on empagliflozin 10mg and by 2.28 on placebo. [EMPEROR-Preserved]: GFR fell by 1.25 ml/min on empagliflozin and by 2.62ml/min on placebo	Minor data corrections.	Accepted. These minor errors had no effect on EAG report. The two studies were included only for information since the modelling was based mainly on the Empa Kidney trial

Issue 27 Generalisibility to the UK context

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

In Issue 8 (Page 18), the following is stated: “The EAG noted that overall smoking prevalence in the diabetes group was 47%, which was likely to be higher than in the UK population , and that the mean HbA1c was 7.17%, which might be better than in the UK population. This might mean that outcomes in the UK might differ from those in the whole study.” On page 51, the following is stated: In the UK Empa Kidney cohort, 7% were active smokers, far fewer than the 45% overall in the trial, but another 42% were previous smokers. No data were available on duration since stopping. The much lower proportion could mean that	The following copy should be removed: “The EAG noted that overall smoking prevalence in the diabetes group was 47%, which was likely to be higher than in the UK population , and that the mean HbA1c was 7.17%, which might be better than in the UK population. This might mean that outcomes in the UK might differ from those in the whole study.” In Table 13 (EMPA-Kidney baseline characteristics), 10.3% should be used for Smokers (%) in the column of the overall population. On page 51, the statement should be amended to: “In the UK EMPA-Kidney cohort, 7% were active smokers, compared with 10.3% in the overall trial population.”	Smoking prevalence in the UK subgroup was provided during clarification exchange. It was largely comparable with EU data and overall trial population. Thus, this statement is not correct. The statement that the mean HbA1c of 7.17%, might be better than in the UK population is not substantiated. National diabetes audit suggests that 63.4% of T2D patients achieved treatment target of </= 58mmol/mol (which is approx. 7.5%). This suggests the % is not far off. In Table 13 of the EAG report, different definitions of patient characteristics have been presented. Smokers (%) 44.60% in the overall population, 7.1% in the UK and 9.7% in western Europe population. These are different characteristics:	HbA1c. No change required. If 63% of UK population achieve 7.5%, then the UK mean will be much higher than 7.17%. Smoking was not reported in the main BI submission or the NEJM paper. It was reported in the bI submission Table 27 for all recruits- 44.6%. But we accept the figure provided in the clarification responses for UK recruits.

the risk of cardiovascular outcomes is lower in UK. .”		44.6% corresponds to these who had smoked in the past, but no longer smokes regularly, the corresponding value for UK is 42.1% that is comparable with overall population and EU population. 7.1% corresponds to currently active smokers, in the overall population it was 10.3% that is close to UK 7.1%. In case active smokers are meant to be reported in this table 10.3% value should be stated for the overall population.	

Issue 28 Optimised care

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On Page 37 the following is stated: “Care in both the empagliflozin and dapagliflozin trials appears	The statement should be replaced with: “Care in the empagliflozin trial (EMPA-KIDNEY) appears to be more similar to UK clinical practice than care in the	The statement is not correct. In DAPA CKD, 99% of patients were on RAS inhibitors. In EMPA KIDNEY, 85% of patients were on RAS	No factual error. We are not comparing the Dapagliflozin and Empagliflozin Kidney trials but the trials versus

to have been more optimised than UK practice as reported in the CKD guideline.”	dapagliflozin trial (DAPA-CKD). For example, in EMPA KIDNEY 85% of patients were on RAS inhibitors, vs 99% in DAPA-CKD.	inhibitors. Thus, care in EMPA-KIDNEY is more similar to care in UK clinical practice.	UK practice as described in the NICE guideline. No change required.

Issue 29 MHRA marketing approval

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 40 the following is stated: The EMA has recently extended empagliflozin indication to include treatment of chronic kidney disease (CKD) in adults, based on final results from study EMPA-KIDNEY.	This statement should be replaced with: “The MHRA and EMA have recently extended empagliflozin indication to include treatment of chronic kidney disease (CKD) in adults, based on final results from study EMPA-KIDNEY.”	On 5 September 2023 the MHRA granted approval for the extension of indication to include treatment of chronic kidney disease.	This is correct, but the EAG report was correct when it was written. No factual error.

Issue 30 Conclusions on published evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 41, it is noted that “The other group worth considering are the	Suggested addition:	Clarity for readers.	No factual error. We did not say that the GLP-1 analogues were

glucagon-like peptide-1 agonists (GLP-1As)"	"GLP-1As are options for the treatment of T2D, they are not indicated for the treatment of CKD."		indicated for CKD. But they are for T2 diabetes and are widely used. No change required

Issue 31 Race-adjusted eGFR formula

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 18, 42 and 82 the 'race-adjusted' eGFR is mentioned in: "The population reflect the entry criteria of the EMPA-KIDNEY trial with race-adjusted: eGFR."	This statement should be replaced with: "The population reflect the entry criteria of the EMPA-KIDNEY trial with CKD-EPI equation eGFR."	This is the preferred term for the equation.	No factual error. No change required.

Issue 32 Trials included in NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 46 the following is stated: "The other three trials were excluded because of the	Suggested addition: "Subgroups of patients with prevalent CKD from these trials were included in the NMA"	To provide an accurate account to readers.	No factual error. No change required.

population (not exclusively CKD patients) but are briefly reported below.”			

Issue 33 Uncertainty around patient characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 51 the following is stated: “Apart from the difference and uncertainties around smoking, statins and ethnicity, the characteristics of the UK cohort seem similar enough to the whole cohort for their outcomes to be also similar.”	Suggested addition: “Apart from some minor differences, the characteristics of the UK cohort seem similar enough to the whole cohort for their outcomes to be also similar.”	The company believes there are no remaining uncertainties.	No factual error. No change required.

Issue 34 % with diabetes in EMPA-Kidney

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 84 the following is stated: "There were other baseline differences such as the proportion with diabetes, 67% in the dapagliflozin trial and 44% in the empagliflozin trial."	This statement should be replaced with: "There were other baseline differences such as the proportion with diabetes, 67% in the dapagliflozin trial and 46% in the empagliflozin trial (44% with T2D)."	Total diabetes in EMPA-Kidney was 46%, of which 44% had T2D.	The EAG accepts the suggested amendment.

Issue 35 Truncated sampling of baseline age

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 170 the following is stated: "The company model noted a maximum age of 94, whereas the actual inputted maximum is only 80. The maximum of 94 was apparently based upon Matsushita 2021, but the	This statement should be replaced with: "The company model noted a maximum age of 94, whereas the actual inputted maximum is only 80. The maximum of 80 was based upon Matsushita 2021. The maximum age	To correct factual inaccuracies. The maximum of 80 was based upon Matsushita 2021, which provides the mortality equations up to the age of 80. The maximum age in EMPA KIDNEY was 94, this was	The EAG accepts the suggested amendment.

company did not clarify what the maximum age was within EMPA-KIDNEY. Sampling with a maximum of 94 years resulted in 5% of patients being sampled as over 85 whereas in EMPA-KIDNEY this was only 2%. While this may be a concern the EAG thinks that the sampling bias that results from assuming an 80 year maximum is more of a problem. A 94 year maximum results in a mean of 63 years, which is aligned with the input values. When sampling according to company method the EAG prefers a maximum of 94 years for these reasons.”	was within EMPA-KIDNEY was 94 years. Sampling with a maximum of 94 years resulted in 5% of patients being sampled as over 85 whereas in EMPA-KIDNEY this was only 2%. While this may be a concern the EAG thinks that the sampling bias that results from assuming an 80 year maximum is more of a problem. A 94 year maximum results in a mean of 63 years, which is aligned with the input values. When sampling according to company method the EAG prefers a maximum of 94 years for these reasons.”	provided in the trial results section.	

Issue 36 Undocumented company analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 99 the following is stated: "**4.8.3. Clinical effect estimates not presented in Document B** The model also includes effects upon HbA1c, SBP and weight or BMI. These estimates are not presented in the company submission Document B. **Table 34: Undocumented clinical effect estimates**"	The titles and copy should be replaced with: "**4.8.3. Clinical effect estimates** The model also includes effects upon HbA1c, SBP and weight or BMI. **Table 34:Clinical effect estimates**"	These estimates were originally omitted from Document B but were included in the model and later detailed during clarification questions. Thus, they are not 'undocumented'.	No factual error, no revision required. The EAG will amend the title of Table 34 to: **Clinical effect estimates not presented in Document B**

Issue 37 Undocumented clinical effect estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 98 the following is stated:	This statement should be replaced with:	The analysis is detailed within the model, and this was explained during Clarification	No factual error, no revision required.

“For those who discontinue the model uses an undocumented company analysis of Coresh et al”	For those who discontinue the model uses a company analysis of Coresh et al	Questions. Thus, it is not an ‘undocumented analysis’.	The EAG has not been able to find any account of the statistical analyses undertaken in terms of functions estimated and input values, goodness of fit etc.

Issue 38 Category G1, A1

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On Page 108 the following is stated: “The EAG has not reviewed these elements of the modelling. It is unclear whether the relative risks are applied within the model and if so what the hospitalisation rate for (G1, A1) is.”	The following should be added: “However, G1, A1 is out of scope of this appraisal.	Clarity on the intended population.	No factual error, no revision required.

Issue 39 Complications without utilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 113 the following is stated: "A range of modelled complications are assumed not to affect quality of life. The company states that this is due to their effects already being within the KDIGO (or ESKD) health state quality of life. In effect, different rates of these complications are assumed to only affect costs and not affect quality of life. These appear to include: • Hypertension • Peritonitis	This statement should be replaced with: "A range of modelled complications are assumed not to affect quality of life. The company states that this is due to their effects already being within the KDIGO (or ESKD) health state quality of life. These include: • Hyperphosphataemia • Hypocalcaemia • Hyperparathyroidism • Infections health state (which includes respiratory tract, gastrointestinal tract, urinary tract infection, skin and soft tissue,	Amended for factual accuracy.	The EAG accepts the proposed amendments.

• AV access thrombosis • Bloodstream infections • Hyperphosphataemia • Hypocalcaemia • Hyperparathyroidism • Respiratory track infection • Gastrointestinal track infection • Urinary track infection • Skin and soft tissue infection • Nervous system infection • Musculoskeletal system infection • Metabolic acidosis • Hyperkalaemia • Hyperuricaemia/Gout • Anaemia	nervous system, and musculoskeletal system infections) • Metabolic acidosis • Hyperkalaemia • Hyperuricaemia/Gout For hypertension, it is assumed this already affects predictions of events, so both costs and utilities are excluded as they are considered to have an impact on the occurrence of those events, therefore indirectly on costs and QALYs. Peritonitis and sepsis cost and utilities are also excluded. For AV access thrombosis, bloodstream infections, and anaemia, costs are excluded.		

• Sepsis			

Issue 40 Proposed model amendments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 184 the following are suggested: "An option to only use the KDIGO health state specific quality of life and costs, coupled with the renal replacement therapy costs."	This option should be deleted	This option is already enabled within the model	The EAG will amend the text to: "The option to only use the KDIGO health state specific quality of life and costs, coupled with the renal replacement therapy costs should be explored further." The EAG would be grateful if the company could supply the model settings for this analysis. The EAG would also be grateful if the company could comment upon why the EAG implementation of SA10 and SA11 results in essentially the same modelled output.

(please cut and paste further tables as necessary)

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td>Give full details of inaccurate marking - document title and page number</td><td>Give details of incorrect confidential marking</td><td>Please copy the impacted section here, with your amended marking.</td><td></td></tr>
<tr><td>EAG Report, Table 13 (EMPA-KIDNEY baseline characteristics)</td><td>Columns 5 and 6 of this table (baseline characteristics of UK and Western Europe cohorts) should be marked as commercial in confidence.</td><td>Table 1. EMPAG-Kidney baseline characteristics
<table>
<tr><th>Parameter</th><th>Full-cohort</th><th>Empag-10</th><th>Placebo</th><th>UK Cohort</th><th>Western-Europe</th></tr>
<tr><td>Number of subjects, N</td><td>6609</td><td>3,304</td><td>3,305</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Age (years),</td><td>63.30</td><td>63.9 (13.9)</td><td>63.8 (13.9)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>The EAG has made the changes as suggested but for the majority it considers AIC marking might be more suitable.</td></tr>
</table>

		mean (SD)						
		Female sex, N (%)	2192 (33.2%)	1,097 (33.2)	1,095 (33.1)	[redacted]	[redacted]	
		History of DM, N (%)						
		Yes	3,040 (46.0)	1,525 (46.2)	1,515 (45.8)	[redacted]	[redacted]	
		No	3,569 (54.0)	1,779 (53.8)	1,790 (54.2)	[redacted]	[redacted]	
		DM type, no./total no. (%)						
		Type 1	68/3,040 (2.2)	34/1,525 (2.2)	34/1,515 (2.2)	[redacted]	[redacted]	
		Type 2	2,936/3,040 (96.6)	1,470/1,525 (96.4)	1,466/1,515 (96.8)	[redacted]	[redacted]	
		Other or unknown	36/3,040 (1.2)	21/1,525 (1.4)	15/1,515 (1.0)	[redacted]	[redacted]	

		HbA1c (%)	6.27%			[redacted]	[redacted]		
		Systolic blood pressure (SBP)	136.50	136.4 (18.1)	136.7 (18.4)	[redacted]	[redacted]		
		Diastolic blood pressure (DBP)	NA	78.1 (11.7)	78.1 (11.9)	[redacted]	[redacted]		
		Diabetes diagnosis (years)				[redacted]	[redacted]		
		Insulin use (%)				[redacted]	[redacted]		
		Proportion on lipid therapy	66.2%	66.3 %	66.2 %	[redacted]		[redacted]	

		(mainly statins) (%)						
		Renin-angiotensin system (RAS) inhibitors (%)	5.2%	85.7%	84.6%	[redacted]	[redacted]	
		Diuretics therapy (%)	42.6%	41.2%	44.0%	[redacted]	[redacted]	
		Smokers (%)	44.60%			[redacted]	[redacted]	
EAG Report. Page 65	The copy in the column to the right should be marked as	[redacted]						OK but should shading be AiC not CiC?

	commercial in confidence	[redacted]	
EAG Report. Page 66	The copy in the column to the right should be marked as commercial in confidence	[redacted]	As above
EAG Report. Page 82	The following copy does not need to be marked as confidential, but should be corrected as shown in the column to the right, and identified as an issue in the section above. "For patients with CKD but without T2DM, [redacted]	"For patients with CKD but without T2DM, there were no meaningful differences between dapagliflozin and empagliflozin"	Agree with amendment

	[redacted]."		
EAG Report. Page 140.	The copy in the column to the right should be marked as commercial in confidence	The central estimates of the above remain are in favour of empagliflozin, [redacted]	AiC not CiC? .

(Please add further lines to the table as necessary)